Quality by Design Procedure for Continuous Pharmaceutical Manufacturing: An Integrated Flowsheet Model Approach

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QUALITY BY DESIGN PROCEDURE FOR CONTINUOUS PHARMACEUTICAL MANUFACTURING: AN INTEGRATED FLOWSHEET MODEL APPROACH

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ABSTRACT

Pharmaceutical manufacturing is crucial to global healthcare and requires a higher, more consistent level of quality than any other industry. Yet, the traditional pharmaceutical batch manufacturing has remained largely unchanged in the last fifty years due to high R&D costs, shorter patent durations, and regulatory uncertainty. This has led regulatory bodies to promote modernization of manufacturing process to continuous pharmaceutical manufacturing (CPM) by introducing new methodologies including quality by design, design space, and process analytical technology (PAT). This represents a shift away from the traditional pharmaceutical manufacturing way of thinking towards a risk based approach that promotes increased product and process knowledge through a data-rich environment. While both literature and regulatory bodies acknowledge the need for modernization, manufacturers have been slow to modernize due to uncertainty and lack of confidence in the applications of these methodologies. This paper aims to describe the current applications of QbD principles in literature and the current regulatory environment to identify gaps in literature through leveraging regulatory guidelines and CPM literature. To aid in closing the gap between QbD theory and QbD application, a QbD algorithm for CPM using an integrated flowsheet models is also developed and analyzed. This will help to increase manufacturing confidence in CPM by providing answers to questions about the CPM business case, applications of QbD tools, process validation and sensitivity, and process and equipment characteristics. An integrated flowsheet model will aid in the decision-making process and process optimization, breaking away from ex silico methods extensively covered in literature.

I would like to dedicate this thesis to my family and fiancé who have always been my support system and motivation.

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LIST OF ACRONYMS AND ABREVIATIONS

API	Active Pharmaceutical Ingredient
cGMP	Current Good Manufacturing Practices
CMA	Critical Material Attributes
CPM	Continuous Pharmaceutical Manufacturing
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CSTR	Continuous Stir Tank Reactor
DoE	Design of Experiments
DP	Drug Product
FDA	United Stated Food and Drug Administration
FMEA	Failure Mode Effect Analysis
FMECA	Failure, Mode, Effects, and Criticality Analysis
FTA	Fault Tree Analysis
ICH	International Council for Harmonization
ISO	International Organization of Standardization
MA	Material Attributes
MSPC	Multivariate Statistical Process Control
NCPP	Non-Critical Process Parameters
NVA	Nonvalue Added
PAT	Process Analytical Tools
PCA	Principle Component Analysis

PFR	Plug Flow Reactor
PHA	Preliminary Hazard Analysis
PLS	Partial Least Squares
PP	Process Parameters
QA	Quality Attributes
QbD	Quality by Design
QTPP	Quality Target Product Profile
R&D	Research and Development
RPN	Risk Priority Number
UPP	Unidentified Process Parameters

CHAPTER ONE: INTRODUCTION

The Definition of Quality Applied to the Pharmaceutical Industry

Initial motivation for the development of quality came from poor quality products being administered to the public. Initial quality experts were primarily chemists who focused on impurities and toxic substance through end product testing (Sklamberg, 2013). However, while the pharmaceutical industry recognized the importance of providing the world with high quality drug products (DP), a definition of quality as it applies to the pharmaceutical industry was still missing. Consequently, what quality looked like and how it was to be achieved still largely remained an abstract concept. Thus, varying ideas on how to define and test for quality in the pharmaceutical industry has developed (Woodcock, 2004).

Woodcock (2004) primarily defined pharmaceutical quality as a DP that was free of contamination and able to provide the therapeutic benefits as described on the label and through clinical trials. Thus, this concept of pharmaceutical quality requires a drug to be able to be used for the intended therapeutic use, be safe to use, and must meet all customer expectations. Pharmaceutical quality can then be stated as a function of the DP, excipients, and the manufacturing processes involved.

This idea is further echoed in the Management Science for Health (2012) who defines pharmaceutical quality as a product's ability to comply with five major categories: identity, purity, strength of potency, uniformity of dosage form, and bioavailability. As a result, pharmaceutical quality is defined by the quality risks by linking drug attributes to critical clinical attributes or expected therapeutic benefits. Identity is simply that the DP contains the correct

active pharmaceutical ingredients (APIs) as stated on the label. Purity requires that the DP to be free from any potentially harmful contaminants, including cross contamination with other DPs. Strength and potency entails not only making sure the correct API is present in the DP, but the correct amount of API is added and is not susceptible to degradation and formation of any harmful by-products. Typically, a range of 90-110% is an acceptable range of an API, where most manufactures produce DPs closer to the maximum API levels to ensure a longer shelf life. Uniformity of dosage form may be broken down into further categories including consistency in shape, size, form, and color. Different dosage forms include tablets, capsules, creams, vapors, and liquids. Bioavailability may be considered as an extension of Woodcock's concept of providing the stated therapeutic benefits by ensuring the benefit is achieved in the correct time frame. Bioavailability is the speed at which the DP enters the blood stream. The therapeutic benefit may be limited if the API is released too fast, too slow, or incompletely (MSH, 2012). Lastly, stability requires the pharmaceutical to retain its properties to avoid physical deterioration, thermal degradation, or chemical decomposition given specific constraints like elevated temperature or humidity. Stability may be affected most by the API, formulation, packaging, and storage. While, both Woodcock and the Management of Science Health define the end product of quality in terms of DP characteristics, each definition of quality has a narrow focus that fails to address the full complexity of the processes involved. These definitions of quality as it applies to the pharmaceutical industry fail to include quality parameters pertaining to manufacturing and economics including the capital and operating costs, process and equipment characteristics, raw materials, intermediates, and final products during the manufacturing process.

As a result, Kessler (2006) has define a definition for pharmaceutical quality that extended traditional pharmaceutical quality definitions by incorporating five categories to define DP quality: product functionality, technical functionality, technological functionality, sensory functionality, and value-oriented functionality. Thus, Kessler's definition of pharmaceutical quality includes manufacturing, economic, and drug characteristic aspects. The first category defines the functionality of the DP as it relates to the chemical and physical properties of the drug that affect its behavior, uniformity, and effectiveness. The second category addresses the effects of manufacturing process on the API, intermediates, and DP as it goes through the system. Thus, emphasizing the durability of the drug and requiring an evaluation of manufacturing technology and unit operations. Meanwhile, the third category, technological functionality, is simply the fitness of use. The fourth category, sensory functionality, focuses on human senses and includes the drug product's appearance and design closely linking it the uniformity of dosage form mentioned above by the Management of Science Health. Lastly, the fifth category takes into consideration the cost-benefit ratio. It is important for manufactures to produce DP using economically feasible processes. This can be aided in evaluating nonvalue added (NVA) processes within the system. This is an extremely important category when taking into consideration of pharmaceutical manufacturing modernization and change. Manufactures will only modernize process and equipment if there is a business case for it. Kessler provides a very broad definition of pharmaceutical quality that is applicable to the pharmaceutical industry. However, some shortcomings of this definition involve a lack of details and expansion of each category that leaves it open to different interpretations risking patient safety. Furthermore, there is a lack of consideration to the overall life cycle and threats of degradation to the quality of DP.

Furthermore, the definition of pharmaceutical quality must also be looked at in terms of how regulatory bodies define it as the pharmaceutical industry is highly regulated. Regulatory bodies including the International Organization for Standardization (ISO) and the U.S. Food and Drug Administration (FDA) have also come up with definitions of product quality. The ISO 9000 standard defines quality as "the totality of features and characteristics of a product or services that bears on its ability to satisfy stated or implied needs." While the FDA (2004) defines pharmaceutical quality as "a function of DP, excipients, manufacturing and packaging whose main goal is to achieve higher understanding about influences of formulation and manufacturing process variables on product quality." Both of these definitions once again echo Woodcock's (2004) definition of pharmaceutical quality and fail to include economic aspects. Furthermore, the question still remains on how to judge and test quality. Quality can be evaluated either in vivo through clinical trials or in vitro through assay, uniformity, purity, and dissolution. Quality can also be tested in numerous ways through end-product testing, at process testing, or in process testing. However, based on the manufacturing method, how quality is judged and tested may be limited.

In addition, the definition of pharmaceutical quality comes increasingly complex when considering international views. While, pharmacopoeias provide detailed descriptions to manufacturers about critical API characteristics and analytical testing techniques, pharmacopoeias are often published separately by major pharmaceutical companies and by region. Consequently, one major challenge towards a universal definition of quality is that quality standards published in pharmacopoeias and government publications vary from one pharmacopoeia to another (MSH, 2012). For example, the *European Pharmacopoeia* establishes

standards adopted by countries within the European Union. While, Great Britain and the United States remain among the top pharmaceutical manufacture countries, each have their own pharmacopeia, the *British Pharmacopoeia* and the *U.S. Pharmacopoeia.* Furthermore, the *European Pharmacopeia* does not specify individual dosage forms like other pharmacopeia and the *U.S. Pharmacopoeia* analytical techniques require expensive technology that many developing countries cannot achieve. As a result, it becomes possible for an API to meet standards of one pharmacopoeia, but not the standards of another pharmacopoeia. Until common standards are finally achieved, manufactures must identify which standards are being used to be accepted. Universal standards are further hindered by countries protecting their local production of pharmaceuticals and markets through selective tariffs providing little incentive for a global standard. Ultimately, a universal definition of quality requires a harmonization of pharmaceutical quality standards.

Background on Motivation for CPM

A pharmaceutical drug typically consists of an API combined with non-active pharmaceutical ingredients and excipients to form the final drug product that is administered to patients. The high patient driven demand for pharmaceutical medications has put a strain on the pharmaceutical industry as they face intensive pressure in both aspects of quality and meeting increasing demand. The manufacturing of pharmaceuticals is expected to become increasingly flexible to respond to increasing patient demand; however, the pharmaceutical industry has been largely conservative when it comes to change in the manufacturing process due to regulation uncertainties and few examples providing a working framework and path toward modernization

(Zomer, Gupta, & Scott, 2010). As a result, the majority of pharmaceutical productions are currently produced using batch production technology to produce both the API and the DP. Examples of batch processing in the pharmaceutical industry includes: tablet coating, milling, crystallization, extraction of a product from a reactor mixture, and autoclaving. However, batch processing is inherent to inefficiencies, delays, and batch to batch variations as the start and stop nature of the process causes breaks in production and introduces more sources for human error. This is particularly troublesome because maintaining constant quality in pharmaceutical manufacturing is very important as it directly impacts the quality of patient care. Quality in the pharmaceutical industry is also unique in that the customers, the patients, cannot evaluate the quality of the pharmaceutical for themselves through physical appearance or immediate use. Thus, the pharmaceutical industry must maintain a higher, more consistent quality levels than any other industries including petrochemical, oil, and chemical (Myerson et al., 2015). By the time patients realize the quality of a pharmaceutical is compromised, the consequences can be devastating including adverse side effects and death. Poor product quality may result in several adverse effects including product recall and disruptions in manufacturing leading to a drug shortage and patient harm (FDA, 2015).

However, with increasing R&D costs, increasing competition, shorter patent duration times, longer development times, and regulation concerns, innovation within the pharmaceutical industry has been slow to evolve. It has remained largely unchanged in the last fifty years as pharmaceutical manufacturers have stuck with the proven methods of batch manufacturing in order to avoid high R&D costs and regulatory obstacles. Batch manufacturing is characterized by all of the required raw materials entering the unit operation at the beginning and being

completely discharged after a set time. No materials enter or leave the unit until the process is complete. Consequently, batch manufacturing has many inherent weaknesses including batch-to-batch variations, slow reactions times, and poor thermal and homogeneity properties. Thus, there has been a recent surge in research efforts and regulatory support for the pharmaceutical industry to modernize. Recent guidelines, conferences, and white papers from both the United States and European regulatory bodies have shown growing support for modernizing manufacturing equipment and manufacturing processes. This combined with the changing market of pharmaceuticals has led to a need for increased manufacturing flexibility and shorter process times while still remaining at a high level of quality assurance. Thus, CPM has emerged at the forefront of efforts to modernize and represents a paradigm shift from batch processing. CPM is characterized by material continuously entering the unit and continuously discharging from the unit throughout the duration of the process. As a result, CPM will not require breaks in production or lead to batch-to-batch variations as experienced with batch processing. However, CPM is a new manufacturing structure for the pharmaceutical industry that requires new technologies and manufacturing concepts.

Literature has shown that through the greater process understanding achieved by CPM, a high level of pharmaceutical quality can be maintained while also leading to lower environmental impacts, lower production times, and lower variations when compared to the traditional batch process. The development of pharmaceutical processes begins with identifying the synthesis and reaction pathway to produce the API. The multistep processes to develop the final DP containing the API includes many unit operations, among those are reactions, separations, purifications, granulation, milling, coating, drying, and blending. Improvements in

the reaction chemistry and unit operations is then improved upon factors related to lowering the number of required steps, increasing yield, increasing purity, scalability, economics, and reaction times. From a manufacturing and technologies perspective, this may be achieved by optimizing operation conditions like temperature, pressure, and flow rate. In addition, since solvents are commonly used in reaction to produce the API, separation processes like distillations, chromatography, liquid-liquid extraction, filtration, membrane separations are also common between the reaction steps to separate the API from solvents, unwanted by-products, and waste. Thus, optimizing separation techniques and sequences is also another opportunity for improvement. Additionally, different process technologies like the use of continuous microflow reactors can offer significant advantages through process intensification in process time, yield, and operating costs.

Thus, it has been established by the scientific community that a data-rich environment and increased product and process understanding leads to significant process improvements. Furthermore, with support from regulatory bodies for modernization, CPM has been a growing minority in the pharmaceutical industry. In order for the pharmaceutical industry to continue to modernize, modernization must be aided through the development of new process technologies and greater understanding of proper implementation and how it fits into the current regulatory environment. The concepts of process analytical technologies (PAT), quality by design (QbD), and the development of a design space have been recently introduced to aid in these efforts. However, the application of these concepts and technologies has been slow. Thus, the scientific community and regulatory bodies must continue to work together and with pharmaceutical

manufacturers to increase understanding and confidence in these concepts while also establishing a business case for CPM.

CPM Quality Tools

CPM will allow for a higher quality pharmaceutical with greater sustainability, agility, and affordability of medications for a growing population and patient demand (Girogiorgis & Jolliffe, 2015). Many examples have been reported of continuous pharmaceutical processes for chemical synthesis in flow, reactions with workup, crystallization, drying, powder blending, and tableting; however, only a few others have considered integration of multistep portions of a process and plant-wide approach (Mascia et al., 2013). However, CPM requires new, innovative technologies and manufacturing processes and concepts to be successfully implemented. The pharmaceutical industry and the FDA are striving to develop a modern pharmaceutical industry that is capable of operating economically while simultaneously consistently delivering high quality, uniform pharmaceutical products that behave as expected to meet an increasing global demand and market. Several methodologies have been developed over the years to aid and encourage pharmaceutical companies in achieving this goal. Furthermore, increased efforts have been made by regulatory committees to remove barriers and obstacles through early involvement and building a path for open communication. Introduction of methodologies developed include QbD, PAT, and the development of a design space. Each considered a milestone in the pharmaceutical manufacturing way of thinking that fosters a higher level of process understanding and the idea that quality must be designed into the system. Each methodology is dependent on the other and must adhere to the philosophy of continual improvement.

Problem Statement

This research recognizes the difficulties and challenges pharmaceutical manufacturers face when modernizing pharmaceutical manufacturing equipment and processes. It will establish the benefits of CPM over traditional batch manufacturing processes reviewed in literature and obstacles CPM faces that has slowed or halted its implementation. Obstacles include a lack of a working framework, inexperience, economics, patent durations, appropriate manufacturing equipment and configurations, establishing process pathways, quality control and measurement tools, high R&D costs, and regulatory environment barriers. Better tools for implementation for increased understanding and control will be presented to address many of these obstacles. It is imperative that the gap between manufacturing confidence in QbD tools and their applications along with the established business case for CPM be closed in order for CPM to be successfully implemented. It is estimated by the FDA in, *Understanding Challenges to Quality by Design,* in that growing product knowledge and understanding during product development and manufacturing can lead to five billion dollars in savings for the pharmaceutical industry.

Research Objectives

The objective of this research is to aid in the development of a QbD framework for implementing CPM QbD tools to aid in the change of manufacturing from batch to continuous and improve on current continuous pharmaceutical manufacturing processes. This research aims to:

1. Explore, develop, and provide guidance on implementation.

2. Analyze current CPM concepts.
3. Develop in depth comprehension of CPM quality tools.
4. Highlight the applicability of CPM concepts.
5. Research the business case.
6. Identify and analyze gaps in literature and regulatory guidelines that may increase understanding and manufacture confidence.
7. Identify computer-based methods for the application of QbD principles.
8. Present a QbD algorithm for CPM using an integrated flowsheet models as the central method.

Research Questions

While conducting an extensive literature review on CPM the central research questions include:

1. How does CPM practices fall within the existing regulatory environment and what efforts are being made to remove any existing regulatory barriers?
2. What are the weaknesses of traditional pharmaceutical batch manufacturing practices and how does CPM compare?
3. What existing pharmaceutical quality concepts, frameworks, and systems are in place to aid in the implementation of CPM? This includes the development of quality concepts like QbD, PAT, and design space.
4. Is there a business case for CPM? Does CPM allow manufacturers to sustain or gain a competitive advantage in the pharmaceutical market?

5. What are current obstacles in implementing CPM? Is there enough confidence in CPM quality concepts and frameworks to encourage switching from batch to continuous manufacturing?
6. Are there sufficient case studies and research on the application of CPM principles and guidelines that demonstrate their significance and successful implementation? Does this research apply to plant operation or unit operation?
7. What are the current methods for implementing QbD principles?

Contributions

This research will aid in the understanding, confidence, and successful implementation of CPM. An in-depth analysis of CPM will be presented to explore the benefits, obstacles, current regulatory environment, and QbD tools central to CPM implementation. Through the development and analysis of a QbD algorithm for the application of QbD principles using an integrated flowsheet model as the central method the gap between manufacturing understanding and manufacturer confidence will be closed. The application of an integrated flowsheet model is in alignment with QbD principles of increasing product and process knowledge. Furthermore, this model will allow pharmaceutical manufactures to create a data-rich environment to document and aid in the decision-making process. This methods will increase manufacturer confidence in CPM by answering economical, project feasibility, process validation and optimization without the initial upfront extensive capital investment required with ex silico methods.

Thesis Outline

This thesis will provide a literature review on CPM manufacturing opportunities and QbD applications and is outlined as follows.

Chapter One discusses the definition of quality as it applies to pharmaceutical manufacturing and the background motivation for CPM and modernization. The problem statement, research questions, and research objectives will also be outlined.

Chapter Two provides an extensive literature review on the advantageous of CPM over traditional batch manufacturing processes traditionally used. This includes a comparison of traditional quality systems, quality by testing (QbT), compared to the CPM quality system, quality by design (QbD). The current regulatory environment and the tools and applications of CPM methodologies being promoted by those regulatory bodies including quality by design (QbD), design space, and quality by testing (QbT) will also be examined.

Chapter Three discusses the research gaps identified through the literature review in Chapter Two. Resulting research ideas and methodologies are also discussed.

Chapter Four presents a QbD algorithm for CPM using an integrated flowsheet model to aid in closing the gap between manufacturer understanding and manufacturer confidence. Literature extensively reviews ex silico QbD tools including first principle modeling, response surfaces, and design of experiments (DoE), but there is a gap in addressing integrated, plant-wide tools and methodologies that align with QbD principle. The applications, advantages, and regulatory implications are also examined.

CHAPTER TWO: LITERATURE REVIEW

Introduction

The previous chapters highlighted both the evolving definition of quality and pharmaceuticals and the importance of maintaining a high, consistent quality standard.

This chapter will provide an extensive literature review on the weaknesses of batch manufacturing and the need for modernization toward CPM. It is also necessary to examine the current regulatory environment and how CPM concepts fit within this environment as the pharmaceutical industry is highly regulated and requires a high level of quality. Once the need for modernization towards CPM methods has been established, CPM methodologies, applications, and literature is discussed to increase understanding in CPM. However, while the need for and advantages of CPM are well established in literature, pharmaceutical manufacturers have been slow to implement CPM. As a result, the obstacles towards successful implementation of CPM will be examined in order to determine the gap between manufacturer CPM understanding and confidence in its applications.

CPM Manufacturing Opportunities Compared to Batch Processes

Compared to the traditional production of APIs and DPs through batch processes, CPM provides manufactures with several advantages that allow for improved product quality and increased flexibility to respond to the required increasing precision of medications and changing demands. Furthermore, the economic savings promised by CPM are well documented on both a model and real-world examples basis (Mascia et al., 2013, Lee et al., 2015, Schaber et al., 2011, Seifert et al., 2012,). The U.S. Food and Drug Administration believe that CPM will lead to

improvements in product quality, purity, safety, and identity outlining four expected benefits to demonstrate the need in modernizing pharmaceutical manufacturing technology from batch to continuous processing:

1. Improved manufacturing efficiency and flexibility with fewer production interruptions.
2. Fewer product failures both before and after distribution leading to a higher quality DP
3. Improved product quality leading to a higher confidence the pharmaceutical will perform at expected clinical performance.
4. Increased availability to patients in need and flexibility to adjust to changing and growing demand.

CMP Process Characteristics

Batch processes are inherently inefficient as it requires multiple breaks in production and long sequential steps of reactions in a batch reactor requiring purification steps in between (Girogiorgis & Jolliffe, 2015, Sing & Sharma, 2015). In addition, these steps are timely due to batch processes' having poor spatial homogeneity that leads to poor mass transfer and heat transfer. Poor mass transfer requires larger mixing times up to days for batch process that alternatively can be achieved by continuous mixing in just seconds in order to achieve a homogenous mix and thorough material distribution. Continuous mixing can also achieve narrow size distributions and size uniformity that aids in the precision needed for many commercial drugs that is unachievable through batch processes (Myerson et al., 2015). Furthermore, poor mass transfer also increases batch to batch variations and can lead to batch failures (Singh &

Sharma, 2015). Poor heat transfer can also lead to thermal degradation of intermediates, APIs, and final products. This leads to the formation of unwanted by-products with an increase in the generation of waste compromising overall product quality, yield, and selectivity (Myerson et al., 2015).

Continuous flow chemistry is often better than batch process due to the capability of process intensification: much higher concentrations, pressure, or temperature process conditions. This intensification allows for the facilitation of new synthetic routes and novel pathways that are not currently achievable though batch processes (Mascia et al., 2013, Lee et al., 2015, Heider, 2015, Girogiorgis & Jolliffe, 2015). For example, utilizing flow micro-reactor technology for CPM allows for quick mixing and reactions to occur and effective heat removal to prevent thermal degradation. This then allows for synthetic routes and novel pathways that may require highly exothermic or hazardous reactions or involve highly unstable intermediates to be safely performed efficiently. Thus, flow micro-reactors can handle a number of pharmaceutical synthesis including hydrogenation, nitration, and organometallic reactions under intensification with reliable control and a high level of maintained quality (Girogiorgis & Jolliffe, 2015). However, micro-reactors would not be suitable for the production of pharmaceuticals that require a slow chemical reaction or reactions mixtures including slurries. Furthermore, the benefits of CPM must be enough to provide a business based economic decision to promote R&D of synthesis and development of CPM technology. R&D on flow chemistry and organic synthesis is vital as continuous flow chemistry may differ from batch chemistry as demonstrated in the synthesis of aliskiren, where the mechanism (i.e. Lower reaction temperature conditions, solvent

consumption, and synthetic steps) of achieving the API and the DP are different than the batch chemistry (Heider, 2015).

CPM Supply Chain

Due to economic constraints and the long process times of batch processing, the supply chain of APIs and DPs may span several manufacturing plants across multiple countries. Thus, potentially hazardous APIs and intermediates, despite being sensitive to degradation over time or changes in environmental conditions, may be stored for long periods of times and shipped to other manufacturing facilities (O'Connor, Yu, & Lee, 2016). This also results in a long production process, up to 12 months from the first synthetic step to DP, due to storage and shipping of material around and between facilities. This extensive supply chain can consequently result in drug shortages and expensive inventories and working capital (Lee et al., 2015). Furthermore, this introduces a number of vulnerabilities in the supply chain of pharmaceuticals and maintaining consistent quality. In addition, the flexibility to meet changes in patient demands is significantly restricted.

However, with CPM the reaction and purification steps are integrated into a single system in order to make APIs and DPs start to finish. The FDA estimates that some batch processes that take months to complete may be completed in hours with CPM, increasing manufacturing flexibility and reducing the risk of drug shortages in the face of a pandemic (FDA, 2015, Lee et al., 2015). Furthermore, the continuous flow results in a much shorter supply chain and a shorter time to market in order to allow more flexibility. By reducing hold times and eliminating storages of APIs and intermediates, product quality is directly improved. The reduction in

material handling due to continuous flow from unit to unit operation also decreases the amount of labor needed and increases operator safety (O'Connor et al., 2016, Mascia et al., 2013). Additionally, CPM is not subject to current scale-up bottlenecks of batch processes. CPM permits scale-up through longer operation times and production capabilities, increasing flow rates of the process, and through the possibility of optimizing commercial equipment (Allison et al., 2015).

Decreased Footprint

Traditional batch manufacturing involves long, sequential steps requiring large residence times and multiple isolations, material holds offline, and lengthy purification steps. CPM significantly reduces capital costs through the reduction of storage facilities and containers needed to hold offline product or intermediates needed for batch processes. Furthermore, CPM often requires fewer units of operations through the application of telescoping: collapsing multistep process into a single unit operation. In addition, operating costs are significantly lowered due to higher throughput rates, increased yield and selectivity of the API and DP, and decreased labor requirements (Lee et al., 2015). Increased yields and selectivity also means CPM produces significantly less waste than batch process. Batch processes can have E-factors (waste-to-product ratio) as high as 25-100 for the production of APIs. This indicates that for every 1 g of API there is between 25-100 g of waste being generated by the batch process. In comparison, the petrochemical industries commonly have E-factors much lower than 1 (Girogiorgis & Jolliffe, 2015). This generation of waste increases operating costs and makes the process significantly less green and sustainable when compared to CPM.

Furthermore, the long reaction times, thermal and mass non-uniformity characteristics, and the limited capability for real time process monitoring leads to NVA process in batch manufacturing including breaks in production and cleaning procedures. In order to maximize the profitability of the production of an API or DP, these NVA steps need to be limited. This may be considered as taking a lean approach. There has been sufficient literature demonstrating the economic and sustainable benefits of CPM.

Heider (2015) was able to synthesize aliskiren using CPM with savings up to 30% when compared to an equivalent batch size in large part due to the improved heat and mass transfer properties of continuous flow resulting in a reduction in operating costs.

Seifert et al. (2012) proved that pharmaceutical manufactures would benefit from the efficiency and increased productivity, in both yield and selectivity, of CPM over batch plants. In comparing the production of four recombinant proteins, CPM had a 30% net present value and faster planning period than the equivalent batch process

Schaber et al. (2011) identified the capital costs of a CPM to be 30 to 76% lower and operating costs to be as much as 40% lower when recycling is utilized when compared to the batch process depending on drug loading, cost of key intermediates, and the process chosen. In most cases, the yield was also higher for CPM process; however, even when the yield is lower than the batch process, operating costs may still be lower due to a decrease in labor and material handling.

Girogiorgis & Jolliffe (2016) were able to successfully model and simulate the continuous manufacturing of artemisinin that generated 66.2% less waste than the batch process for the same 100 kg per year production level of API. The continuous process has an average E

factor of 22.52; while, the batch process had an average E factor of 65.28. This signifies that continuous processes have an enhanced sustainability due to lower waste production which is especially important with a growing emphasis on green process (Mascia et al., 2013, Heider et al., 2015)

Table 1: CPM Manufacturing Features and Benefits Over Batch Processing

CPM Manufacturing Features	**Benefits**
Continuous Flow Properties	• Lower batch-to-batch variations • Improved spatial homogeneity • Improved heat and mass transfer characteristics • Facilitation of new synthetic routes and novel pathways
Non-stop Production of Material	• Shorter time to market/ faster responses to changes in patient demand • Shorter supply chain • Reduced degradation/storage of APIs and intermediates • Increased throughput rates • Potentially easier to scale-up/scale-down
Smaller Equipment Footprint	• Reduced safety hazards • Less labor required

CPM Manufacturing Features	Benefits
	• Less space and equipment needed • Decreased capital costs
Integrated Process with Fewer Steps	• Fewer unit operations • Faster response times • More efficient • Less equipment needed • Decreased capital and operating costs • Integrated control
Online Monitoring and Control	• Real time product quality information • Reduce lengthy testing of end product • Enhanced development approach
Reduced Waste Generation	• More sustainable/environmentally friendly • Higher yield and selectivity • Decreased operating costs • Decreased costs of key ingredients

Current Regulatory Environment

One major challenge to innovation is that there remains limited knowledge and experience in the pharmaceutical industry with continuous manufacturing that can provide a working framework for successful implementation (FDA, 2015). This in large part can be

attributed to the fact that pharmaceuticals are often manufactured on an intermediate production scale (hundreds of grams to kilograms) where most research in continuous manufacturing has been done on a large production level for chemical commodities, oils, and petrochemicals (Heider, 2015). As a result of a lack of experience and understanding of CPM there remains many questions in how CPM will fit into the current regulatory environment. Manufacturers may face delay as regulating agencies attempts to achieve a comprehensive understanding of the new continuous processes and how it affects product quality and fits into existing regulations (FDA, 2015, Myerson et al., 2015). In order for modernization in the pharmaceutical industry to occur, regulatory bodies need to ensure regulations and regulatory practices do not hinder the implementation of CPM. This includes reducing associated regulatory risks that may provide a barrier for manufactures, encouragement of other federal agencies to support CPM to protect public health, and provide financial support for training of both regulatory staff and universities in the area of CPM control systems and approaches (Myerson et al., 2015). Ultimately, the regulatory agencies support CPM and are aiding in the removal of barriers associated with regulatory review and delays. The FDA and a number of other regulatory agencies promote CPM and maintaining consistent product quality through the combination of Quality by Design approaches (QbD) and Process Analytical Technology (PAT). Guidance, cGMP regulations and statutes have all been released to address CPM.

Regulation Considerations

Current good manufacturing practices (cGMP) defines a batch as a designated amount of product that is produced during the same cycle of manufacturing and intended to have uniform

quality characteristics within specified limits. Thus, the term “batch” has regulatory implications under The Code of Federal Regulations:

21CFR 211.101: the weight and measure of each **batch** must match the Batch Production Records; each **batch** should me made with the intent to provide no less than 100% of the API as indicated on the label

21 CFR 211.180 (e): Establish procedures and recordkeeping for a review of a representative number of **batches** and whether that **batch** was accepted or not

21 CFR 211.165 (a): Each **batch** must be determined to meet final DP specifications before release

21 CFR 211.188: **Batch** product and control records must be prepared for each batch

21CFR211.192: Extended investigations shall extend to other **batches** that may be associated with unexplained failures or discrepancies with specifications

Since the term batch does not specify a mode of manufacturing, it is possible for a continuous process to produce batches and thus a concept of batch for a continuous process must be developed and defined (Lee et al., 2015). For CPM, a batch may be defined based on a certain amount of product produced within a given time frame during the duration of the continuous process (Allison et al., 2015). However, (Lee et al., 2015) extends the possible definitions of batch for CPM to be defined by amount of quantity produced, equipment run time capability, or based on production variations (i.e. lots of incoming raw materials).

In addition, since continuous manufacturing will have different in process control systems and testing/sampling procedures, acceptable procedures for detecting disturbances, handling deviations, rejection of nonconformance material, and sampling considerations must be

taken into consideration by regulatory bodies to see how it fits within existing regulations and if it will provide an acceptable product quality. The evaluation of changes in manufacturing from batch to continuous should be considered by regulating agencies as to the relevant risks associated to product quality, product contamination, dosage form, manufacturing processes (design, scale-up, start-up/shut/down), and testing technology (Allison et al., 2015).

International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guidelines

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) attempts to bridge the gap between regulatory bodies and the pharmaceutical industry in order to promote and support advanced pharmaceutical technology. ICH guidelines emphasize a science and risk based approach to the development of innovative manufacturing technology in order to facilitate a deeper understanding of the product development and process involved. As a result, quality is based on a sound, risk-based approach that must be built into the design in order to have a robust process capable of maintaining a consistent quality. ICH Q8, Q9, Q10, and Q11 (as cited in Allison et al., 2015, Lee et al., 2015, Nadpara et al., 2012, Pramod et al., 2016, Yu et al., 2013) outline an integrated systems approach for the implementation of quality.

ICH Q8: A systematic approach identifying predefined objectives that affect the DP materials and properties and planning a set of controls from product and process understanding to ensure product uniformity and quality. ICH also defines what QbD and the design space are. Control parameters may include drug attributes, operating conditions, real time monitoring, and finished product specs (Pramod et al., 2016).

ICH Q9: Focuses on quality risk management. Opportunity to use structured process thinking

ICH Q10: Focuses on the pharmaceutical quality system across a products lifecycle

ICH Q11: Defines the development and manufacture of Drug Substances

United States Food and Drug Administration Guidelines

There has been a growing emphasis on the need for CPM and support from the FDA to promote manufactures to work towards building CPM. In 2002, the FDA launched an initiative, Pharmaceutical cGMPs for the 21st Century: A Risk Based Approach, to encourage the early adoption of new manufacturing technology and committed to the practice of having all regulatory regulations based on the most advanced pharmaceutical technology available. In 2004, in two FDA guidances titled *PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* and *Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites*, the FDA promoted quality assurance through Quality by Design (QbD) and Process Analytical Technology (PAT).

QbD is defined by the FDA (FDA, 2009) as: "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."

Whereas, PAT is defined by the FDA (FDA, 2009) as: "Mechanisms to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA)"

As a result, quality should be built in and evident in the design of the manufacturing process to ensure quality is inherent to the system. Conversely, quality cannot be simply tested into the process (FDA, 2009, FDA, 2015). In their *Strategic Plan for Regulatory Science*, the FDA (2011) commits support to the development of improved continuous manufacturing methods through active research and collaborative efforts with external partners to determine the effects of CPM on product quality, safety, efficacy, and product failure rates. However, despite these initiatives the year 2011-2014 was marked with quality lapses that lead to drug shortages. These drug shortages included cancer drugs, anesthetics, emergency medicine, and IV medications. Furthermore, the FDA indicated that the major reason for these drug shortages were quality and manufacturing issues. In addition, the FDA insinuated that since consumers are unable to determine pharmaceutical quality for themselves, manufactures who were not investing in quality might be compromising patient safety.

In 2015, the FDA found that raw materials, quality manufacturing issues, and quality delays caused 27%, 37%, and 27% of drug shortages. Thus, quality issues accounted for approximately 91% of all drug shortages, with loss of manufacturing sites, increase in demand, and discontinuation accounting for the final 9% of drug shortages. This resulted in manufacturers' moving away from retrospective quality and closer to process design. The industry recognized that QbD and PAT lead to a robust, predictable process that allowed for a high product quality and better management of business goals (FDA, 2016).

While a growing minority of pharmaceuticals are being produced through continuous manufacturing, like the cystic fibrosis drug Orkanmbi (lumacaftor/ivacaftor) produced by Vertex since its approval in 2015, most resistance to modernization of pharmaceutical drugs is coming

when a change in production (batch to continuous) is required. As a result, in 2016, the FDA showed further support for CPM and aiding this production change with their drafted guidance from the agency's Emerging Technology Team (ETT), *Advancement of Emerging Technology Applications to Modernize Pharmaceutical Manufacturing Base.* The guidance was in alignment with the FDA and the Center for Drug Evaluation and Research's mission to protect and promote public health (FDA, 2015). The FDA aimed to aid in the modernization of pharmaceutical technology by getting engaged with manufactures as early as possible to meet and discuss manufacturing issues, recommendations, and regulatory reviews of submission (FDA, 2015). This guidance has already resulted in the FDA approving their first ***change*** in production methods from a batch to continuous manufacturing for the production of Janssen Supply Chain's medication, Prezista (darunavir), used for the treatment of HIV-1 infections. The CPM process integrates all the required manufacturing steps of weighing, milling, blending, compression, and coating into a single continuous line to produce a solid 600 mg oral dosage at full production levels. This resulted in a shorter time-to-market as the manufacturing and testing cycle time was reduced from two weeks to one day; thus, also significantly increasing plant capacity and drug availability to patients.

However, despite successes, the FDA still has a number of obstacles and challenges to face (Pramod et al., 2016):

1. Implementation of these new concepts to industry requires a cultural change.
2. Heavy workload and limited resources: The Office of Generic Drugs remains backlogged due to a large number of applications.
3. Adaption of regulations to meet the expectation of QbD based submissions.

4. Varying approaches to manufacturing and quality operations across the industry and how it fits into existing regulations.
5. The time required for regulatory approvals for facilities improvement including site changes and equipment upgrades may hinder the ongoing innovation of manufacturing.
6. FDA has yet to identify quality indicators that would help to predict drug shortages and recalls.

Table 2: Guidance, Regulation, and Statute Applications to CPM Lifecycle

Guidance, Regulation, or Statute	**Product Design**	**Process Design**	**Manufacturing**	**Process Control**	**Continuous Improvement**
ICH Q8Pharmaceutical Development	X	X			
FDA's PAT Guidance	X	X	X	X	X
ICH Q9 Quality Risk Management	X	X	X	X	X
FDA Quality System Guidance	X	X	X	X	X

Guidance, Regulation, or Statute	Product Design	Process Design	Manufacturing	Process Control	Continuous Improvement
ICH 10 Pharmaceutical Quality Systems	X	X	X	X	X
ICH Q11 Development and Manufacturing of Drug Substances	X	X	X	X	X
FDA's Strategic Plan for Regulatory Sciences		X	X	X	X
FDA Process Validation Guide		X	X	X	X
cGMP		X	X	X	X

Quality Assurance

Quality assurance and consistency has remained a foundation in pharmaceutical manufacturing and DPs. The pharmaceutical requires a higher level of quality than most industries as quality defects can lead to detrimental adverse effects. The Management of Health Sciences identifies key risks associated with poor pharmaceutical quality: lack of therapeutic

effect leading to prolonged illness or death, induced toxic or adverse reactions leading to more costly treatments, a waste of financial resources, and a negative effect on the health system credibility. Thus, the approach to quality has evolved within the pharmaceutical industry from quality by testing to quality by design.

Quality by Testing

Quality by testing is the traditional quality methods through the reliance of analytical tests of end products to prove performance functionality. End-product testing alone is considered to be Quality by Testing (QbT). If the end-product passes the tests, it is accepted. As a result, QbT have strict specification limits that are not grounded in process or product understanding, but instead based upon observations and data from historical manufactured batches. This leads to limited regulation flexibility as each change requires approval from the FDA. Consequently, QbT is not a powerful means of ensuring quality and has been limiting factors (Sangshetti et al., 2014). Those factors include:

1. Highly dependent on determining an accurate representative sample is tested.
2. A small portion of defective material can only be detected if 100% of the material is tested which is impractical due to time, resource, and financial constraints.
3. Manufacturers only test what they expect to find.
4. Testing provides little opportunity for continual improvements in quality.

An example of the limitations of QbT includes the manufacturing of penicillin. The cross-contamination level of penicillin with other DP is zero because of the high probability of extremely low levels of penicillin to cause serious adverse effects in certain individuals.

However, detecting penicillin at extremely low levels is not possible with existing analytical techniques even if cross contamination was suspected. Also, penicillin may not be evenly distributed throughout the DP it is contaminating magnifying the difficulties associated with testing for its presence. As a result, current regulation states penicillin cannot be made in the same manufacturing facility as other medications because this is the only way to ensure compliance and patient safety (Pallagi et al., 2016).

Furthermore, the total cost companies spent on quality is highly correlated to internal and external failures of the end-product. Internal failures would be non-conforming end products that were caught through end-product testing at the manufacturing site. Costs associated with internal failures include reworking and scrapping. External failures were non-conforming end-products that was distributed to the consumer and failed while in consumer use. This kind of failure is much more costly than internal failures because of the costs associated with poor quality drugs including adverse side effects, prolonged illness, death, and perceived unreliability. However, through quality by testing alone, it was impossible for organizations to reduce and eliminate failure rates. As quality became increasingly expected, the total cost of quality became a driving force for no longer testing in quality, but instead designing into the system through trend analysis and prevention. While, there are costs associated with prevention methods and controls, the savings from the reduction of internal and external failures outweighed the upfront costs.

Quality by Design

Quality by Design (QbD) is a holistic based approach to pharmaceutical development through product and process understanding and continual improvement. It is primarily science

driven through empirical models, scientific literature and frameworks, design of experiments (DOES) and based on sound risk assessment. (Nadpara et al., 2012; Singh & Sharma, 2015; FDA, 2009; FDA, 2015). The FDA (2009) defined QbD as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. While, the ICH interpreted the QbD concept in the ICH Q8 guidelines as a systematic approach to pharmaceutical development which starts with defining objectives and furthermore continues with emphasizing product/process understanding and process control, based on science and quality risk management. Ultimately, QbD in literature is characterized as involving thorough product understanding, process understanding, and process control. Product understanding is then achieved through understanding product performance to critical quality attributes to meet patient needs. Process understanding is achieved through risk management to understand impacts of variability on product performance and developing a design space to operate within. Lastly, a process control may be achieved through continuous process monitoring and assessment to ensure consistent quality over time and continual improvement. This process is cyclical in nature and requires continuous improvement as demonstrated by the figure below.

Benefits of QbD align with the importance of process understanding and risk management stressed by the FDA and other regularity bodies. The benefits outlined in literature are:

1. Good Business: By improving consistency and reducing variation in the end product, subsequent investigations, scrap, rework, and recall costs are lowered. CPM also eliminates batch to batch variation seen in batch processing.

2. Evidence Based Decision Making: QbD requires building a scientific knowledge base for all products and process parameters. Decisions can be based on science rather than empirical data.
3. Higher Quality Assurance: By increasing product and process understanding there is a stronger knowledge base for understanding factor interactions and the impact on the DP quality.
4. Higher Manufacturing Efficiency: Through QbD the process is much more predictable and flexible to responding to disturbances and changes in process parameters to ensure quality is met. Thus, there is a reduced cost in product and process waste.
5. Incorporated Risk Management: Risk management minimizes product deviations and costly investigations, reduces regulatory compliance problems, and increase understanding.
6. Continual Improvement: Continual improvement is essential to quality efforts and ensuring quality assurance.

Product Design:
Target Product Profile and Critical Quality Attributes

The target product profile summarizes the clinical objectives and therapeutic benefits the drug needs to achieve. The TPP may be built based on label information, packaging insert information, patent, literature, and clinical studies and trials. The components of a TPP may include dosage form, strength, route of administration, and proposed indication. The quality target product profile (QTPP) must be identified to determine specifications of the drug such as dissolution/release, dosage form, safety, efficacy, and stability in order to achieve the desired in

vivo performance and clinical expectations. The central idea is that ensuring in vitro performance will than provide assurance of in vivo performance. As a result, a pre-determined product quality is determined and is not dictated by the manufacturing capability. Analyzing QTPPs help link the manufacturing processes with the product and patient for patient health care and benefits (FDA, 2009; Heider, 2015). Furthermore, QTTP should align with the therapeutic benefits and concepts on the label with a primary focus on safety and efficacy (Singh & Sharma, 2015). Label concepts may include dosage and administration information, level of API in the DP, adverse reactions, warnings, pharmacology, and description (Nadpara et al., 2012). This may then translate to QTPP parameters relating to identity, assay, dosage form, purity, stability often identified as critical quality attributes (CQAs) (Pramod et al., 2016.) CQAs is defined as the by ICH Q8 as the "physicochemical, biological, or microbiological properties or characteristics that should be within the defined limit or distribution to ensure the desired product quality." Thus, a DP must conform to the CQAs to ensure consistent product quality performance.

Process Design:
Critical Process Parameters and Critical Material Attributes

The drug formulation design and process development is an interdependent process as the formulation is dependent on the set process and operating conditions to achieve the desired product quality. Thus, manufacturers must identify which process parameters are critical to the product quality and identify the risks and best approaches to manage them (24). (Lionberger et al., 2008 defines three kinds of process parameters. (1) Unidentified Process Parameters (UPP): process parameters that are unknown and whose effect on the design space and QTPP has not been determined. (2) Non-Critical Process Parameters (NCPP): process parameters that do not

interact with other parameters and who has no significant effect on the QTPP. (3) Critical Process Parameters (CPP) are process parameters that interact with other parameters and affects CQAs. Consequently, all CPPs need to be monitored and controlled to ensure all CQAs are within specifications. Lastly, Critical Material Attributes (CMA) are also important to identify and may be defined as the characteristics of inputs (physical, chemical, or biological) introduced to the process that must be controlled within a given range to ensure there are no resulting process disturbances (FDA, 2009). It is important to note that level of criticality may differ depending if the manufacturing process is for the production of an API or DP. Identifying CQAs, CPPs, and CMAs is an iterative, life-cycle process that will enable manufactures to make better decisions and increase product consistency. All DP CQAs should be considered including physical attributes, assay, uniformity, dissolution, degradation, and moisture. A CQA may further be identified as the level of severity of harm to a patient when that CQA is not met. Conformity of CQAs often is a function of the level of control and conformity of CPPs and CMAs. For example, if your CQA was content uniformity, CMAs would be particle size and particle size distribution; while CPPs may include mixer load level, environment temperature, and number or revolutions per time. The higher the risk a CQA poses, the higher the level of control that is imposed on the CPPs and CMAs that affect it. Thus, risk assessment has become an integral part of determining the CPPs, CQAs, and CMAs. Yu et al. provides an extensive review of typical CMAs, CPPs, and CQAs for varying pharmaceutical Unit Operations including blending/mixing, wet granulation, drying, extrusions, tableting, and encapsulation.

An example of product and process understanding and identifying CPPs and CQAs is presented below.

Table 3: An example of linking CPPs to CQAs to increase product and process understanding

Form	Parameter	Critical Quality Attributes
API	Physicochemical	Identity
		Impurity
		pH
		Melting Range
		Particle Size Distribution
		Density
		Water Content
	Biological	Permeability
		Activity
	Microbiological	Bacteria
		Aerobic Organisms
		Yeasts
		Mold
Excipients	Physicochemical	Concentration
		Stability
		Particle Size Distribution
		Density
	Biological	Bioavailability of API
	Microbiological	Bacteria

Form	Parameter	Critical Quality Attributes
		Aerobic Organisms
		Yeasts
		Assay
Drug Product	Physicochemical	Identity
		Assay
		Impurities
		Correct Dosage Form
		Uniformity of Dosage Form
		Dissolution
		Hardness
		pH
		Particle Size Distribution
		Drug Functionality
	Biological	IVIVC
	Microbiological	Sterility
		Parental Drug Products
		Aerobic Organisms
		Mold

Source: Adapted from Yu et al., 2013

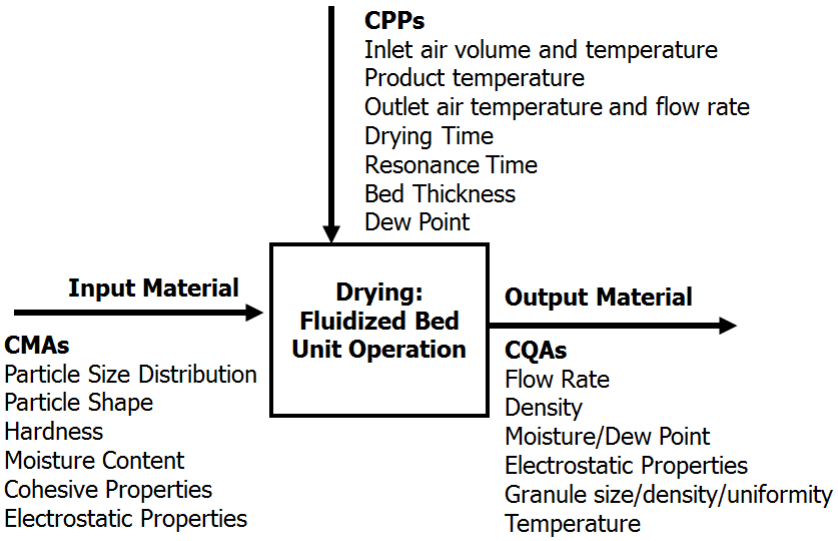

Figure 1: Block Flow Diagram a fluidized bed unit of operation and identification of possible CMAs, CPPs, and CQA
Source: Adapted from Yu et al., 2013

Process and Process Understanding: Quality by Design Tools

Risk Assessment and Management

A robust risk assessment allows manufacturers to systematically determine, communicate, control, and study which variables are most critical to the DP quality over its lifetime. Tools commonly used for risk assessment include:

1. Fishbone diagram to identify potential variables including material, instrumental and environmental factors
2. Failure mode effect analysis (FMEA) to determine where the system may fail and rank variables based on risk factors including probability and severity

3. Failure, Mode, Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Preliminary Hazard Analysis (PHA), and a Pareto chart to determine which variables affect the pharmaceutical characteristics the most (Nadpara et al., 2012, Haleem et al., 2015, Pallagi, 2016). Defining a clear definition for "risk" is vitally important for the pharmaceutical industry as there a large number of various stakeholders that have diverse interests and stakes in the process (Haleem et al., 2015).

The principles of quality assessment may be defined are to use scientific knowledge to evaluate the risk to quality as it linked to a patient healthcare and therapeutic benefits. In addition, formal documentation and evaluation of the severity and probability of a risk occurring in order to determine the level of risk involved is also essential

Pallagi (2016) used a risk estimation approach in early stage development for a dry powder with meloxicam as the API for pulmonary applications, where each QTPP and CQAs and then the CPPs and CQAs. Factors were ranked high, medium, or low and interactions together with an estimation of occurrence was used for rating. Next, using the Pareto principle of the 80/20 rule which states that while there are a number of variables effecting the process 80% of those effects will come from about 20% of the cause variables. Edina was then able to determine that particle size, pulmonary irritation, wettability, solubility, and toxicity properties were the main CQAs to affect the API. For the CPPs, composition, pressure, temperature and the feed rate had the highest impact on the final product. Thus, the risk assessment helped to identify which CQAs and CPPs needed the most attention during drug development and manufacturing. Meanwhile, Harry and Lanju (2012) performs risk assessment through statistical methods and parameters to determine the shelf life for excipients.

While, risk management is spoken mainly in the terms of early pharmaceutical development and continuous monitoring, risk management should be done by all parts of the business including the quality, regulatory, production, sales, marketing, business, clinical, and legal units of the organization and product lifecycle.

Design Space

The CQA space and CPP space is often mapped in a multidimensional space called the design space. The design space is defined by the FDA and ICH Q8:

"The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality."

A full understanding of the design space will lead to a better understanding of sources of variation and process disturbances and their resulting impacts downstream on the CQAs' ability to meet product quality requirements. This in return can for a tighter control of the system and shift controls upstream, instead of relying on length end product testing (Lee et al., 2015). Regulatory agencies allow each manufacturer to define their own design space and submit it for approval. Once a design space is determined, the operating ranges chosen is usually a subset of the design space. As a result, the FDA does not require regulatory approval for changes within the design space; however, changes outside of the design space are subject to regulatory approval in order to demonstrate the DPs ability to meet product quality requirements (Mascia et al., 2013, FDA, 2009). Having a larger approved design space is especially advantageous as it allows for process improvements within the DP lifecycle that would require fewer regulatory submissions including characterization of process and product performance, monitoring and corrective

actions, and validation of filing changes to the design space. Thus, leading to increased manufacturing flexibility. However, potential challenges commonly identified among pharmaceutical manufacturers to developing a design space are the cost of running experiments to define the design space and applicability of the design space during scale up or ramp in production.

Design of Experiments

The design space may be mapped using various techniques based on the products CQAs and amount of data available at each stage of the product lifecycle. Thus, the design space may be mapped using DoE. DoE is a systematic approach to determine the relationship between process factors and their impact on product quality. The basic steps of DoE include choosing an experimental design, conducting randomized experiments, analyzing data, and mapping the resulting design space. DoE requires experimentation and is aided by previous process knowledge about potential CQAs and CPPs. Based on the allowable CQA limit, a design space can be mapped using DoE.

QbD is highly dependent on the capability and accuracy of the DoE procedure chosen for design space mapping the process. Assumptions and estimations of the API and other chemical components need to be able to accurately depict the physical, chemical, and biological properties of the substances including solubility, selectivity, and yield. In addition, modeling of unit operations must be reliable enough to allow for scale-up and provide results for starting conditions for modelling of the following unit operation in the manufacturing process. Lastly,

system modelling must provide an accurate foundation for further risk assessment, capital and operation costs analysis, and plant scheduling. (Pallagi, 2016)

DoE may be used to gain general process understanding, study effects of individual variables, identify interactions between variables, and characterize acceptable ranges of critical process mapping. It is also able to take into account variability within the experiments, the processes, or raw material. All of this aids in developing and identifying a design space. Shivhare and McCreath (2010) state that DoE can have returns of four to eight times greater than the cost of running of the experiments. The Design Space may be determined through various DoE levels of approaches:

Level 0: Mapping

Mapping an operational space through a large number of experiments varying CPPs in order to determine the optimal conditions to yield the desired CQAs within specification. This is a brute force designs that requires a very large number of experiments. Level 0 DoEs are not commonly used to the infeasibility of the very large number of experiments that are required due to economical, time, or drug availability reasons.

Level 1: Factorial DoEs and Response Surfaces

Using DoEs to fit the data to a response surface. This requires fewer experiments; however, requires experiments for center points and determining if curvature is present. Level 1 are most commonly found throughout literature due to the reduced number of experiments from Level 0 while still providing a good experimental understanding of the overall system. An example of a Level 1 DoE includes a full factorial design in the form 2^k, where 2 is the number of

levels of each variable (high, low) and k is the number of variables being tested. Thus, the number of experiments requires increases exponentially with each new variable that needs to be tested. As a result, the number of variables being tested may need to be systematically reduced through risk analysis and process knowledge to limit the number of experiments further. The most simplified form of a Level 1 DoE is a 2^2 factorial design requiring four experiments. If a large number of variables must be tested, the number of experiments can then be systematically reduced through fractional factorial design. This is an efficient method requiring fewer number of experiments to determine the relationship between multiple process parameters and the impacts on the process response. Anderson et al. (2013) aimed to optimize tablet formulation that was highly complex and accurate using the fewest number of experiments and variables possible. He stressed the importance of using as few of experiments as possible because of the economics and the limited availability of the drug. Other examples of factorial designs include Plackett-Burman, central composite design, and Box–Behnken. Applications include optimizing process and product parameters to increase conversion, product purity, and yield.

Weiyong and Henrik (2003) identified impurities for optimizing the operation conditions for columns screening and separating organics for pharmaceuticals using Plackett-Burman. Torrealday at al. (2003) used a combination of fractional factorial designs and central composite designs to determine the optimal conditions of quantitation telmisartan to fit the data to a response surface. Miroslav et al. (2010) used a 2^4 factorial design and 16 experiments to determine the effects and optimize the conditions of CPPs including temperature, flow rate, and composition for the CQA dissolution. David at al. (2012) used Box- Behnken DoEs to evaluate

the main, interaction, and quadratic effects of peptide peaks of protamine sulphate to obtain a response surface and acceptable ranges for a design space.

Level 2 : First Principle Approach

Level 2 DoEs use experimental data and multidisciplinary knowledge of physics, chemistry, and engineering principles to predict and model product performance and enhance process understanding. This includes both chemometric and available mechanistic knowledge to fit the data and predict product performance and quality. First principle process modeling is also essential beyond mapping the design space for rapid evaluation of a process and operation alternatives like solvents. Level 2 DoEs are also commonly found throughout literature. First Principle modeling as successfully been used to model CPM in the manufacturing of artmisinin (Girogiorgis & Jolliffe, 2016), crystallization (Lakerveld et al., 2015), ibuprofen Gerogiorgis & Jolliffe, 2015a). First principle examples in literature include Seifert et al., 2012, Schaber et al., 2011, and Su, Naggy, & Rielly, 2015.

Level 3: Multivariate Statistical Process Control

Mapping utilizing DOE and multivariate statistical analysis methods to the linking of feed-forward controls. Multivariate methods include principle component analysis (PCA) and partial least squares (PLS). Silva et al. has used multivariate statistical control and PCA to evaluate optimal operating conditions for a twin-screw granulation, fluid bed drying process, and tablet press for a continuous tablet manufacturing lines. Rosas et al. (2011) used multivariate statistical process control (MSPC) for the determination of a design space for pharmaceutical gel manufacturing, which determined water content and temperature as the most influential CPPS

for the CQAs viscosity and pH. The CPPs were then optimized and used to define the design space. While, Level 4 DoEs are not commonly found in literature or in practice for CPM due to a lack of experience and knowledge, MSPC is well documented throughout literature in both mathematical concepts and applications, including batch pharmaceutical manufacturing. Burggraeve et al. (2011) used MSPC and PLS for the batch process of fluid bed granulation. Barla et al. (2014) used MSPC and PLS for the evaluation of chemometric models for a fluidized be dryer.

With each level, there is an increase in process understanding and growing accuracy and confidence in the design space for a fixed number of experiments. A risk based approach should be used when conducting DoEs. If a risk based approach is not done before DoE, the manufacturer will not know how to allocate resources effectively. Furthermore, risk analysis will eliminate variables of least significance and levels decreasing the number of experiments required to be performed. Furthermore, process and product knowledge should also be used to determine an acceptable experimental range of operating factors to further ensure the number of experiments performed is economically feasible.

Process Control: Process Analytical Technology

A control strategy is typically used to monitor CQAs through ensuring CPPs are within the design space. If a control space is smaller than the overall design space, then the process is robust. Control strategies are closely linked with PAT in QbD practices.

PAT is a system that allows for the measurement of CPPs and CQAs of raw and in process materials for ensuring a high, consistent final product quality. This aids in the effort of

process understanding and control to help design quality into CPM and allow for continuous improvement (Maikern, 25). The FDA defines PAT as:

"A system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."

Once the design space has been mapped and the acceptable ranges of critical parameters are established, PAT allows for the online monitoring and actively control the drug quality system. PAT can help to monitor attributes like particle size uniformity, granulation, and polymorphism. This method of online monitoring allows for increased manufacturing flexibility through direct, real time, continuous assessment of CPPs and CQAs. Within the PAT framework, a process end-point is when a material has been achieved that satisfies all CQAs and is not time dependent. In addition, it can be used a process control technique allowing for reduced cycle times, real time process control, limiting occurrences of unconfirming material, greater automation, real time release, and identification of continued improvement opportunities.

PAT also naturally lends itself to real time release testing (RTRT). The FDA defined RTRT as "the ability to evaluate and ensure the quality of in-process materials and/or final product based on process data." While ICH Q8 expands RTR as also "typically including a valid combination of measured raw material attributes and process controls." RTR includes: analysis of raw material and API to meet specifications and NIR monitoring to determine blend uniformity, identity, or assay, and laser diffraction to determine particle size. In line with PAT, RTRT measurements typically takes place on-line, in-line, or at-line. Benefits of PAT include higher quality insurance, better process understanding, reduce end product testing, and

increased manufacturing flexibility. In addition, through the large amounts of process data collected, PAT also allows for evidence based decision making and corrective actions to be implemented in real time.

PAT tools are categorized in literature and by the FDA in the following categories: multivariate tools, process analyzers, process control tools, and continuous improvement and management tools. It is possible to use one or a combination of many types of PAT tools for both a single unit of operation as well as plant operation.

Multivariate tools include DoE methods previously discussed as well as using process simulation and pattern recognition software and tools. This will help to determine the reliability of models and identify critical factors and their interactions that often times one-factor-at-a-time experiments do not reveal.

Process analyzers include on-line or in-line measurements. On-line measurements are where samples are temporarily diverted off the manufacturing process to be tested and then is returned to the process stream after. While, in-line process measurements are when the sample is tested while remaining in the process stream and may be either invasive or noninvasive. Examples include weighing the tablet after compression, determining blend uniformity after mixing, particle size after compaction or granulation, or present moisture after drying. Process analyzers may also include fast at-line measurements where the sample is removed from the process stream and closely examined. For example, in the case of NIR or disintegration tests for tablets. Process analyzer PAT tools provide a large volume of data that relate to the biological, physical, or chemical properties of the material and can be used for quality assurance or regulatory needs. Process analyzers also allows for real time control of the process stream.

Process Control PAT tools are important to ensure that CQAs are being achieved through control and manipulation of CPPs. PAT also provides an opportunity for statistical process control to define acceptance of CQAs.

Continuous Improvement and Management PAT tools are also commonly used. This involves collecting data over the products lifecycle to continue to optimize controls, process parameters, and material attributes for better performance and reduction of waste. This data may also be used in requesting regulatory approval for changes in the design space and facilitate in clear, transparent communication with regulatory bodies. Today's information technology infrastructure aids in the maintained and collection of data. However, improvements in automation, algorithms, and process technology is still needed to further aid an integrated systems approach (FDA, 2004).

Process Analytical Technology Tools

PAT tools can also be defined in literature according to the level of PAT. The three levels commonly identified include:

Level 0: Tight Specifications and CMA and CPP Constraints

The likelihood of nonconforming material is lowered through extensive end-product testing. Most common for batch processing with the assumption that a tested sample from the batch is a representative sample of the batch as a whole. Infeasible for continuous manufacturing due to possible transient process disturbances during continuous production.

Level 1: End Product Testing

Level 1 consists of end-product testing and process models with flexible process parameters accounting for variations in raw materials. General understanding of the effects of process variability and impacts on quality.

Level 2: Active Process Control Systems

Active process control system to monitor CPPs and CMAs in real-time. Automatically adjusted to respond to disturbances to ensure constant conformance. Represents thorough product and process knowledge and understanding. Less likely to have a product out of spec. operating in a design space.

Overcoming process disturbances is one of the main advantages of CPM over batch processing. While, in theory CPM is to operate in steady state, this is not realistic in multivariate processes like in pharmaceuticals. Steady state is obtained when all process state variables are constant over time and do not change. For steady state to be achieved all process state variables including pressure, temperature, volume, enthalpy, entropy, and chemical composition must not vary as a function of time (Myerson et al., 2015). However, steady state is theoretical in nature and instead is used as an approximation for a state of a process in order to substantially reduce the mathematical computation involved and avoid solving differential equations. This concept does introduce an underlying error due to the assumptions involved. A control engineer knows that steady state process cannot be achieved due to fluctuations in disturbances and unit operations. Thus, the desired objectives of CPM should be satisfying all Critical Quality Attributes (CQA's), not operating all variables at steady state. Operating a system at steady state

would actually result in lower product quality (Myerson et al., 2015). Instead as a control strategy, non-CQAs are manipulated by process control systems to produce smaller variations over time in CQAs. For example, the level of a tank is often not a CQA and has no value added to maintaining the level of the tank at a set point. As a result, the level of the tank may be used to manipulate CQAs like concentration and DP purity.

PAT are often used in a control strategy to monitor and vary variables over time within a controllable range to suppress effects of process disturbances and CQA variations over time. Heider et al., 2014 was able to synthesize aliskiren through utilizing an integrated CPM process using an advanced intermediate two synthetic steps away from the final API and finished with the final formulated tablet dosage. The CPM process integrated many manufacturing steps including two synthetic reactions, a dilution, and a membrane liquid-liquid extraction all linked together and ran continuously, without offline holding, isolation steps, or breaks in production. A high level of quality and yield (90%) were maintained despite process disturbances a closed-loop control. For example, fouling of the membrane based liquid-liquid extraction led to a retention of the organic phase and fluctuations in pressure which the process was able to automatically adjust to changes in throughput and pressure using two back pressure regulators downstream in a close-loop mode. The process was proven robust enough to maintain product quality.

Relationship between Control Strategy, PAT, RTRT, and QbD

RTRT and PAT are commonly used as part of the control strategy for monitoring CQAs of raw materials, in-process materials, and the end product. However, PAT does not always imply RTRT. PAT methods can be designed to control CQAs without contributing to RTRT.

Furthermore, both RTRT and PAT do not require QbD or a design space and vice versa. However, the incorporation of al four elements is most beneficial to CPM. Both RTRT and PAT can be hard to justify without the process understanding and risk based approaches involved in QbD. In addition, having a defined design space allows for PAT to manipulate CPPs in real time within that design space without additional regulatory approval, increasing manufacturing flexibility. Furthermore, the use of QbD concepts without PAT or RTRT could result in extensive and costly end product testing that can be difficult for continuous process where a sample in time cannot be a representative of a whole as is applicable to taking a batch sample representing the batch as a whole. As a result, all concepts should be implemented together; otherwise, the manufacturer will lose out on all that CPM has to offer.

Batch and Quality by Design vs. CPM and Quality by Testing Overview

Traditionally quality is determined through QbT whose steps to achieve quality may be outlined as determining a target to meet the quality and having fixed process parameters resulting in variation in product quality. Then end product testing leads to reworking, scrapping, and possible quality investigations of nonconforming material. However, the steps to achieve QbD may be outlined as developing product and process understanding to allow for flexible process parameters that may be manipulated and monitored in real time leading to consistent quality.

Table 4: Batch processing and QbT Approach compared to CPM and QbD approach for different stages of a product's lifecycle

Aspect	Batch and QbT Approach	CPM and QbD Approach
Product Development	Empirical	Systematic
Process Development	Data intensive; no "big picture"	Scientific understanding of product and process design
Quality Targeted	Tight specifications from historical manufactured batches	Specifications based on product performance requirements
Manufacturing Flexibility	Rigid; changes require FDA approval	Flexible; adjustable within design space
Response to Deviations	Strict adherence to tight specifications results in waste and nonconforming products	Designed to be robust allowing for small process variations (i.e. raw material, column filtrations, temperature)
Risk Management	Lack of science and risk evaluation; discourages changes	Risk based control; evidence based decision making
Product Specification	End product testing	Real time monitoring of CPPs and CQAs
Control Strategy	End product testing	PAT and risk based

Aspect	Batch and QbT Approach	CPM and QbD Approach
Life Cycle and Knowledge Management	Reactive, post approval changes needed	Continual improvement within design space

CHAPTER 3: RESEARCH METHODS

This chapter gives an overview about the research methodology applied in this thesis in order to achieve the research objectives. The methodology starts with the problem identification and ends with proposed solution.

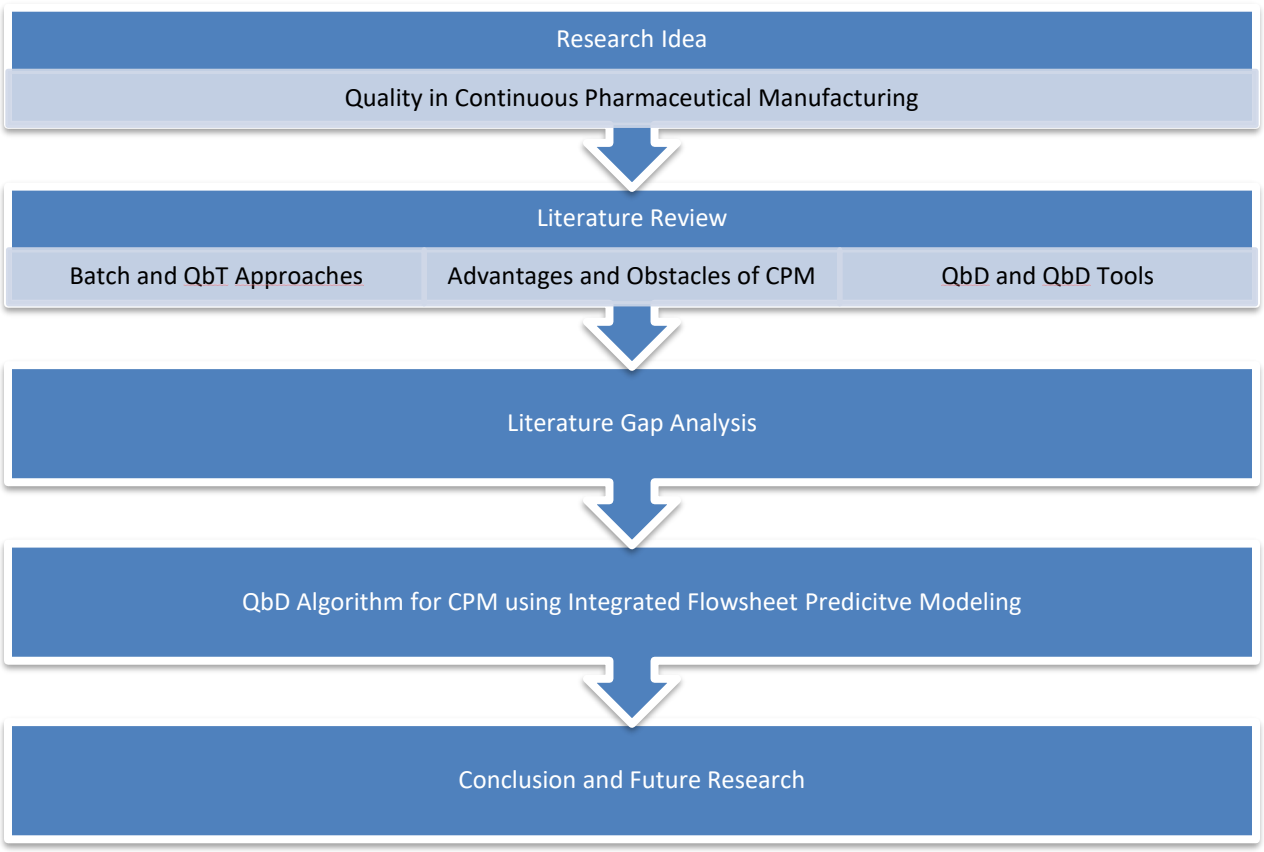

Figure 2: Research Methods and Approach

Research Methodology

This thesis began with exploring the weaknesses of the traditional batch manufacturing processes that dominates the pharmaceutical manufacturing industry as the predominant manufacturing method. Batch manufacturing has remained largely unchanged in the last 50 years and consequently has failed to see process improvements and innovations that characterizes other chemical and process industries. Change has been slow due to the regulatory, competitive, and educational environment despite the weakness of batch manufacturing and need for modernization being well recorded throughout literature.

Next, continuous pharmaceutical manufacturing is analyzed as the dominant proposed method towards modernization by both regulatory bodies and existing literature. CPM was compared to batch manufacturing in order to determine the benefits of CPM and further establish the need for the pharmaceutical industry to modernize manufacturing methods. The issue of achieving a consistent, high quality level required by pharmaceutical drugs in an economical way using CPM was also examined. A business case for CPM is necessary in order to encourage manufacturers to modernize.

Obstacles to the implementation of CPM was also examined to determine what challenges manufacturers can expect to face and identify key reasons why modernization has not already occurred. The term batch versus continuous in regulations requires a shift in manufacturing thinking and an accepted definition of continuous pharmaceutical manufacturing among all stakeholders. Regulation uncertainty and a lack of understanding and confidence in CPM may reduce the acceptance of CPM among pharmaceutical manufacturers.

The above research objectives were achieved through a literature review. Once a literature review was conducted, gaps in literature were identified.

Research Gap Analysis

Gaps in research identified are:

1. Regulation and Guidelines are broad in nature:

Regulation guidelines and practices are too general. Regulation bodies like the FDA are addressing a diverse drug market in a very broad way that may cause manufacturers to be hesitant in adopting QbD principles. Despite the potential benefits from CPM, due to a lack of a working framework and how it applies to their own manufacturing process. The FDA needs to provide more specific tools and decisions tools. In addition, The FDA has failed to define batch as it applies to CPM

2. Work with institutions and other research areas to build confidence and understanding:

CPM Requires knowledge of process control, high data analysis like DoE, risk assessment, and CPM quality concepts that is not covered in today's curriculum

3. Lack of Integrated Flowsheet Predictive Models:

Integrated flowsheet models are extensively research in other industries including chemical and petrochemical industry; however, there is little literature on computer simulated integrated flowsheet models as it applies to CPM. Integrated flowsheet models can be used for process development and risk mitigation at a reduced cost than approaches that solely focus on DoE approaches

4. Lack of Plant Wide Frameworks:

There is a lack of case studies providing real work exampled and evidence for how to achieve switching from batch processing to CPM. Most literature reviews discuss the characteristics of QbD and QbD tools principally speaking in comprehensive terms, theory and definitions. Furthermore, those few case studies provided seem to focus predominantly on unit operations rather than plant wide

There is a gap between the works of academics to develop continuous manufacturing technologies and the successful implementation of that work to the commercial sector.

5. CPM as it applies to upstream processes of manufacturing

Failure to address QbD efforts/benefits in other areas before manufacturing in the stages of pre-clinical and clinical trials in order to establish a better understanding of the DP's critical attributes and objectives.

For QbD to implemented properly in the manufacturing stage, most of the knowledge about the pharmaceutical drug should be generated during R&D and clinical stages then translated downstream. This helps to encourage product understanding and to properly build in quality in the process. This also saves time and effort required to develop the design space and control the process.

6. Oversimplifying pharmaceutical processes

Pharmaceutical process are complex processes estimated to be upwards of a 100-multivariate process and increasingly autocorrelated. Most CQAs and CMAs are over simplified and treated as independent to one another. Using a single component specification for CQAs and CMAs oversimplifies the process and can lead to misleading results.

Research Ideas

One major gap in literature identified was a QbD approach on a plant wide level rather than by unit operation. In addition, an integrated flowsheet modeling is not extensively reviewed in literature as it applies to CPM processes despite being extensively researched in other industries including the chemical and petrochemical industry. As a result, an algorithm was developed for CPM process development that was aligned with QbD principles using the central method of an integrated flowsheet modeling. Research of integrated flowsheet modeling for CPM includes advantages over current unit operation QbD and DoE approaches, applications, and possible regulatory constraints.

CHAPTER 4: FINDINGS

Integrated Flowsheet Models

While potential CQAs, CPPs, and CMAs are extensively discussed throughout literature, there is gap in how to identify these CQAs, CPPs, and CMAs in a fully integrated continuous flow system. While there are some literature demonstrating how to determine these critical design parameters that potentially affect the quality of the DP for a unit operation (a single piece of equipment), using QbD tools on a unit operation deceivingly lends to manufacturers believing their process is continuous when in fact it is only a semi-continuous process. Many of the inefficiency and constraints of batch processing are still present. However, with a fully integrated system that is inherently more complex and multivariate in nature, it is increasingly difficult to determine which design parameters are critical and affect quality. In addition, the interaction of critical design parameters must also be considered. As a result, a systematic framework was developed utilizing computer simulated process flow and process flow diagrams to aid in the development and application of an plant-wide integrated flowsheet model for a plant wide operation.

As the pharmaceutical industry begins to modernize manufacturing practices and equipment from batch to continuous, it remains important to assess the continuous flow system for design elements that may infect overall product quality. While the optimization of individual unit operations remains important, the focus now shifts to identifying and managing risks to product quality as an integrated system. With this in consideration, it is also then important to consider the multivariate and autocorrelated nature of the system. Integrated flowsheets are a

process system engineering tool used for process integration, simulation, and development that allows for controller design, sensitivity analysis, and the evaluation of process parameter ranges.

An integrated flowsheet model is a tool commonly used in chemical and process engineering to illustrate the flow of a plants process and order of equipment. In a continuous process, the integrated flowsheet model will show the equipment in series without isolation of any intermediates or breaks in production. The output of one unit will be the input of the next unit in the series. Information that this model will provide includes a process topology, stream characteristics, and equipment characteristics. As a result, a typical integrated flowsheet model will include the following:

1. Each piece of equipment will be represented by an icon and assigned a unique number or name to distinguish it from other equipment. This allows for the analysis of each unit operation and to determine equipment characteristics and operation parameters including temperature, horsepower, size, flow capacity, and enthalpy. In changing from batch to CPM, this will aid manufacturers in determining whether or not the existing batch equipment can be utilized or retrofitted for a continuous process.
2. All process flow streams are identified, typically by a number, each with their unique characteristics including to chemical composition, molar flow rate, inlet temperature, and outlet temperature. This is particularly advantageous in increasing process knowledge which in return allows for process optimization and to determine critical control points within the process.
3. All waste streams, recycle streams, and utility streams are also identified.

4. All equipment and streams will be depicted in sequential order to aid plantwide understanding and thus a plant wide approach to design and quality.

Aspen Plus Software

While, it is evident that an integrated flowsheet model may take extensive work to prepare, there are multiple software packages including AspenPlus (V7 and V8) that have been demonstrated to be accurate for the design of continuous systems and widely used throughout the chemical and petrochemical industry. Aspen Plus provides a software engineering practice that focus on chemical engineering and analysis principles including process control, process engineering, optimization, and continual improvement. It is capable of handling particulates, solids processing, and mixed liquid/vapor streams with or without particle distribution common to pharmaceutical processes. Streams can be manipulated using 19 different property methods through an extensive thermodynamic and physical property library of which most commonly used are the ideal property method, Raoult's Law, and Henry's Law. Furthermore, there is diversity in the process models Aspen Plus provides by manipulating the operation mode or equipment configuration. For example, this includes the reactor design, which is the vessel where the chemical reactions take place and are often designed to optimize yield, efficiency, chemical kinetics, and operating conditions including energy input/removal, pressure exchange, frictional pressure loss, and agitation. Thus, different pharmaceutical processes may require different reactors; Aspen Plus provides various options including the two most common reactors for continuous processes: Continuous Stirred-Tank Reactor (CSTR) and a Plug Flow Reactor (PFR). Each reactor has its own set of energy and heat balances that contains their unique differential

equations that Aspen Plus uses to simulate the behavior of the reactor. This trend continues for a variety of unit operations including crystallizers, crushers, distillation columns, mixers, and condensers. From a process stream standpoint, Aspen Plus also allows the user to simulate input variables. Each unit may also be further defined by defining unit characteristics such as pressure, inlet temperature, outlet temperature, molar flow rates, reflux ratio, product purity output, enthalpy, horsepower, and more depending on the unit being defined. Furthermore, users may use C++, Fortran, and VBA to allow flexibility and user-defined units to handle their system. From a material and process stream perspective, Aspen also allows the user to set a number of input variables through either calculation blocks or equation-oriented modeling.

Use of Aspen Plus software for modeling continuous pharmaceutical manufacturing processes is not extensively reported in literature. However, Aspen Plus has been used to model a number of chemical processes in both the chemical and petrochemical industry including integrated flowsheet models for wet granulation, solids handling, continuous direct compression, dry granulation which are applicable to the pharmaceutical industry for process design, development, and optimization (Rogers et al., 2013).

Applications of an Integrated Flowsheet Models for CPM Quality Systems

When designing a pharmaceutical plant, the process may involve a large amount of equipment and process streams. From a design point of view, an integrated flowsheet model will help the manufacturer evaluate optimal equipment configuration. This would be particularly advantageous when considering the pharmaceutical industry whose traditional form of manufacturing is batch processing. Using, this integrated approach, pharmaceutical

manufacturers will be able to evaluate the feasibility of a continuous process for their DP. The route of synthesizing the API and excipients can be evaluated and potential risks and challenges are more easily foreseen with challenges faced with either upscaling processes or switching from bath to CPM. This may increase manufacturing confidence in CPM and aid in convincing many manufactures to take the upfront initial investment costs currently required when switching from a batch to continuous process. Furthermore, computer simulated integrated flowsheet models will also provide information on equipment efficiencies, dimensions, and other characteristics that may aid in determining the capital costs of CPM equipment and build a business case for CPM. Capital cost may also be reduced using this model by determining the feasibility of retrofitting batch equipment to be utilized for a continuous process.

Integrated flowsheet models also provide an advantage over traditional DoE approaches by allowing the integrated plant to be studied on both a unit and plant level to obtain process information without using additional resources. Process feasibility, sensitivity analysis, risk analysis, process and equipment design and optimization could all be done through computer simulation without using APIs, excipients, creating waste, exposure to high-risk materials and parameters, and without distribution in production. Ideally, this integrated flowsheet method and DoEs would be used as complimentary tools. The integrated flowsheet model would help to provide an initial foundation of process knowledge to then narrow the scope of study for DoEs and further process investigation. Through this method, manufacturers could identify, optimize, and control CPPs and CMAs, leading to an increase process understanding in line with QbD and building quality into the process. This in return may result in quicker regulation approval of a design space and a larger design space to operate within.

Furthermore, integrated flowsheet models allow for the CPM process to be evaluated on a plant wide level rather than unit operation. This is extremely advantageous for risk assessment, which is a key feature in QbD. Risk assessment cannot have a narrow focus; rather, the impact of both upstream and downstream process and critical elements must be both known and understood to efficiently mitigate risks. Integrated flowsheet models allow for the equipment to be evaluated in both series and parallel in the sequential order of the CPM process. As an API, intermediate, or DP flows out of one unit of operation it then becomes the input of the next unit of operation in series. Cheaper than the iterative, factorial design of DoE, experimental, and empirical approaches.

For example, the process stream characteristics of the output of a feeder becomes the input characteristics of the mixer to follow. This then follows that the mixer must be able to handle any disturbances introduced from the feeder and not feed those disturbances to the following units of operations and affect product quality. This example can be easily evaluated in a computer simulated integrated flowsheet model by simulating the process in a software package like ASPEN Plus and performing a sensitivity analysis. This type of sensitivity analysis allows for increased process understanding of process flexibility and robustness. In return, this helps to determine process parameters and tolerances for the further establishment of a design space.

Once the established range of parameters has been established, deviations from these ranges must be managed and controlled in order to ensure a high, consistent product quality. These disturbances are most commonly controlled using actuators, sensors, feed forwards, and feedback controls through an integrated control system and interface. Integrated flowsheet

models may aid in the implementation of these control systems by aiding in the evaluation of the process and associated risks. Thus, the proper control methods and locations of controls along the process stream may be determined. As a result, integrated flowsheet models may be applicable to all stages of product design and process development as demonstrated in the following figure:

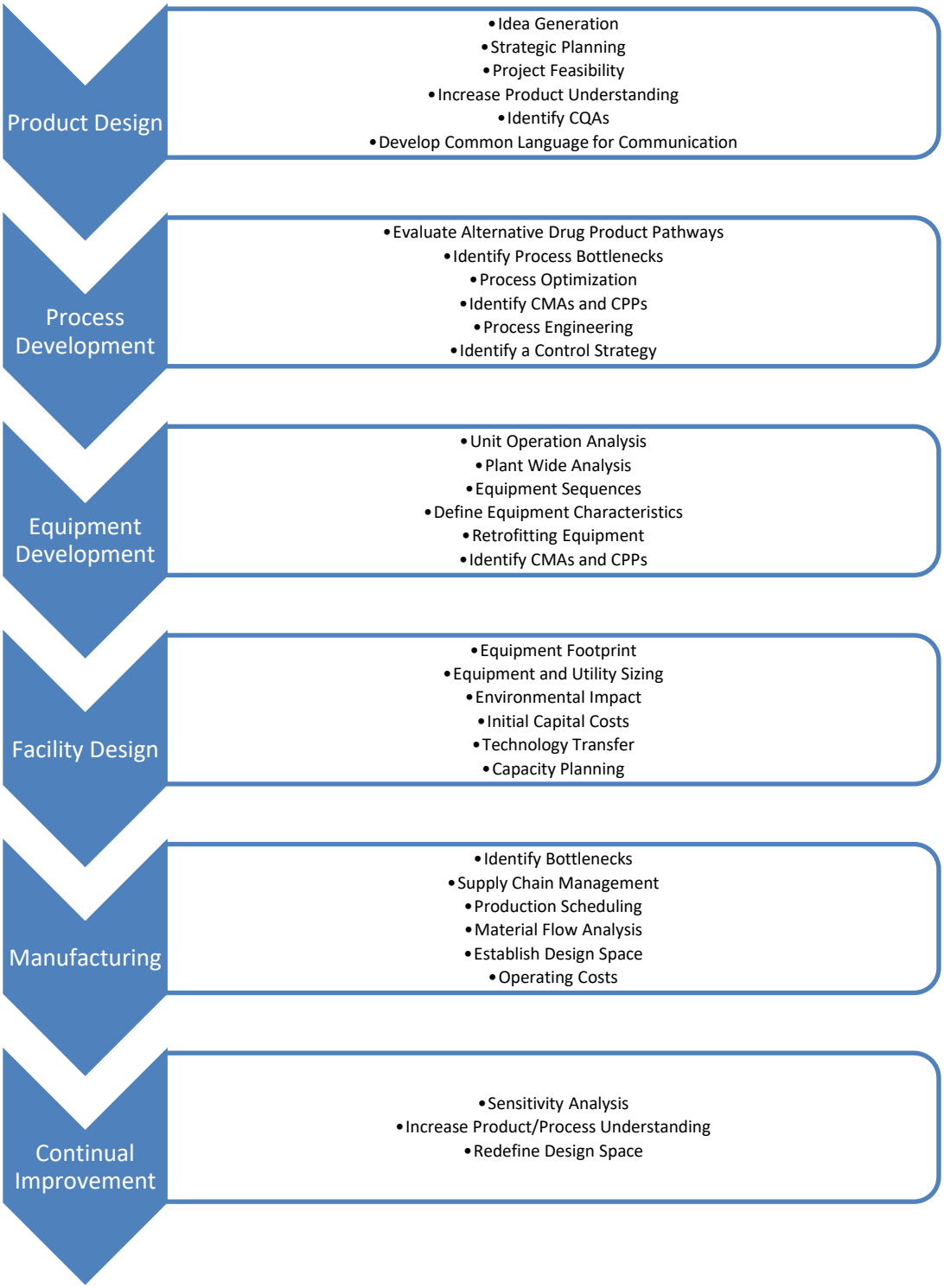

Figure 3: Applications of an integrated flowsheet models to different stages of product and process development

Benefits and Advantages

Integrated flowsheet models for CPM provide manufacturers with information on both the process design and process development. For example, it may be used to answer some of the following questions:

1. Can the DP be manufactured within the existing plant framework or is a new plant required?
2. Can the existing equipment be used or retrofitted for the development of the DP?
3. What is the total capital investment, manufacturing costs, operating costs?
4. What is the total throughput per unit of time of the DP?
5. What is the plant capacity?
6. What is the final product purity of the DP?
7. Which unit operations, material resources, or process are likely to create bottlenecks or process disturbances?
8. Is the process robust enough to handle process disturbances?
9. What unit operations or processes may be optimized to increase total throughput or efficiency?
10. What is the environmental impact of the process (e.g. waste, by-products, resources required)?
11. Upon evaluation of alternatives, which plant design provides the best decision for the plant based on the plant's priorities (e.g. fastest time to market, least expensive, smaller equipment footprint)?

As a result, this plant wide level approach provides many advantages to manufacturers over QbD approaches that focus solely on unit operation analysis in the areas of increased product understanding, design and optimization, plant wide analysis, reduced cost, and risk mitigation.

Table 5: Advantages of an Integrated Flowsheet Models

Area of Improvement	**Advantages**
Increase Process Understanding	• Evaluate how CPPs and CMAs interact to affect CQAs rather than a univariate approach • Process stream information • Design quality into the Process in align with QbD principles • Encourage the QbD mindset • Larger Design Space • Risk assessment and mitigation
Design and Optimization	• Process design and optimization, especially of high-risk parameters • Equipment design and optimization • Sensitivity Analysis • Feasibility Analysis
Plant Wide Analysis	• Evaluation of equipment in sequence

Area of Improvement	Advantages
	• Evaluate how units upstream and downstream interacts
Reduced Costs	• No material usage of APIs, intermediates, or excipients • Narrow scope for DoEs • Helps to build business case of CPM • Minimize development time/time to market

QbD Integrated Flowsheet Algorithm

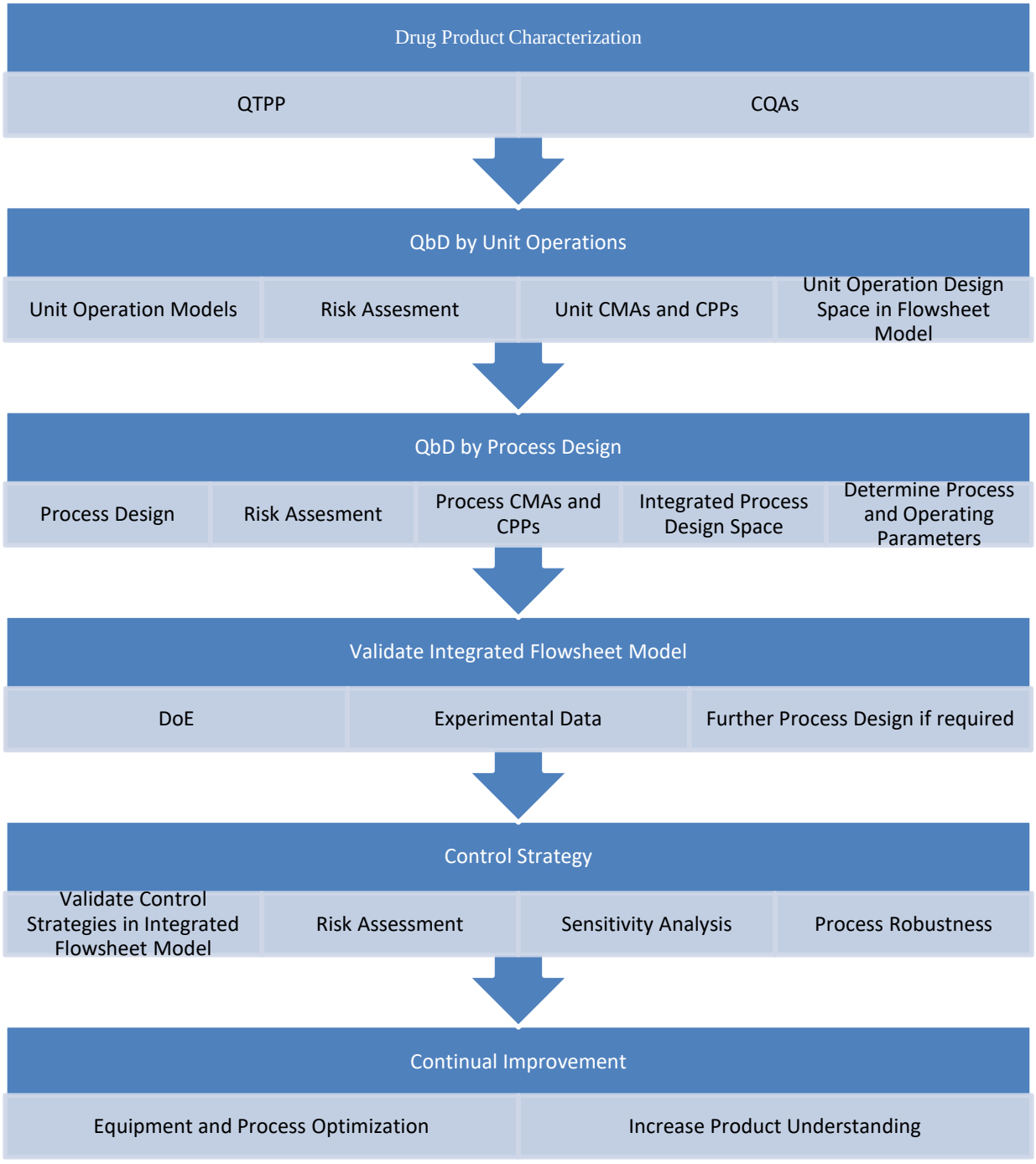

Figure 4: Process flow diagram for the application of QbD for CPM using integrated flowsheet models as the central method

The process should always begin with characterization of the DP to increase product understanding. Drug product understanding should begin upstream of the manufacturing stage of the product lifecycle during pre-clinical trials, clinical trials, lab scale plants, and test plants. Thus, the CQAs may be identified and developed from information provided from the label, intended use, efficacy, and any R&D performed during these stages. If the product is not a generic drug previously manufactured, the QTPP needs to be developed, followed by a risk assessment to identify potential CQAs. While a process may contain numerous quality attributes, not all quality attributes are critical. The manufacturer must consider the promised therapeutic effects, mechanisms of actions, dosage form, efficacy, clinical safety, patient demographics and more to select CQAs and establish a link to clinical performances. Another risk assessment may be performed to determine the risk priority number (RPN) as part of a FMEA to determine the probability of occurrence, likelihood of detection, and severity to prioritize CQAs. Once all CQAs have been identified, unit operation design may begin.

QbD by unit operation may begin taking place working from the QTPP and CQAs identified. For each unit operation, the CQAs must be identified for that unit operation to help identify possible CMAs and CPPs that affect CQAs. Through another FEMA risk assessment, CMAs and CPPs may once again be prioritized to determine PPs and MAs that could affect the output, CQAs, other PPs and MAs, and input variables to identify which are CPPs and CMAs. Using integrated flowsheet modeling, each unit may be modeled as an individual model and be tested. A design space may then be developed and operating parameters within that design space may be determined based on unit optimization and efficiencies. However, it is important to also be considering that an output of one unit of operation becomes the input of the next unit of

operation. No unit of operation operates independently of the process itself. As a result, it possible not all units will be optimized when the process itself is optimized.

Once unit operation design spaces have been established for each individual unit of operation, the process must now be designed by evaluating CQAs on a plant wide level. In literature, QbD is often defined on a unit basis, but fails to address the interdependencies and autocorrelation of these pharmaceutical processes and how CPPs, CMAs, and CQAs are interrelated and may affected one another. By evaluating on a plant wide level. A deeper understanding of the DP and processes is developed in alignment with QbD principles. By combining unit operation design spaces using integrated flowsheet modeling, these design spaces may be used to determine the optimal manufacturing operating parameters while ensuring each CQA is addressed throughout the manufacturing process with a total of n manufacturing steps. Often, through integrated flowsheet modeling, a larger design space is created allowing for higher manufacturing flexibility and a more robust process.

Once process parameters and material attributes have been determined, it is always recommended to validate the model with experimentation. One advantage of predictive modeling is that the scope and focus of experimentation has now been focused through the use of the integrated flowsheet model data and risk assessments performed without. This means less time and material are being used reducing costs when compared with QbD approaches that forgo computer simulated integrated flowsheet modeling. Similarly, computer simulated integrated flowsheet modeling allows manufacturers to test operating conditions that may be to hazardous or impractical for experimentations.

Once the integrated flowsheet model has been validated, a control strategy may now be identified and implemented. With the use of data from both the integrated flowsheet modeling and experimental data, process robustness may also be validated. Different control strategies may also be tested and evaluated using the integrated flowsheet model allowing for evidence based decision making by manufacturers. A risk assessment is also performed to help identify control strategies that link to the quality system and spec limits. Once a control strategy is implemented, the process may be further tuned and optimized leading to continual improvement and possible changes in the process design space. Continual improvement is a foundation of QbD that leads to further product and process understanding.

Below is a process flowsheet as an example of applying the QbD algorithm for CPM using in silica integrated flowsheet models as the central method. While it is not meant to be used at checklist of items to successfully implement QbD, it helps to facilitate the QbD way of thinking when using integrated flowsheet models.

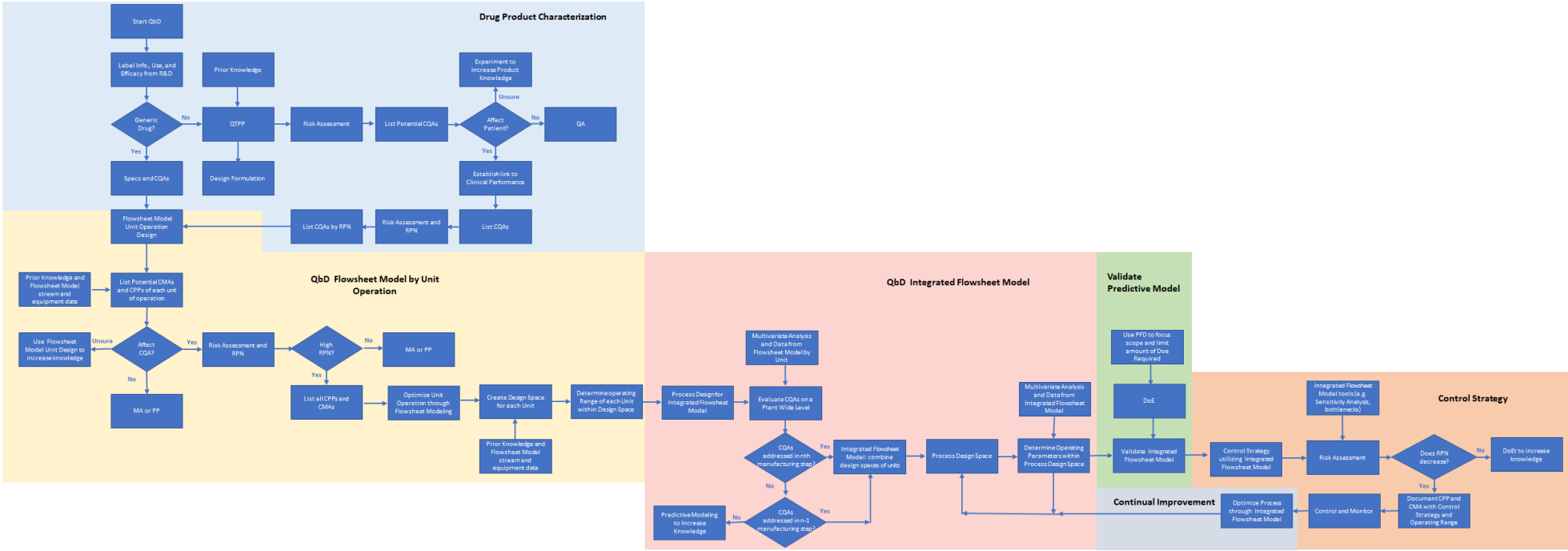

Figure 5: QbD Algorithm for CPM using integrated flowsheet models as the central method

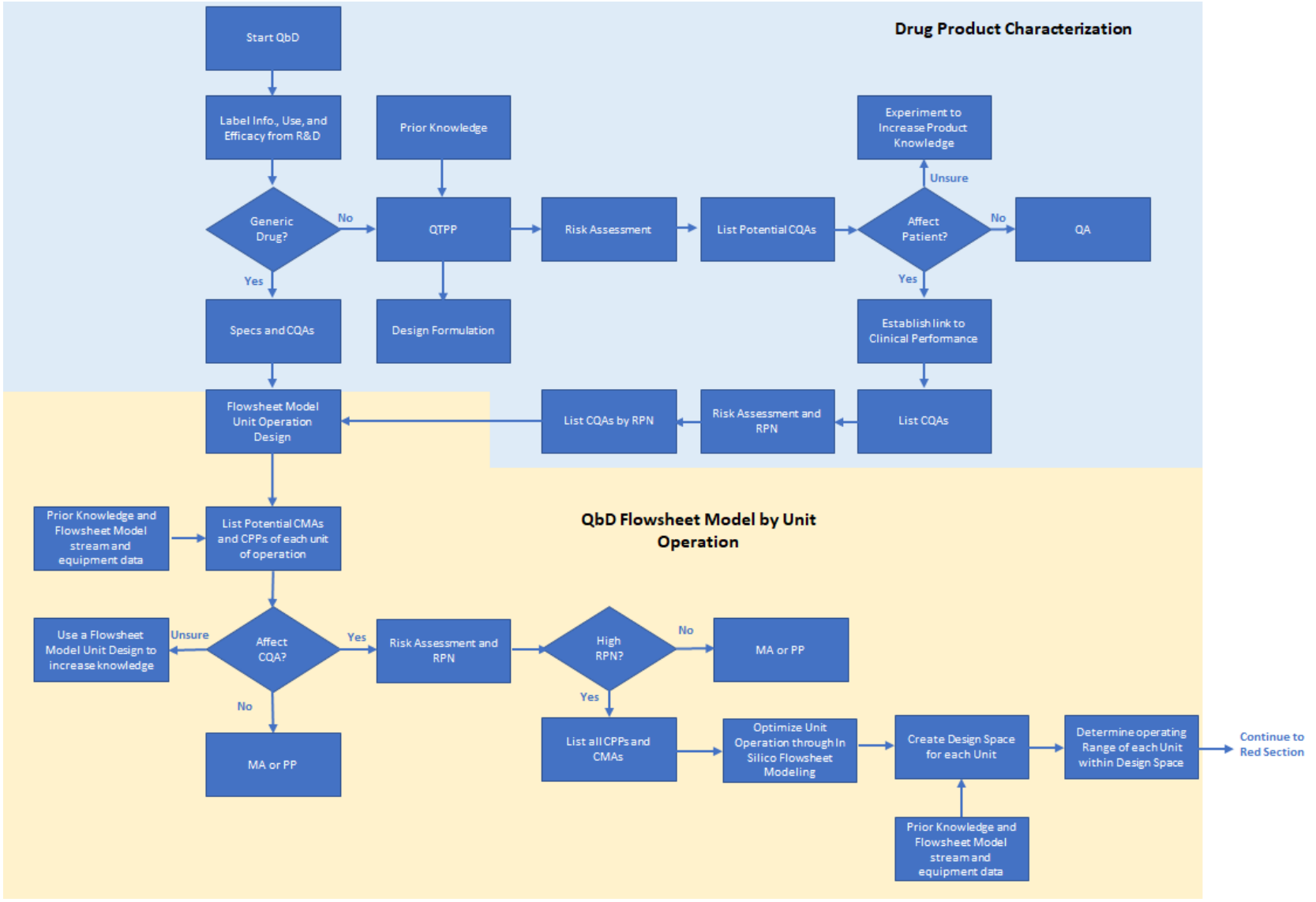

Figure 6: Blue and Yellow Section of QbD Algorithm for CPM using integrated flowsheet models as the central method

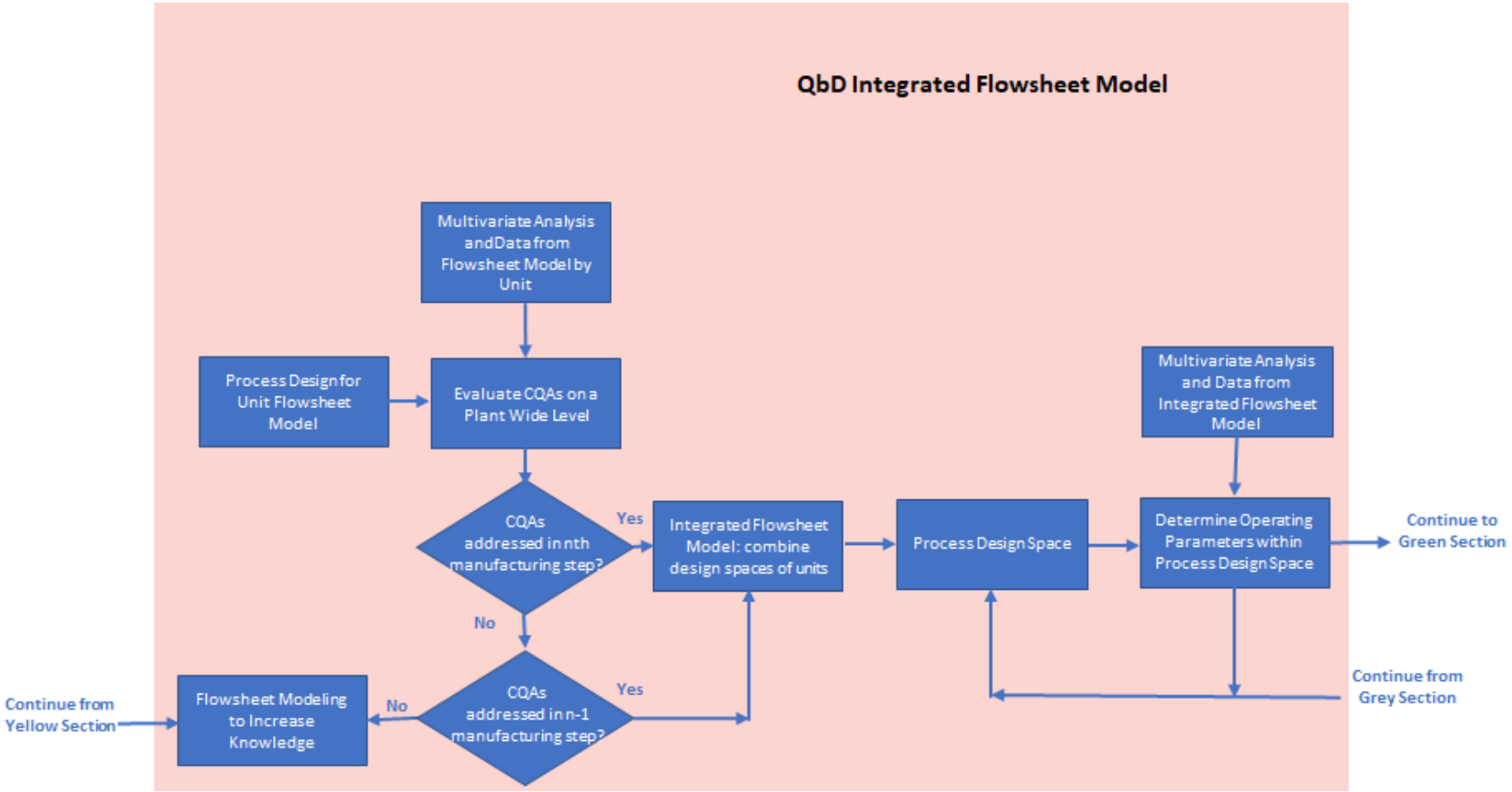

Figure 7: Red Section of QbD Algorithm for CPM using integrated flowsheet models as the central method

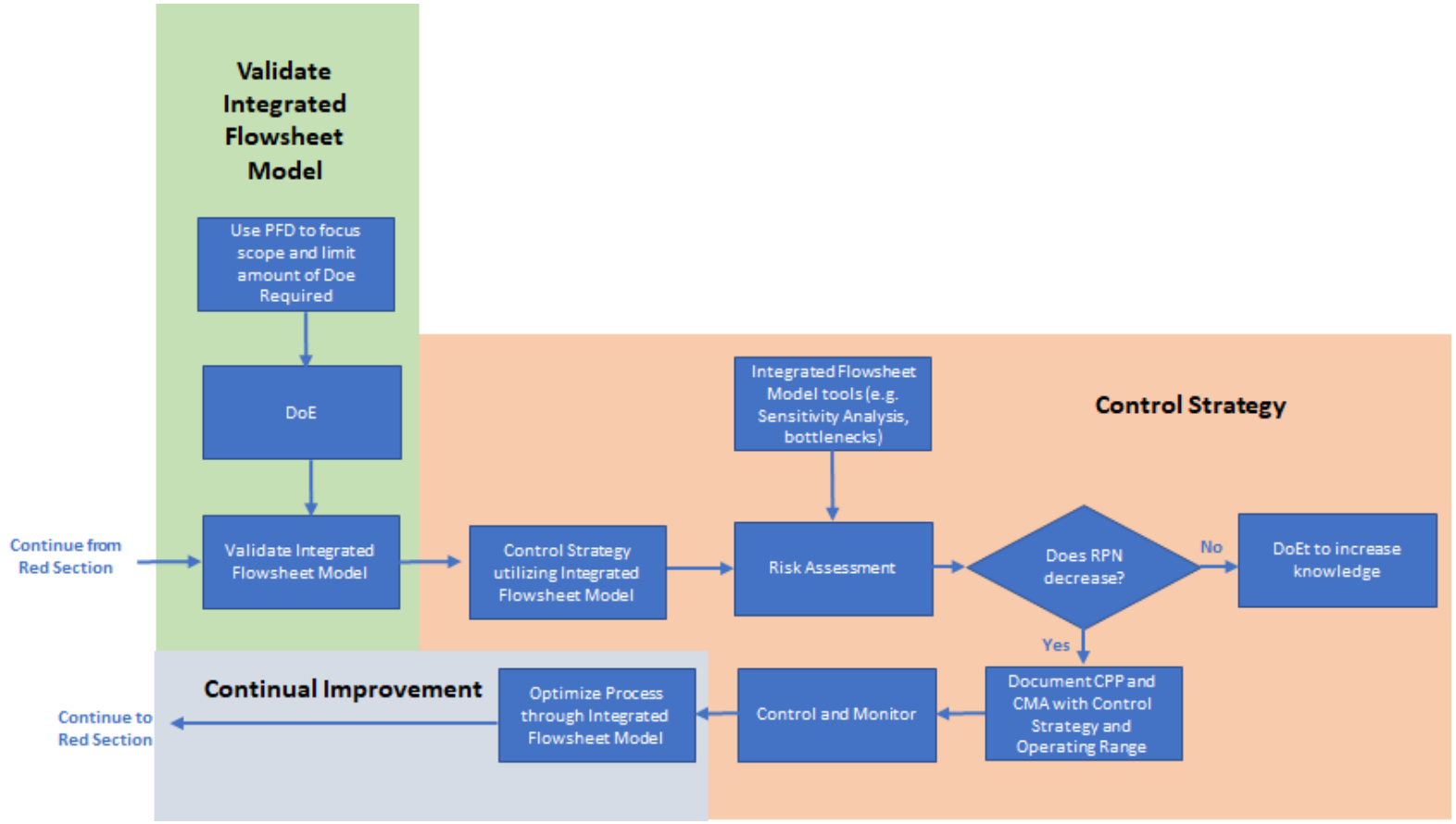

Figure 8: Green, Orange, and Grey Section of QbD Algorithm for CPM using integrated flowsheet models as the central method

Potential Regulatory Implications

The use of models for FDA regulation review and approval is not a new concept to the FDA or pharmaceutical manufacturing. Pharmaceutical manufacturers have used pharmacokinetics, drug adsorption modeling, activity relationship models, and bioequivalence models to support regulatory reviews. Furthermore, it is recognized that computer simulated integrated flowsheet modeling results in deeper product and process understanding, aligning with the QbD mindset promoted by the FDA and other regulatory bodies.

However, the level of acceptance of integrated flowsheet models in FDA regulatory submissions is highly dependent on the amount of reliance and support being placed on the integrated flowsheet model to assure the final DP quality. Integrated flowsheet modeling also helps to build a business case for CPM while enhancing product knowledge consistent with both FDA and ICH QbD guidelines and mindset.

Using a plant wide approach allows for a deeper understanding of both the DP and manufacturing process yielding a larger design space to operate within, without requiring regulatory submission and approval. Rogers and Ierapetritou (2014) identify the two levels of impacts as low and medium impact models. Low impact models are integrated flowsheet models only being used for process development support of experimental data and risk assessments such as potential toxicity and impurity risks. These models may be used in support of decisions made during process development. Medium impact models are integrated flowsheet models used to aid in determining the process design space, operating parameters, and control strategy.

While, computer simulated integrated flowsheet modeling is being utilized in other industries, it is not yet being utilized in the pharmaceutical industry. The FDA has recognized

this gap and sponsored two grants to further develop continuous pharmaceutical manufacturing process computer based simulations and modeling, in particular for solid oral dosage DPs. The FDA hopes that integrated flowsheet modeling may increase confidence in CPM among manufacturers and aid in project feasibility, product understanding, and process development. Integrated flowsheet models may be used as a platform for risk assessment, control strategies, and aid in developing common communications between manufacturers and regulatory bodies.

CHAPTER 5: CONCLUSION

Recommendations

While regulatory bodies have made strides towards decreasing the regulatory uncertainty surrounding CPM, there are still some major strides that need to be made to enhance the current regulatory environment. The FDA needs to define "batch" as it applies to CPM and current regulatory guidelines and statutes using the term "batch" in the requirements. Similarly, the FDA must adapt regulations to meet the expectation of QbD based submissions. This includes addressing the varying approaches to manufacturing and quality operations across the pharmaceutical industry.

In addition, technology advancements remain an obstacle towards CPM applications for both integrated and unit based methods. If manufacturers are to change from batch to continuous manufacturing, the technology must be able to support it. This technology includes technological advancement in continuous equipment, process analytical technology, common operating systems, and computer based simulation software. While technological advancements have been established extensively in literature as a requirement for continued CPM implementation, no technology pathway has been developed. Regulatory bodies, manufacturers, and universities should create a symbiotic relationship to aid in the recognition of technological needs and innovation of technology to meet those identified needs.

Lastly, regulatory bodies should work with universities to help create a workforce for the pharmaceutical industry that is already well established in the QbD and PAT methodologies to help create a cultural shift towards the QbD way of thinking and aid in the paradigm shift of the

manufacturing way of thinking towards increase product and process understanding. This includes not only being active in creating university partnerships for increased research into CPM quality tools, but also incorporating the CPM methodologies into the existing university curriculums in applicable fields. This includes, but is not limited to: chemical engineering, manufacturing engineering, pharmaceutical sciences, pharmaceutical engineering, process engineering, and industrial engineering. Thus, engineering and pharmaceutical curriculums need to be examined holistically to determine areas of improvements.

Future Research

The FDA and other regulatory bodies have been reducing barriers to the implementation of CPM and promoting QbD tools and principles; however, pharmaceutical manufacturers have been slow to modernize. Research could be done to determine the attitudes and confidence of pharmaceutical manufacturers towards QbD and CPM to see what major challenges prevent the successful implementation of these tools. In addition, the extent of application of these methodologies and intent to continue to apply these tools should also be determined. Furthermore, as the pharmaceutical industry is a complex industry with varying DP dosage forms and therapeutic benefits, an analysis could also be performed to determine the feasibility and applicability of CPM by dosage forms. Since manufacturing process vary by dosage forms, some dosage forms may be more suitable for CPM processes than other dosage forms. In addition, while CPM of unit operations is a progressive step towards an integrated CPM plant wide operation, there should be a distinction made in literature. CPM of unit operations leads to a

semi-continuous manufacturing process and not a true continuous process. Many of the inherent disadvantages of batch manufacturing will still be present.

While, computer simulated integrated flowsheet models are extensively reviewed in literature for other industries including the chemical and petrochemical industry there remains a gap in literature as it applies to the pharmaceutical industry. Future research should be done on the applications of integrated flowsheet methods as a tool for successfully implementing both QbD and PAT methodologies for CPM. The benefits of computer simulated integrated flowsheet methods and case studies should be performed in order to demonstrate the successful application of this method to pharmaceutical manufacturing process. Furthermore, the technology used for developing computer simulated integrated flowsheet models needs to be continued to be advanced and taught in chemical engineering, pharmaceutical engineering, pharmaceutical sciences, and other applicable coursework to aid in increase CPM knowledge, understanding, and confidence. Furthermore, while the use of models is not new to the application of regulatory approval, regulatory bodies need to determine how computer simulated integrated flowsheet models fit within the existing regulatory environment. This is in addition to continuing to determine how CPM quality is measured and judges.

Conclusion

Innovation and change in the pharmaceutical industry is imperative to meet the growing and increasingly customizable drug product market and world demand. CPM provides many advantages in both optimization of processes, increased DP quality, and economics over the traditional batch manufacturing process and is extensively reviewed in literature. However,

continued innovation and research needs to be done to increase manufacturing confidence in CPM. CPM should not be only implemented on a unit operation basis, but in order to receive all of the advantages and benefits CPM has to offer, needs to be implemented on an integrated plant wide basis.

An integrated flowsheet model aims to increase manufacturing confidence and aid in the implementation of CPM on a plant wide basis, by allowing manufacturers to simulate the pharmaceutical process and answer many operation and economical questions upfront without a large initial capital investment solely applying ex silico methods entails. In addition, integrated flowsheet models can be used as tool for both QbD and PAT by providing a data-rich environment.

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