DEVELOPING THE BUSINESS CASE FOR QUALITY BY DESIGN IN THE BIOPHARMACEUTICAL INDUSTRY

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
JUN 10 2009
LIBRARIES

By

Julie Matthew

B.S. 2000 Chemical Engineering
University of Massachusetts Amherst

Submitted to the MIT Sloan School of Management and the Department of Chemical Engineering in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration
AND
Master of Science in Chemical Engineering

ARCHIVES

In conjunction with the Leaders for Manufacturing Program at the
Massachusetts Institute of Technology
June 2009

© 2009 Massachusetts Institute of Technology
All rights reserved

Signature of Author _____
May 8, 2009
Chemical Engineering, MIT Sloan School of Management

Certified by _____
Charles Cooney, Thesis Supervisor
Robert T. Haslam Professor of Chemical Engineering

Certified by _____
Roy Welsch, Thesis Supervisor
Professor of Statistics and Management Science, MIT Sloan School of Management

Accepted by _____
William Deen, Chairman, Committee for Graduate Students
Department of Chemical Engineering

Accepted by _____
Debbie Berechman
Executive Director of MBA Program, MIT Sloan School of Management

This page has been intentionally left blank.

Developing the Business Case for Quality by Design in the Biopharmaceutical Industry

by

Julie Matthew

Submitted to the MIT Sloan School of Management and the Department of Chemical Engineering
on May 8, 2009 in Partial Fulfillment of the
Requirements for the Degrees of Master of Business Administration and
Master of Science in Chemical Engineering

ABSTRACT

Quality by Design (QbD) is a systematic, science-based approach to pharmaceutical development that was defined in the International Conference on Harmonization (ICH) Q8 guideline in 2005. Expectations are that QbD will ultimately become a regulatory expectation and prerequisite for drug approval. The pharmaceutical industry has made significant progress in applying QbD principles for small molecules, and efforts to adapt the new paradigm to biologic products are gaining momentum. Although the primary motivation for adopting QbD is regulatory expectation, the business impact of QbD has not yet been defined. The purpose of the business case is to examine the internal impact of QbD using Amgen, Inc. as a model large biopharmaceutical company. This assessment aims to identify the most critical areas of focus and to align expectations around the impact of QbD.

The business case captures the impact of QbD throughout the commercialization process, from drug discovery to commercial production, by applying a conceptual framework that divides the commercialization process into four major elements: Molecule Selection, Process Development, Technology Transfer, and Marketing Application & Commercial Production. Examples of on-going activities were identified within each of these elements to estimate the economic and operational impact of QbD. One of these examples was based on a deep-dive technical analysis of Smart Freeze Dryer technology, a novel means of lyophilization cycle development and temperature control.

The business case demonstrated that internal drivers do exist for the systematic implementation of QbD. Up-front investment early in the product life cycle offers economic and operational benefits later in development and commercial production. In addition, organizational learning and process development evolution lead to cumulative benefits for subsequent pipeline products. Though the magnitude and timing of investment depends on the available resources and long-term strategy of the business, investment should be concentrated in three key areas: Science & Technology, Knowledge Management Systems, and Business Processes.

Thesis Supervisor: Charles Cooney
Title: Robert T. Haslam Professor of Chemical Engineering

Thesis Supervisor: Roy Welsch
Title: Professor of Statistics and Management Science

This page has been intentionally left blank.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

The author wishes to acknowledge the Leaders for Manufacturing (LFM) program at MIT, her peers in the LFM class of 2009, and her advisors Roy Welsch and Charles Cooney for their support of this work.

The author would also like to express her sincere gratitude to Deborah Wong, whose guidance provided an unparalleled opportunity to learn and whose energy and efforts guaranteed an extremely successful internship. The author would also like to thank Cathryn Shaw-Reid, Feroz Jameel, Ed Walls, Erwin Freund, Joe Halcomb, and Bob Maroney for their mentorship and support of this work. For their time and their patience in helping her to assemble the business case, she also wishes to thank Chakradhar Padala, Christian Ruitberg, Wei Liu, Cenk Undey, Joseph Phillips, Karen Parker, and Ricardo Diaz.

Finally, and most importantly, the author is extremely grateful to her parents for their wisdom, support, understanding, and encouragement through the years.

GLOSSARY

Bioactivity: A measure of the effect of a drug on living materials or systems.

Biologic License Application (BLA): Application to obtain marketing approval from the U.S. FDA for a new biologic drug.

Cake: The solid product structure remaining after the lyophilization ("freeze drying") process

Chemistry, Manufacturing, and Controls (CMC): The portion of a drug marketing application describing the nature of the drug, how it is made, and how quality is guaranteed (non-clinical information).

Common Technical Document (CTD): Standardized set of specifications for applications for marketing approval of a new drug in the U.S., E.U., and Japan. The CTD includes Chemistry, Manufacturing, and Controls (CMC) information as well as clinical data.

Comparability: Verification of consistency in the product. This is critical in the biotechnology industry, where the product is complex and often nearly impossible to characterize completely, but it is imperative that the material made for clinical trials be comparable to the material made for commercial use (approval of the commercial product is based on clinical trial results).

Critical Quality Attribute (CQA): "A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." (ICH Q8 (R1), 2008)

Design Space: "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." (ICH Q8 (R1), 2008)

Excipient: An inactive substance used as a carrier for the active ingredients in a pharmaceutical or biopharmaceutical product.

Modality: The form of a pharmaceutical product. For instance, small molecules, therapeutic proteins, and monoclonal antibodies are all common modalities.

New Drug Application (NDA): Application to obtain marketing approval from the U.S. FDA for a new drug (not a biologic).

Product Pipeline: The collection of a company's products at all stages in the product lifecycle, from discovery and pre-clinical to commercial.

Quality Target Product Profile (QTPP): "A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." (ICH Q8 (R1), 2008) In the text that follows, the QTPP is referred to more simply as the Target Product Profile (TPP).

Titer: A measure of concentration; in the text, refers to concentration of the product of interest in cell culture during biologics manufacturing.

1 Introduction

1.1 Project Drivers

Innovators in the pharmaceutical and biotechnology industry are taking on a series of new challenges in recent years as their business environment continues to evolve. Among the most pressing issues are drying-up product pipelines, a shift towards personalized medicine (in contrast with the traditional blockbuster model), changing regulatory policy, and the emergence of generics and biosimilars (which have the potential to rapidly and drastically reduce an innovator's market share). The industry has taken a number of steps to address these challenges; among them is focusing increasing attention on the development process with the goal of bringing more high-quality drugs to market faster. Quality by Design is one of several tools with the potential to help streamline development activities while building in product quality.

Quality by Design (QbD) is a new approach to pharmaceutical development defined in 2005 by the International Conference on Harmonization (ICH), a joint initiative involving both industry and regulators in the US, the EU, and Japan. QbD represents a paradigm shift in development, applying more systematic and streamlined methodologies with a focus on end-product quality. Under QbD, pre-determined product specifications define the drug manufacturing process – the process no longer defines the product. Additionally, thorough process understanding and control minimize product variability so that quality is proactive rather than reactive (i.e., no more "quality by inspection").

The pharmaceutical industry has already begun to embrace QbD, which was originally developed with a small molecule focus. However, due to greater product and process complexity, the biopharmaceutical industry is still working closely with regulatory agencies such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) to determine what QbD should look like for biotechnology products. While much of the current discussion focuses on shaping future regulatory requirements, a key to successful implementation of QbD is determining whether it is a sound investment from an internal enterprise perspective and identifying how it will impact an innovator's business.

1.2 Problem Statement

Pharmaceutical and biotechnology companies are currently approaching QbD under the assumption that it will ultimately become a regulatory expectation. Since a company's success at applying QbD could then impact whether or not their products will be approved, regulatory compliance is a major driver for implementation. However, the economic and operational impact of QbD in a biopharmaceutical enterprise is not yet clear. The purpose of the business case is to examine the internal impact of QbD using Amgen, Inc. as a model large biopharmaceutical company. The magnitude of investment in QbD depends primarily on resource availability and the company's long-term business strategy. However, this assessment should serve to identify the most critical areas of focus and to align expectations around the impact of QbD.

1.3 Thesis Overview

The document is organized as described below:

Chapter 1 outlines the general motivation for the thesis and provides an overview of the thesis contents.

Chapter 2 provides a brief discussion of the industry and company background, as well as a description of the evolution of QbD in the pharmaceutical industry and the progress of QbD adoption to date.

Chapter 3 presents the hypothesis for the study undertaken.

Chapter 4 describes the general approach to data collection as well as the conceptual framework applied in the development of the business case.

Chapter 5 details the impact of QbD in each of the four major areas of the drug commercialization process: Molecule Selection, Process Development, Technology Transfer, and Marketing Application & Commercial Production. In each section, an overview of the potential applications for QbD is presented, followed by an in-depth example.

Chapter 6 provides recommendations from the business case, including three suggested areas of investment.

Chapter 7 presents an overview of the business case, including a summary of key findings.

2 Background

2.1 Biopharmaceutical Industry

Though there is still some debate over the meaning of the term "biopharmaceutical", the biopharmaceutical industry is generally considered to be a subset of the pharmaceutical industry where products are therapeutic agents derived from biotechnology.[1] This is in contrast with traditional pharmaceuticals ("small molecules"), which are typically produced through chemical synthesis. Biopharmaceutical products ("large molecules" or biotech products) include living cells, sugars, proteins, and nucleic acids such as DNA and RNA, and they are used to treat a wide variety of illnesses from cancer to rheumatoid arthritis.[2]

The biopharmaceutical industry has experienced considerable growth since the first non-vaccine biologic product was approved in 1982. In 2007 there were more than 150 biopharmaceuticals on the market in the United States, with more than 600 in development for more than 100 different diseases.[3] The global market for biopharmaceuticals in 2007 was $64.5 billion, with approximately 75% of the market in North America. Analysts predict that biotech products will drive growth in the pharmaceutical industry with a compound annual growth rate (CAGR) of approximately 11.6% through 2014.[4]

Biopharmaceuticals and traditional pharmaceuticals can be differentiated on the basis of product complexity. Whereas small molecules are often 100 atoms or less, large molecules can be two to three orders of magnitude larger with many subunits. The relative complexity of the two types of drugs is shown in Figure 1: where a small molecule would be analogous to a bicycle, a large molecule would be analogous to a jet aircraft. A similar comparison can be made for manufacturing processes. Chemical synthesis of small molecules involves combining fixed quantities of reagents through a highly standardized process to yield a compound readily identifiable with available analytical techniques. In contrast, large molecules are typically derived from recombinant technologies and produced through live cell culture. Each cell acts like a miniature factory, and

---

[1] (Rader, 2008)

[2] (Frost & Sullivan, 2008)

[3] (Frost & Sullivan, 2008)

[4] (Frost & Sullivan, 2008)

although synthesis is generally quite robust, certain variations within the cell or in the cell's microenvironment have the potential to affect any of the molecule's hundreds of subunits. Further complicating manufacturing control, biopharmaceuticals often defy traditional analytical approaches due to their inherent intricacy.[5] Hence, product and process complexity present a considerable challenge in the biopharmaceutical industry.

[5] (Rader, 2008)

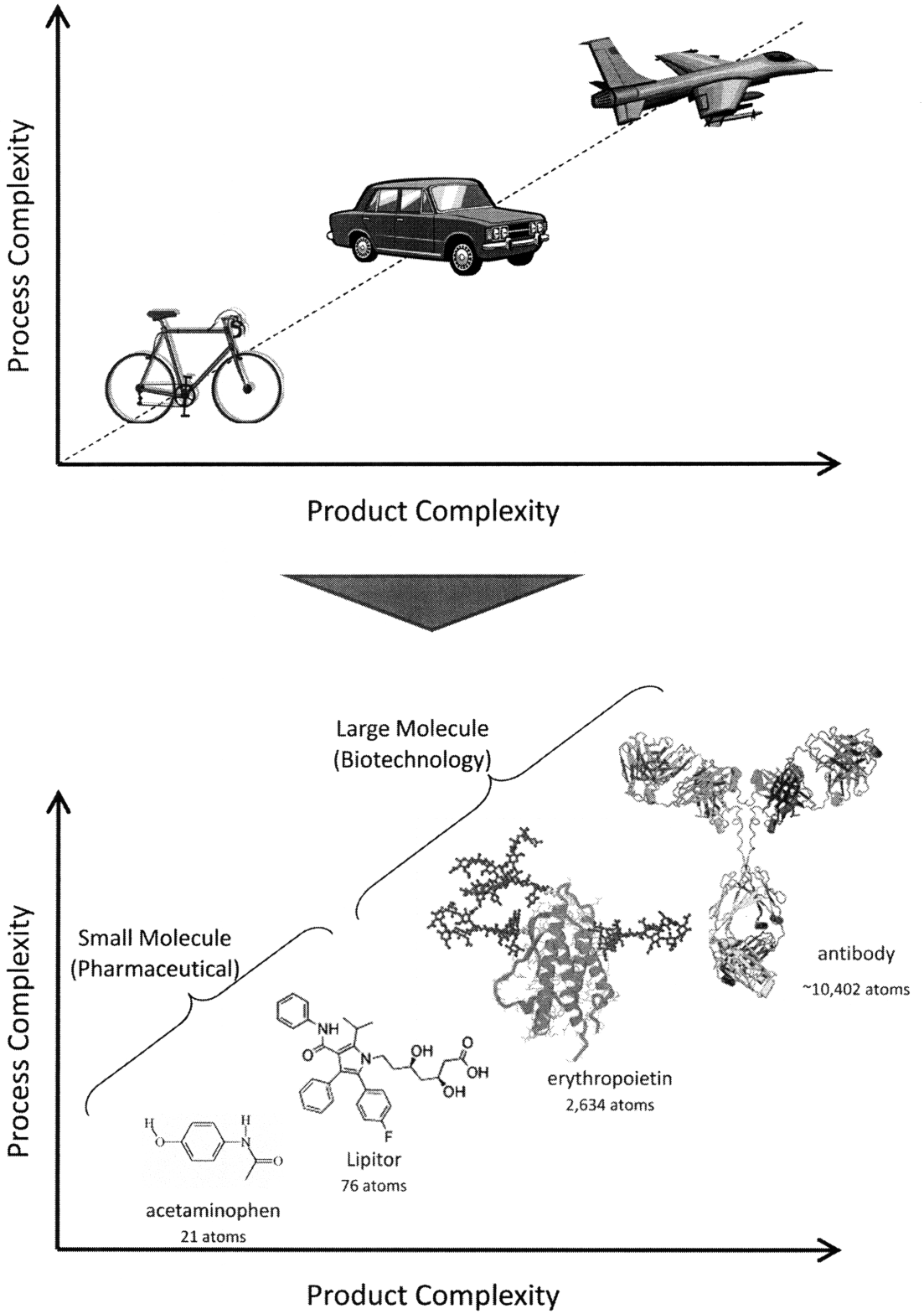

Figure 1: Relative product and process complexity for small and large molecules

The biopharmaceutical industry, like the rest of the pharmaceutical industry, manages a long, complex development process from drug discovery to product launch (Figure 2). The process can take ten or more years, and estimates place the cost of bringing a new drug to market between $800 million and $1.7 billion per successful drug.[6] Though much of the time and cost is consumed with the execution of clinical trials, considerable effort is expended in developing and characterizing both the product and the manufacturing process. Such development and characterization work is a primary focus in the business case for Quality by Design.

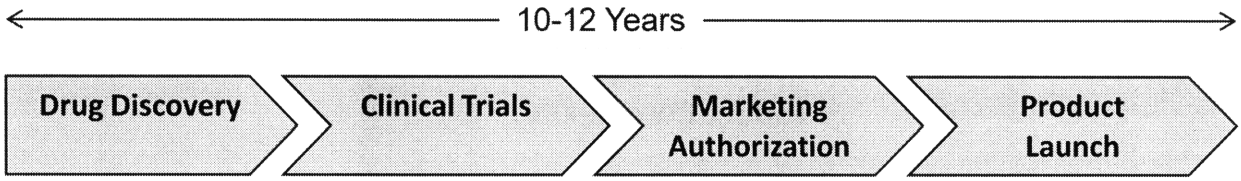

Figure 2: Biopharmaceutical development process, from discovery to product launch.

2.2 Amgen, Inc.

Amgen, Inc. is a leader in the biopharmaceutical industry with more than 25 years of experience applying a science-based approach to drug development. After it was founded in 1980, Amgen pioneered the use of recombinant DNA and molecular biology to develop biologically derived therapeutic products. In the 1990's, the company introduced the biopharmaceutical industry's first blockbusters, EPOGEN® (Epoetin alfa) and NEUPOGEN® (Filgrastim), which have since improved the lives of hundreds of thousands of patients. The company currently has eight products on the market that provide supportive cancer care and treat a variety of conditions from anemia to rheumatoid arthritis and other autoimmune diseases.[7]

Although most of the company's products are biologics, its approach to drug discovery is largely modality independent. That is, any of several modalities, large molecules (large molecule proteins or antibodies) or small molecules, may be pursued during drug discovery depending on which modality

[6] (Landers, 2003), (Miller, 2009)

[7] (About Amgen – Company History, 2009)

most effectively impacts the disease target.[8] In this respect, Amgen's development activities support its mission to serve patients – they have expertise with a broad range of tools to find the best possible treatments.

Amgen is headquartered in Thousand Oaks, CA and has approximately 17,000 staff worldwide. In 2008, product sales were $14.7 billion, and the company invested $2.9 billion in research and development. Amgen has facilities around the world and operates manufacturing sites in California, Colorado, Rhode Island, Washington, and Puerto Rico.[9] As a leader in the biopharmaceutical industry with a proven development track record – specifically, seven biologics currently on the market and a full product pipeline – Amgen can offer valuable insight in the development of the QbD business case.

2.3 Quality by Design (QbD)

2.3.1 QbD Prior to 2002

Quality by Design is not a new concept in manufacturing industries; rather, it has been an important part of the evolution of quality control since late in the 20th century (Figure 3). The concept of "quality through robust design" or "quality engineering" was introduced to the United States by Dr. Genichi Taguchi in the early 1980s and adopted as the Taguchi Method.[10] In 1992 another expert in quality and quality management, J.M. Juran, described "planning for quality" as "the activity of (a) establishing quality goals and (b) developing the products and processes required to meet those goals." [11] Juran explained that product features and failure rates are largely determined during development stages, and emphasized the importance of understanding the costs of poor quality.

[8] (About Amgen – Fact Sheet, 2009)

[9] (About Amgen – Fact Sheet, 2009)

[10] (Noori, 1989)

[11] (Juran, 1992)

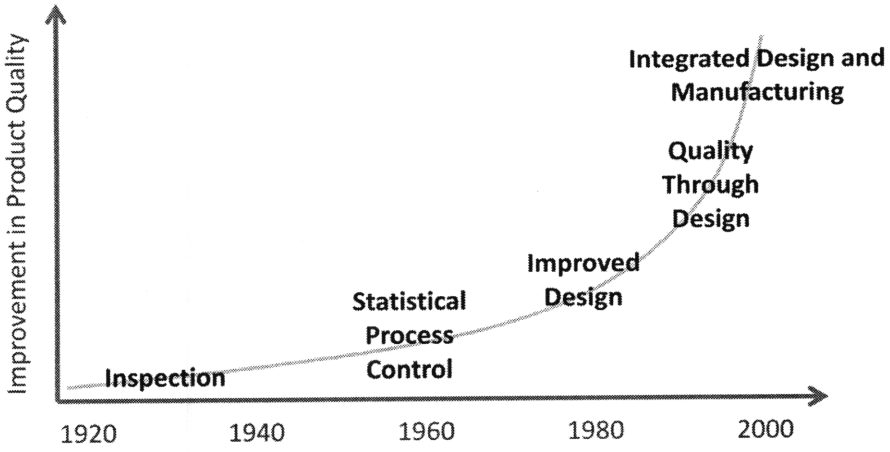

Figure 3: Evolution of quality control in manufacturing industries (adapted from Karbhari, 1994)

Quality by Design began in the automotive industry and spread to other industries, including at least one branch of healthcare. The medical devices industry began applying QbD principles to its development processes in the mid-1990s, building on ISO 9000 standards and the FDA's Quality System Regulations (21 CFR 820). In a 1997 paper, Lasky et al. outlined a procedure for QbD in devices: the process begins with product (device) attribute definition, which is then followed by risk analysis, verification and validation of product attributes and correct product function, and finally conformance monitoring and complaint tracking.[12]

Product quality is of the utmost importance for pharmaceuticals, and advanced quality systems are in place to guarantee product safety and efficacy. However, the industry has lagged behind these others in the adoption of QbD principles through development. One reason may have been that long and complex development timelines make it much more difficult to gain perspective of the entire process from early discovery (the product design phase) through commercial manufacturing. Another reason may have been technological hurdles. Whereas it is possible to touch and observe the components of an automobile or even a medical device, it is far more difficult to design and characterize a product on the molecular scale. Analytical methods are still evolving to measure biopharmaceutical product attributes, and the relationship between product attributes and manufacturing process parameters or clinical performance is complex.

[12] (Lasky & Boser, 1997)

Ultimately, the delay in QbD adoption in pharmaceuticals was most likely because of the difficulty of changing existing, effective quality processes in such a highly regulated environment; the response from regulators was uncertain, making significant changes risky. Quality in the pharmaceutical industry has traditionally been controlled adequately through prescriptive and inspection-based systems. As technology and the regulatory environment have evolved, however, the need for and feasibility of an approach such as that described by Taguchi and Duran have become much more apparent.

2.3.2 QbD following the 21st Century Quality Initiative

In 2002, the FDA announced a new initiative, "Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach". The purpose of the initiative was to promote the adoption of advanced technology, facilitate the application of quality management techniques, encourage a risk-based approach, and ensure that regulatory guidelines and review processes were science-based and aligned through quality systems.[13] Recently re-named "Pharmaceutical Quality for the 21st Century – A Risked Based Approach", the initiative marked the agency's acknowledgement that although pharmaceutical manufacturing and quality are adequate, the industry is generally less efficient and innovative and has higher costs than other high-tech industries.[14]

Since the launch of the Pharmaceutical Quality for the 21st Century initiative, the FDA has initiated several additional quality programs to support its goals. Specific to encouraging new manufacturing technologies, the agency issued a process analytical technology (PAT) guidance in 2003 (finalized in 2004). PAT, as defined in the guidance, is

> ... a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. [15]

In the broadest sense, PAT involves applying "chemical, physical, microbiological, mathematical, and risk analysis" to improve process understanding and facilitate innovation and risk-based

---

[13] (FDA Pharmaceutical Quality for the 21st Century – Progress Report, 2007)

[14] (Van Arnum, 2007)

[15] (FDA PAT Guidance for Industry, 2004)

decision-making.[16] Practically speaking, PAT can include anything from a physical in-line process sensor to the advanced statistical techniques described in section 5.4.2. While the technological tools themselves are important, PAT fundamentally means applying the tools appropriately to better understand the process.

In addition to issuing the PAT guidance, the FDA has also participated in the International Conference on Harmonization (ICH). ICH is an international collaboration between industry and regulators whose mission is to develop guidelines that ensure drug regulatory processes are efficient and uniform across the three major regulatory regions, U.S., E.U., and Japan.[17] Among the guidelines developed by the group is ICH Q8 (Pharmaceutical Development), which was finalized in November 2005 and most recently revised in November 2008. The Annex (Part II) to ICH Q8 defines Quality by Design for the pharmaceutical industry:

> Quality by Design (QbD) [is] 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.[18]

The pharmaceutical development process prescribed by QbD (that is, by ICH Q8) begins with definition of the target product profile (TPP), which forms the basis of design and includes elements such as route of administration, therapeutic agent release or delivery approach, and drug product quality criteria.[19] Next, critical quality attributes (CQAs) are identified; these are properties or characteristics of the drug that must be controlled within a certain range to ensure the desired product quality. Manufacturing process selection follows; process development includes identifying critical process parameters (CPPs), those process parameters that have an impact on CQAs. The final step is to develop an appropriate control strategy with guidance from a thorough risk assessment, which evaluates the relationships between CPPs and CQAs, among other criteria. The FDA's view of QbD is shown in Figure 4 below.

---

[16] (FDA PAT Guidance for Industry, 2004)

[17] (About ICH, 2009)

[18] (ICH Q8 (R1), 2008)

[19] (ICH Q8 (R1), 2008)

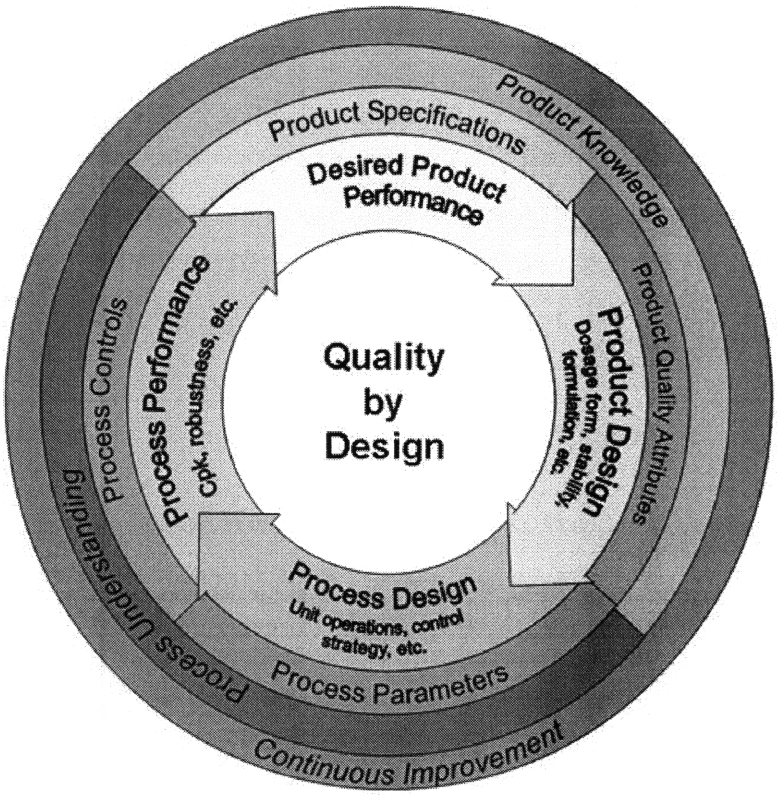

Figure 4: FDA perspective of Quality by Design, from the FDA's Pharmaceutical Quality for the 21st Century progress report, 2007.

Another important concept introduced in ICH Q8 is that of design space, "[t]he multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." [20] Design of experiments plays an important role during process development as the relationships between CPPs and CQAs are evaluated to create design space. Once design space is approved by the FDA, a manufacturer would have the freedom to adjust operating conditions anywhere within that space without requiring regulatory approval. The concept of design space has the potential to afford a manufacturer considerably greater process flexibility.

It is valuable to note that ICH Q8 defines QbD from a traditional, small molecule perspective. While many of the concepts can be applied to large molecule development, the added product and process complexity render much of the guideline insufficient or impractical. The FDA is currently

[20] (ICH Q8 (R1), 2008)

working with industry representatives to develop guidelines that are more applicable to biopharmaceuticals.

Quality by Design is a systematic approach to pharmaceutical development that can incorporate prior knowledge, design of experiments, quality risk management, and knowledge management. (The latter two concepts are the subject of the ICH Q9 and Q10 guidelines, respectively.) Additionally, PAT is one of many tools that facilitate the implementation of QbD.[21] At a high level, QbD is intended to help innovators demonstrate process understanding and build-in product quality while providing the necessary flexibility and support for innovation and improved efficiency.

2.3.3 Recent Progress in QbD for Biopharmaceuticals

The pharmaceutical industry and the FDA have made considerable progress in applying QbD since it was first defined in 2005. Given the relative simplicity of the product, the focus of the guidelines, and the availability of small-molecule technologies adapted from the fine chemical industry, adoption has been more rapid for traditional pharmaceuticals. However, the efforts of biopharmaceutical firms and regulators around QbD for biotech products are gaining momentum.

In 2005 the FDA launched a QbD pilot program for small molecules through its newly created Office of New Drug Quality Assessment (ONDQA). The pilot program provided innovators with an opportunity to submit for agency review NDAs or supplements incorporating key elements of QbD. The goal of the program was to allow the FDA to work closely with industry so that both could gain insight into how QbD can be applied in practice. As of May 2008, the ONDQA had approved six pilot applications, with several more awaiting review.[22]

The FDA launched a similar pilot program for biotech products in July 2008. The program is managed by the FDA's Office of Biotechnology Products (OBP), and is open to new submissions until September 2009.[23] Building on the successes of the program launched in 2005, this program is intended to encourage biopharmaceutical manufacturers to improve product and process understanding and control. Through the pilot the FDA hopes to delineate an approach to implementing QbD that will provide further guidance for industry. The agency's commitment to

---

[21] (Nasr, 2008)

[22] (Wechsler, 2008)

[23] (Office of Biotechnology Products – Notice of Pilot Program, 2008)

helping innovators improve their product & process development processes is consistent with the goals of their 21st century quality initiative.

Separate from the FDA's pilot programs, industry groups have also been working towards biotechnology-specific guidelines for QbD. Most notably, Conformia, a product/process lifecycle management (PPLM) solutions firm, formed a QbD working group for biotech products in 2008. The group is comprised of seven industry leaders: Amgen, Genentech, Abbott, MedImmune (Astra Zeneca), Glaxo Smith Kline, Eli Lilly, and Pfizer.[24] Building on a similar project for small molecules initiated in July 2007 (the "ACE Tablet" case study), the group will develop a case study based on a fictitious biological molecule (specifically, a monoclonal antibody) to outline potential interpretations of the ICH guidelines and to illustrate a science- and risk-based development approach. The results of the case study are expected in spring 2009.[25]

While industry and regulators have made progress in applying QbD principles to biopharmaceutical development and manufacturing, significant barriers remain. One of the greatest barriers is the perceived regulatory risk. Submitting a marketing application that incorporates QbD principles when the standard for such a regulatory filing is not yet established increases the risk of getting a negative reaction from regulators. In the early stages of biotech QbD when regulatory expectations are still not entirely clear, companies need to work closely with the FDA to ensure that a new approach to development or a new technology is acceptable. A related concern is that providing too much information to regulators might increase the likelihood of a negative response.[26] From a market perspective, disclosing full product knowledge and process understanding could also increase the threat of biosimilar competition in the future.

Another hurdle to implementation is organizational momentum. QbD represents a fundamental change in the way that people think about pharmaceutical development. Implementing the new paradigm requires changing processes that have successfully churned out blockbusters in the past. Hence, innovator companies wishing to apply QbD must carefully re-design the business processes and incentive systems within their organizations to align with the principles of systematic and science-based development.

---

[24] (Conformia, 2008)

[25] (Conformia, 2008)

[26] (Nasr, 2008)

One final hurdle to implementation is cost. QbD requires a considerable up-front investment in technology and business process re-design. Although theory suggests that the up-front investment is repaid as a lower cost of quality, the business case has not yet been clearly communicated across the biopharmaceutical industry.

As a leader in the biopharmaceutical industry, Amgen continues to work with regulators and its peers to interpret and apply the ICH guidelines for biotech products. In addition, the company had already achieved great success using QbD principals internally in various applications across the organization. However, one of the biggest challenges facing the company (and its peers) specific to QbD is deciding how best to align on-going activities, determine the appropriate level of investment, and define a path forward. The business case is intended to inform these decisions by highlighting the impact of QbD across the entire development process. A successful approach to QbD implementation could enable greater flexibility, innovation, and efficiency, thereby strengthening Amgen's leadership position in the industry.

3 Hypothesis

Quality by Design has both external and internal drivers. While the primary driver, regulatory expectation, is external, QbD can have considerable benefits to Amgen's internal operations. Up-front investment in QbD throughout commercialization, particularly early in the product lifecycle, can positively impact a biotechnology company's business in at least four different areas:

- Operational cycle times, including time to market and production cycle times
- Extent of regulatory compliance and status of quality management systems
- Ability to meet demand while reducing scrap and inventory
- Ability to minimize business costs, directly and through cost avoidance

4 Methodology

4.1 Data Collection and Analysis

All interviews, data collection, and analyses were performed at Amgen, Inc., primarily at the Thousand Oaks, CA site.

Quality by Design is a lifecycle approach to product and process development. Consequently, when developing the business case it was important to consider the lifecycle as broadly as possible. Interviews of over 40 subject matter experts (SMEs) within several functions at Amgen, including Research & Development, Process Development, Quality, Regulatory, Finance, Supply Chain and Manufacturing, were integral to the business case.

Given the enterprise-wide scope of the project, analyses could not practically be exhaustive and are instead example-based. Representative examples within Amgen were identified and data were analyzed with assistance from SMEs. The business case also includes two deep-dive analyses based on hands-on work done in the Drug Product and Device Development (DP&DD) function in Process Development. DP&DD is responsible for the Fill/Finish and packaging portions of the process. Fill/Finish includes filling active drug substance into vials, syringes, or other delivery devices, lyophilizing (freeze drying) the product when necessary, and inspecting final product for delivery to patients. These deep-dives were intended as a technical proof-of-concept for one unit operation: lyophilization (freeze drying).

4.2 Conceptual Framework

To ensure a holistic approach to the business case, a framework was developed to capture the key elements of the biopharmaceutical lifecycle. Commercialization, the process by which a product is identified, developed, and brought to market, was divided into four major elements:

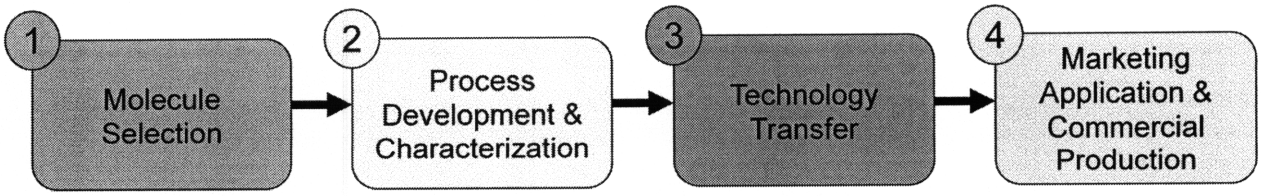

Figure 5: Strategic framework for the business case

1. Molecule Selection: During this phase of commercialization, a small group of product candidates identified during early development is screened to identify the one molecule that will move on to the next phase of commercialization. Each of the candidates is screened for bioactivity, stability, and manufacturability, among other criteria. This phase also includes cell line selection.

2. Process Development & Characterization: During this phase of commercialization, a process is defined for the production of the selected molecule. Once the process has been defined, additional studies are performed to identify critical interactions, set operating conditions, and challenge the process. Analytical methods for product characterization are refined, and a process control strategy is identified. Considerable process knowledge is generated during this phase.

3. Technology Transfer: During commercialization, product is made for many different reasons: some is made only for development purposes, some is intended for use in clinical trials (small scale production), and the majority is intended for sale as commercial product (large scale production). The Technology Transfer phase of commercialization encompasses transfer of the production process either between scales (e.g., from the development or pilot scale to the commercial scale) or between sites (e.g., from one commercial site to another). The primary concern during technology transfer is that the process and product remain comparable across sites and scales. For instance, product manufactured at the commercial scale must be highly similar to product manufactured at the clinical scale in order for the manufacturer to rely on data obtained during clinical development for marketing authorization.

4. Marketing Application & Commercial Production: This phase consists of two major elements: the production of commercial product and the creation of the Common Technical Document (CTD), which forms the basis of the Biological License Application (BLA) or Marketing Application (MA) to be filed with the FDA for approval. The CTD contains clinical trial data and demonstrates in-depth knowledge of the product and production process. FDA approval of the marketing application and a pre-approval facility inspection

are required before a company can launch a commercial product. Commercial production may begin prior to approval of the BLA, however the material may not be released into the market until approval is obtained.

The impact of QbD in the biopharmaceutical lifecycle is described in the next section in the context of the framework outlined above. Opportunities to apply QbD principles, the anticipated outcome, and an example of the impact of QbD at Amgen are detailed for each element of commercialization. Final results for each element are related to the impact to the business in four major areas: economics, product supply, quality, and cycle time.

5 The Impact of QbD in the Biopharmaceutical Lifecycle

5.1 Molecule Selection

A product is first defined during Molecule Selection. This is the ideal starting point for Quality by Design, with the creation of a target product profile (TPP) and identification of critical quality attributes (CQAs).

5.1.1 Applying QbD to Molecule Selection

Quality by Design can enhance and increase the efficiency of Molecule Selection through the application of innovative screening methods and analytical tools. For instance, high throughput tools such as Seahorse Bioscience's SimCell™ system allow more rapid and thorough screening than was previously attainable. SimCell™ is a micro bioreactor array that simulates a scale-down bioreactor with 1ml culture volumes. The technology has a variety of applications for both Molecule Selection and Process Development, including clone selection and culture media optimization in early process development.[27]

QbD can also help by providing the impetus to harness the organization's collective product and process knowledge. For instance, a modality-specific knowledge bank can be created to facilitate organizational learning and leverage work done with prior molecules. Such a knowledge management system can incorporate learnings from later-stage development and commercial production; this information can be used to select the molecule with the best possible manufacturability. The concept of knowledge management is discussed in greater detail in section 5.5.

The ultimate benefit of QbD in Molecule Selection is the identification of molecules with the optimal balance of bioactivity, stability, and manufacturability. In addition, a solid knowledge management system leverages information across the product pipeline. The end result is acceleration of products through commercialization and a reduction in attrition (when pipeline products fail to make it to market).

[27] (Seahorse Bioscience, 2009)

5.1.2 Example: Monoclonal Antibody (mAb) Platform

A monoclonal antibody (mAb) platform was implemented at Amgen six years ago and has since undergone a number of revisions. The platform is a library of knowledge specific to the mAb modality; it is a means of capturing and applying molecule and process knowledge gained during the development of previous mAb product candidates. Molecule characteristics such as bioactivity, stability, and manufacturability can all be optimized during selection of a new product candidate based on the successes and failures of prior mAbs. The platform can also provide preliminary production process conditions for the new molecule with typically only minor revisions required during process development. **Table 1** shows the operational impact of the platform since its introduction. The operational metric most impacted by the platform is Speed, specifically speed to market, since these early activities typically lie on the critical path to product launch.

Metric	Description	Change Since Platform Introduction
Average Titer	Concentration of product in cell culture; a measure of culture productivity	> 2-fold increase
Cycle Time to Tox Release	Time from selection of molecule to first toxicity studies with animal models; includes early process development	1.4-fold decrease
FTE Requirements	Number of resources required to advance a molecule to the next stage in commercialization	1.6-fold decrease

Table 1: Benefits of the monoclonal antibody (mAb) platform

Amgen has already seen considerable operational benefits as a result of the platform, which will continue to evolve over time as it captures organizational learning. The mAb platform is an example of applying knowledge management, a backbone of QbD, in Molecule Selection. QbD at this point in commercialization can positively impact the business primarily by reducing cycle times.

5.2 Process Development & Characterization

The majority of process knowledge is built during Process Development & Characterization. It is during this phase when relationships between a product's critical quality attributes (CQAs) and the

critical process parameters (CPPs) will ideally be mapped and understood, defining the design space. Consequently, the majority of the investment in QbD will be focused here. It is important to note that building process understanding can be extremely costly (financially and in terms of time to market); it is critical to balance the cost of development with the value of the knowledge obtained.

5.2.1 Applying QbD to Process Development & Characterization

QbD principles encourage the use of statistical tools such as Design of Experiments (DOE) along with Process Analytical Technologies (PAT) and high throughput development tools to verify relationships between CPPs and CQAs, identify optimal process conditions and process boundaries, and make process development more efficient. Process characterization using statistical tools allows for the identification of those parameters and interactions which can impact product quality. Critical parameters for a cell culture unit operation, for instance, may include raw material characteristics, pH, and temperature.

Risk analysis techniques may also be applied during Process Development & Characterization to identify the most critical process parameters and prioritize development work. An initial risk assessment may be on prior knowledge or experimental data (e.g., from design of experiments or mechanistic models); ICH guidelines recommend repeating the risk assessment throughout the development process.[28] Quality Risk Management is described in great detail in the ICH Q9 guideline.

The benefits of applying QbD to Process Development & Characterization are considerable. First among them is a clear definition of process boundaries. With the tools described above, the range of process inputs that yield good quality product can be defined, creating the multi-dimensional design space. When presented clearly in the CTD, a well-defined design space demonstrates a thorough process understanding, which increases regulatory confidence and the likelihood of product approval. In addition, design space can allow for greater commercial process flexibility, as described in section 5.4.

The benefits of establishing clear process boundaries can be extended to earlier-stage pipeline products through organizational learning. Once design space is established for one product, the

[28] (ICH Q8 (R1), 2008)

amount of development work required to create design space for a similar, subsequent product can be significantly reduced. However, as with the mAb Platform example in section 5.1.2, the usefulness of the information depends on how carefully the knowledge is captured and applied. The concept of knowledge management is discussed further in section 5.5.

An additional benefit of QbD is that optimal process conditions can be identified sooner and more efficiently: more knowledge is available prior to commercial launch. The primary result is improved commercial process performance (e.g., yield & cycle times), but earlier optimization may also lead to greater product consistency between scales and therefore simplified comparability.

While Amgen has long used DOE during process development, application of this and other statistical tools is increasing rapidly. Amgen has also begun to use several PAT tools for development purposes. The next section describes one of these tools, SMART Freeze-Dryer ™ (SFD) technology, in detail.

5.2.2 Example: Smart Freeze Dryer ™ (SFD) Technology (Deep Dive #1)

The purpose of this deep-dive project is to evaluate SMART Freeze Dryer ™ (SFD) technology as a PAT tool for lyophilization cycle development and for more accurate measurement and control of product temperature, a critical process parameter. This section begins with background information for lyophilization, SFD technology, and manometric temperature measurement (MTM) and then describes the experimental plans, results, and key findings from this project.

5.2.2.1 Lyophilization Overview

Lyophilization, or freeze drying, is a common unit operation in the production of biologic products such as therapeutic proteins and monoclonal antibodies. Lyophilization is typically one of the last steps in production before final packaging. During this process, water is removed from the liquid formulation of the product to enhance stability, increase shelf-life, and allow for rapid reconstitution prior to injection. Unlike other drying methods which can damage proteins, lyophilization can produce a solid product cake with minimal impact to product quality. Freeze drying has been used in the pharmaceutical industry since the mid-1900s (beginning with antibiotics), and it is the most common method for producing solid dosage forms of products that are heat-sensitive and less

stable in the presence of water.[29] Consequently, the process is well-understood both in the industry and among regulators.

Lyophilization consists of a series of controlled phase changes. First, the liquid formulation, an aqueous solution of the product and excipients such as sugars or surfactants, is filled into glass vials and then frozen. The primary goal of the freezing step is to create a crystal matrix that will allow sublimating water to escape while locking the remaining constituents in a sponge-like configuration. Once the vials are frozen they are placed under vacuum, and heat is applied gradually to sublime the ice crystals. This stage, when unbound, crystalline water is driven out of the frozen matrix, is known as primary drying. At the end of primary drying the product typically has only 3-5% moisture. Additional heat is applied during secondary drying to remove most of the remaining bound moisture from the product/excipient matrix.[30] The lyophilization process described above is shown overlaid on the water phase change diagram below (Figure 6).

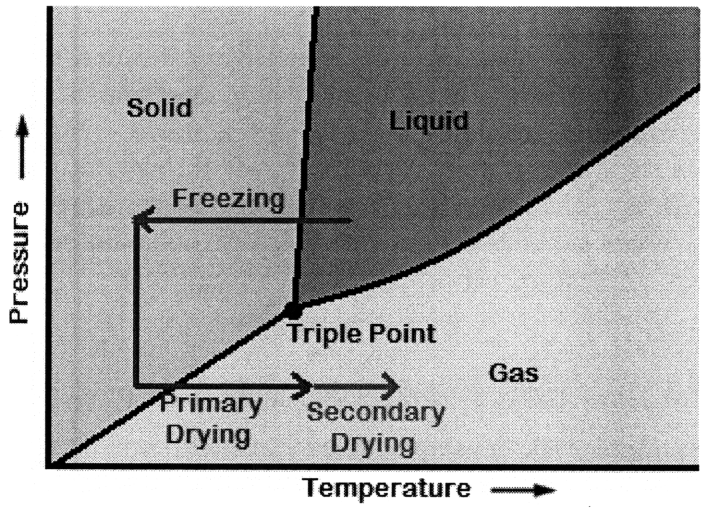

Figure 6: Phase change diagram for water showing freezing, primary drying, and secondary drying steps.

A freeze drying cycle may contain additional phases beyond those described above. For instance, an annealing step is commonly added during freezing to ensure that crystals in the frozen matrix grow as large as possible. Large water [and excipient] crystals ensure final product quality and help create

[29] (Trappler, 2005)

[30] (Freeze Drying/Lyophilization Info Online, 2009)

an "elegant" product cake. Annealing is accomplished by raising the temperature for a portion of the freezing step. **Figure 7** shows a hypothetical lyophilization cycle, including an annealing step.

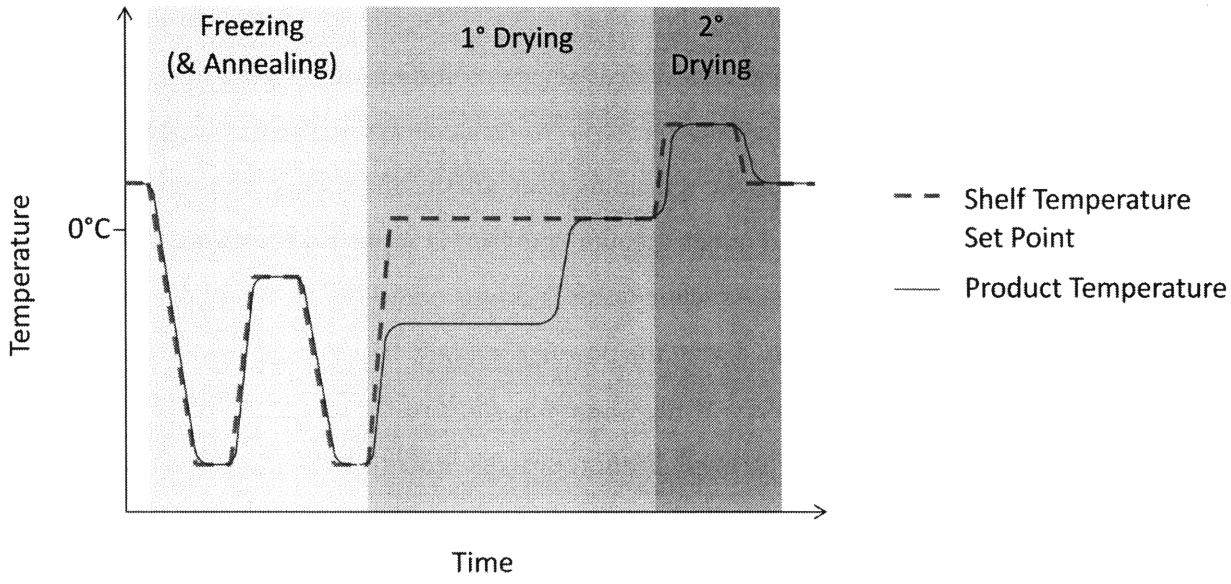

Figure 7: Hypothetical lyophilization cycle, generalized and drawn by the author. Temperatures and ramp rates for each step vary depending on the product; optimizing these values is the focus of cycle development. Note that product temperature tracks shelf temperature set point closely throughout the cycle, except during primary drying when the heat required for sublimation keeps product temperature low. When sublimation nears completion (unbound moisture has been removed), product temperature warms to the shelf temperature.

The optimal conditions for freeze drying depend on the nature of the product and the excipients, but the primary objectives during cycle development are consistent: achieve good product quality in the shortest possible cycle time. Product quality considerations include moisture content and cake structure. A dry, "elegant" cake stabilizes the product and is easy to reconstitute (reconstitution is facilitated by the sponge-like microstructure of the dried product matrix). In addition, the absence of visual cake defects such as cracks can be crucial in clinical trials, where visual defects in the product make it discernible from the placebo, thereby "unblinding" and potentially invalidating the study.

Lyophilization cycle time is an important area of focus during development, because it can be on the order of hours or days. Longer cycles negatively impact commercial operations by decreasing scheduling flexibility. Additionally, fixed costs are typically a large component of drug product

costs, so long cycle times have a significant negative economic impact. Cycle time may be a particularly important consideration for outsourcing, as most contract manufacturers providing lyophilization services charge based on the duration of the cycle. Cycle times can often be shortened by increasing drying temperatures and ramp rates.

Conditions identified during cycle development are carefully controlled by the freeze drying equipment. Basic elements of a lyophilization system are a product chamber, a condenser, and a vacuum system (See **Figure 8**). Vials are arranged in the product chamber on temperature-controlled shelves. During primary and secondary drying, when the entire system is under vacuum, moisture from sublimation in the primary chamber collects in the condenser, where it freezes on cold coils. The isolation valve installed between the chamber and condenser remains open during drying.

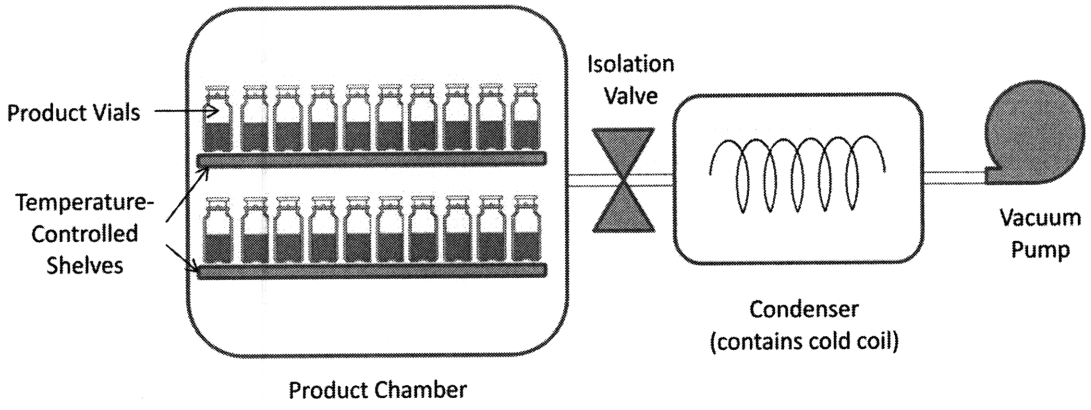

Figure 8: Lyophilizer configuration

5.2.2.2 SMART Freeze-Dryer ™ (SFD) Technology Overview

The SMART Freeze-Dryer ™ (SFD) is software based on technology originally developed jointly between the University of Connecticut and Purdue University. The technology was licensed to FTS Systems in 2003 and incorporated in their Lyostar II laboratory-scale lyophilizer. The integrated product was officially released in 2005.[31] SFD is primarily intended as a tool for accelerating and streamlining lyophilization cycle development. Whereas cycle development has traditionally been done experimentally, requiring approximately 10 runs, the SFD can predict and test the optimal

[31] (Gieseler, 2006)

cycle in 1 or 2 runs. FTS anticipates a reduction in average cycle development time of up to 78%.[32] The SFD incorporates manometric temperature measurement (MTM), which is a novel, non-invasive means of measuring product temperature (a critical process parameter). MTM and SFD are described in greater detail below.

SFD technology and MTM rely on a fundamental understanding of heat and mass transfer within a product vial during primary drying. Key concepts are illustrated in **Figure 9**. Primary drying begins once freezing is complete and the product chamber and condenser are placed under vacuum. Shelf temperature is raised, and heat from the shelf is transferred through the bottom of the glass vial to the frozen contents. With the application of heat at low pressure, ice at the surface of the frozen layer begins to sublime into the vial headspace. Vials are only partially stoppered, so water vapor can escape into the product chamber via a small opening in the neck of the stopper. As the ice sublimes out of the frozen matrix, a porous dried product layer begins to form. The interface between the frozen layer and the dried product layer is known as the sublimation front; this front moves from top to bottom as the contents of the vial dries. Once the frozen layer is gone and only the product/excipient matrix (dry layer) remains, heat is no longer required for sublimation and product temperature rapidly rises to equilibrium with the shelf temperature. This temperature rise can be used to signal the end of primary drying.

[32] (Sesholtz, Debra; Mather, Leslie, 2007)

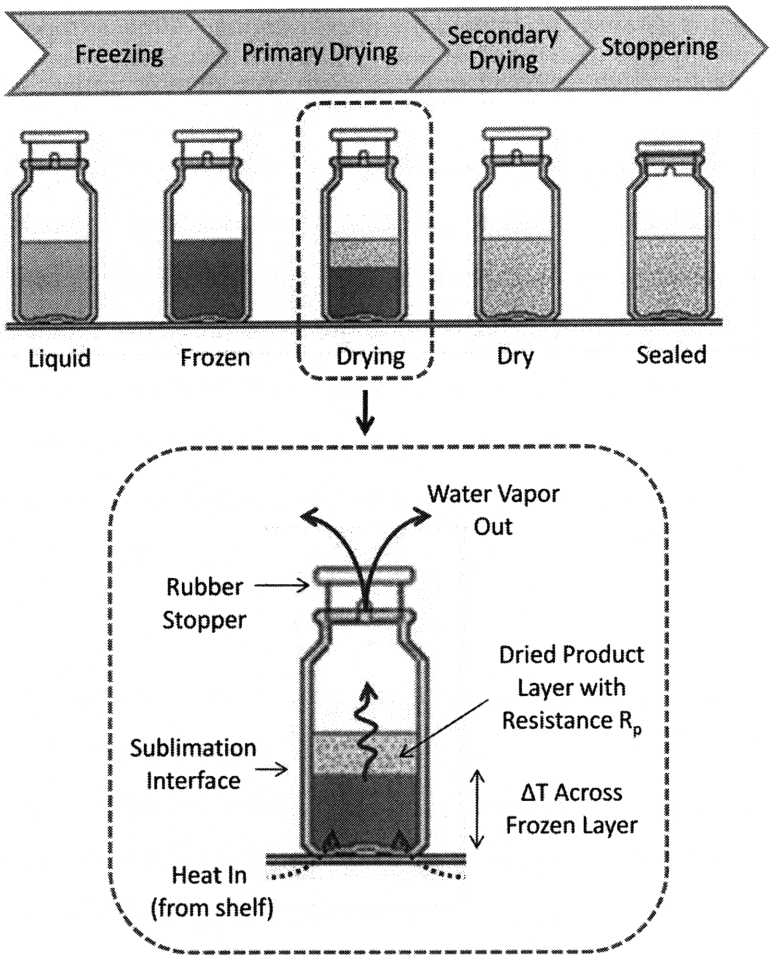

Figure 9: Heat (red arrows) and mass (blue arrows) transfer in a product vial during lyophilization

Two additional primary drying phenomena are important to note here:

1) Temperature gradient across the frozen layer: While heat is applied to the bottom of the vial from the shelves, heat is removed at the sublimation front (heat of sublimation). Consequently, the temperature at the bottom of the frozen layer is greater than the temperature at the sublimation front. This is an important consideration for accurate product temperature measurement.
2) Mass transfer resistance from the dry product layer (R_P) and the stopper (R_S): During drying, water vapor must pass through both the dry layer and the opening in the stopper. Both dry-

layer and stopper resistance can impact the rate of drying. While stopper resistance is often considered negligible, high dry-layer resistance can considerably impact sublimation rate.[33]

As mentioned earlier, product temperature control is extremely important during freeze drying. Temperature is most critical at the sublimation front, where the product/excipient matrix may begin to collapse during sublimation if the temperature is too high. Collapse, or "meltback", occurs as material in the frozen matrix undergoes a phase change to a more mobile state and is no longer rigid enough to support its own weight. A collapsed product cake is highly undesirable not only for cosmetic reasons but also because it leads to incomplete drying, product stability issues, and difficult reconstitution.[34] Collapse temperature depends on the product and formulation, but it can be determined experimentally with a small sample using differential scanning calorimetry (DSC) or freeze drying microscopy.

Unfortunately, because product temperature results from a balance between heat input from the shelves and cooling from sublimation, product temperature cannot be controlled directly. Instead, adjustments are made to shelf temperature or chamber pressure. Estimates of product temperature are most often made using thermocouples (TCs), which may be placed in the bottom of a subset of vials prior to the start of a cycle. While TCs can provide vial temperature data throughout the cycle, there are several disadvantages to this method. First, because of the temperature difference across the frozen layer, temperature measured at the bottom of the vial by the TC does not accurately reflect the temperature at the sublimation front. Second, TCs cannot be used in a clinical or commercial manufacturing setting because they may compromise sterility. Finally, the presence of the thermocouple may act as a nucleation site during freezing, impacting both freezing and drying behavior.[35] MTM, proposed as a complement (or possibly an alternative) to TC temperature measurement during development, uses the heat and mass transfer phenomena described above to accurately measure product temperature at the sublimation front without interfering with the product.

---

[33] (Tang, Nail, & Pikal – Part II, 2006)

[34] (U.S. FDA – Guide to Inspections of Lyophilization of Parenterals, 2008)

[35] (Tang, Nail, & Pikal – Part I, 2006)

5.2.2.3 Manometric Temperature Measurement (MTM)

Manometric temperature measurement is performed during primary drying by closing the isolation valve (see **Figure 8**) for a short, fixed period of time, thereby isolating the product chamber from the condenser and effectively "pausing" the lyophilization cycle. Sublimation continues during this period, causing chamber pressure to rise. Chamber pressure vs. time data are recorded for as long as the isolation valve is closed, typically less than 30 seconds. The resulting pressure-rise curve (see **Figure 10** for an example) can be used to determine the temperature at the sublimation front.

Chamber pressure rise is described by the MTM equation (Equation 1)[36]:

Equation 1: MTM Equation

$$P(t) = \left\{ P_{ice} - (P_{ice} - P_0) \cdot exp^{\left[-\left(\frac{3.461 \cdot N \cdot A \cdot T_S}{V \cdot (R_p + R_s)}\right) \cdot t\right]} \right\}_{Term\ 1} + \left\{ 0.0456 \cdot P_{ice} \cdot \Delta T \cdot \left[1 - 0.811 \cdot exp^{\left(-\frac{0.114}{L'} \cdot t\right)} \right] \right\}_{Term\ 2} + \{X \cdot t\}_{Term\ 3}$$

Where P_{ice} is the vapor pressure of ice at the sublimation front (to be determined, or "fit"); P_0 is the chamber pressure (set); N is the number of vials in the chamber (known); A is the total cross-sectional area of all vials (known); T_S is the shelf temperature (set); V is the product chamber volume (known); R_P+R_S is the product and stopper resistance (to be determined, or "fit"); ΔT is the temperature difference across the frozen layer; L' is the ice thickness (calculated from other data); and X is a constant (to be determined, or "fit").[37]

Chamber pressure rise is attributed to three different factors, each of which is represented in the MTM equation. Term 1 accounts for pressure rise controlled by dry layer resistance and the temperature at the sublimation front. Term 2 accounts for chamber pressure rise due to the transfer of heat across the frozen layer (from shelf to sublimation front). Finally, Term 3 accounts for chamber pressure rise due to the MTM measurement itself: closing the isolation valve increases

[36] (Milton, Pikal, Roy, & Nail, 1997)

[37] (Milton, Pikal, Roy, & Nail, 1997), (Tang, Nail, & Pikal – Part I, 2006)

chamber pressure and slows sublimation, reducing heat dissipation at the sublimation front and increasing product temperature.[38]

A commercial software package, such as that included in the SFD, can be used to fit pressure rise data to the MTM equation. The vapor pressure of ice at the sublimation front, P_{ice}, and the total resistance (R_P+R_S) can be determined from the fit, and the product temperature at the sublimation front, T_P, can be determined from P_{ice} according to Equation 2.[39] SFD uses these data to calculate additional system and cycle parameters such as product resistance (R_P), vial heat transfer coefficient (K_V), frozen layer thickness (L_{ice}), and the temperature difference across the frozen layer (ΔT)(see Appendix for these relationships).

Equation 2: Product temperature calculation from the vapor pressure of ice (P_{ice})

$$T_P(MTM) = \frac{-6144.96}{\ln(P_{ice}) - 24.01849}$$

Tang et al. have identified two distinct regions in an MTM pressure rise curve that are critical for the accuracy of the fit. As shown in **Figure 10**, the initial, rapid pressure rise is dominated by resistance to mass transfer (R_P+R_S), corresponding to Term 1 in the MTM equation. The more gradual plateau region is dominated by temperature (heat transfer across the frozen layer), corresponding to Term 2 and Term 3 in the MTM equation. Tang et al. demonstrated that MTM accuracy is considerably reduced if both regions of the curve are not allowed to develop, i.e. if pressure rise is too gradual. Though extending the duration of the measurement may allow the full curve to develop, this approach is unacceptable because it increases the impact on product temperature (Term 3 in the MTM equation). Tang et al. have found that data collection times of more than 30 seconds can adversely affect product stability and lead to collapse. The MTM measurement is typically restricted to 25 seconds.[40]

---

[38] (Tang, Nail, & Pikal – Part I, 2006)

[39] (Tang, Nail, & Pikal – Part I, 2006)

[40] (Tang, Nail, & Pikal – Part I, 2006)

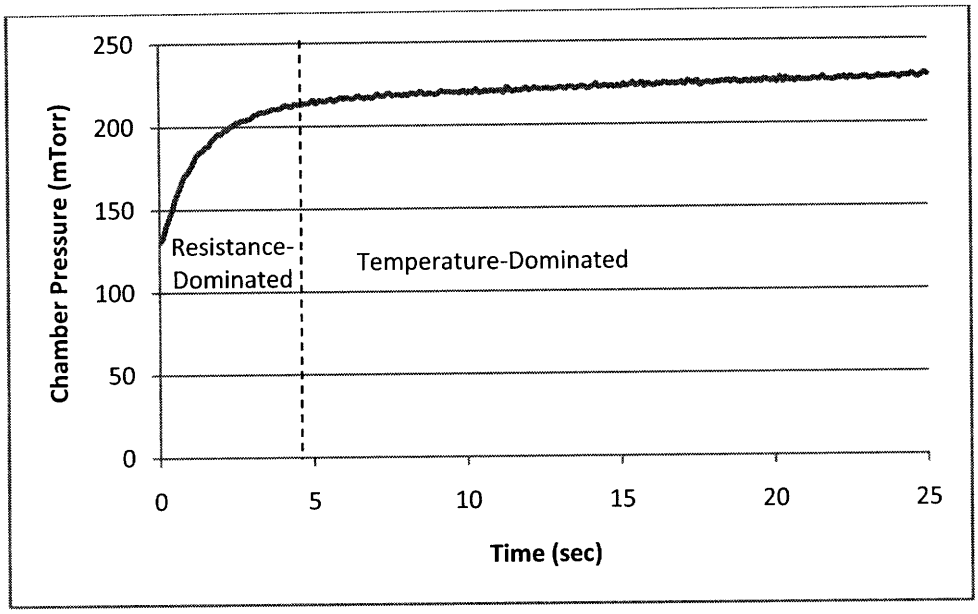

Figure 10: Sample pressure-rise data. (Data are from Run #4 described in Table 2 below)

There are three issues which can slow the development of the resistance-dominated (rapid-rise) region of the curve and thereby negatively impact MTM accuracy:

1) Low vial count (small sublimation surface area, A)
2) High chamber volume, V
3) High total resistance, R_P+R_S

Several investigators have identified limits for each of these parameters within which product temperature can be measured accurately with MTM.[41] These values were used as guidelines for the studies described below, and they must be considered carefully for any new stock-keeping unit (SKU; SKUs may vary by vial size, dose, etc.). For instance, if a new product formulation has an unusually high R_P, MTM may not be appropriate for product temperature measurement.

Finally, it is important to note here that MTM provides only one measure of product temperature, presumably some average temperature for all of the vials in the chamber. Hence, vial temperature heterogeneity can also impact MTM accuracy. It is generally accepted that temperature varies depending on a vial's position on the shelf: vials on the edges of a shelf are typically warmer due to

[41] (Gieseler, 2006), (Tang, Nail, & Pikal – Part I, 2006)

chamber wall and door radiation effects, and vials at the center of a shelf are cooler due to shielding from edge vials (**Figure 11**). Edge effects are reduced for larger (commercial) lyophilizers (lower ratio of edge vials to center vials and smoother internal equipment surfaces with less radiation), so this phenomenon is of greater concern at the laboratory and development scales.

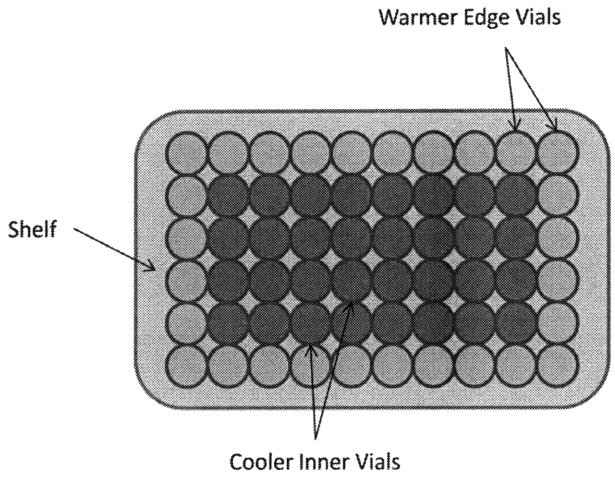

Figure 11: Edge effects on a lyophilizer shelf; vials closest to the edges of the shelf are slightly warmer than inner vials during drying due to radiation from the chamber walls and door.

Interestingly, Tang et al. have found that the MTM product temperature is heavily weighted towards the temperature of the colder, inner vials.[42] Thus, temperature heterogeneity is a critical consideration for MTM: because shelf temperature control is based on the center vials, there is a potential for edge vials to become too warm and cause collapse. Before applying MTM, an effort should be made to understand the temperature distribution across a shelf with temperature mapping and to minimize temperature heterogeneity by reducing edge effects (e.g., adding thermal shields).

5.2.2.4 Performing a Lyophilization Cycle Using SFD

The SMART Freeze Dryer ™ software employs MTM during a "Smart" run on the FTS LyoStar II laboratory-scale lyophilizer. First, the user inputs key parameters including the number of vials, fill volume, vial size, vial type, solution concentration, product type, excipient type, collapse temperature, MTM measurement duration (typically 25 seconds) and measurement interval (typically 60 minutes). Based on these inputs, SFD estimates cycle conditions, including *initial* primary drying

[42] (Tang, Nail, & Pikal – Part I, 2006)

conditions. The set points are automatically entered into the cycle recipe, which defines the sequence of steps to be executed during lyophilization. The recipe includes shelf temperature set points, chamber pressure set points, and temperature ramp rates for each phase of the cycle.

Once the cycle is initiated, the software automatically advances the equipment through each stage of lyophilization. When primary drying begins, the first MTM measurement is taken: the isolation valve is closed and the chamber pressure rise is measured for 25 seconds. The isolation valve is then re-opened, and the software fits the pressure-rise data to the MTM equation (Equation 1) to calculate product temperature at the sublimation interface. The software then makes any necessary shelf temperature adjustments to maintain product temperature 2-3°C below the collapse temperature. Product temperature measurement and shelf temperature adjustment occur during primary drying at the interval specified at the start of the cycle. SFD is able to determine the end of primary drying based on significantly reduced pressure rise. Once pressure rise falls off dramatically (i.e., once the frozen layer is gone and sublimation ends), SFD transitions the cycle to secondary drying.

The SFD software logs valuable MTM data during primary drying. These data include, for each MTM time point, a pressure rise curve and several "fit" or calculated values: product temperature (T_P), frozen layer temperature difference (ΔT), sublimation rate (dm/dt), vial heat transfer coefficient (K_V), frozen layer thickness (L_{icc}), and dried product resistance (R_p).

If product quality is deemed acceptable following the SFD run, the process conditions and times recorded during the cycle may become the new, optimal lyophilization recipe for that particular SKU. The SFD run may be repeated or conditions may be tested on a separate lyophilizer in order to confirm results.

5.2.2.5 Evaluation of SFD at Amgen

SFD technology has been available at Amgen since 2005,[43] but the system had not yet been fully tested and was not being used as of the start of this project. The purpose of this project is to evaluate the technology and confirm whether or not it would be a useful tool for cycle development and product temperature measurement. As a development tool, SFD could significantly reduce the

[43] (Gieseler, 2006)

amount of time required to develop an optimized lyophilization cycle for an Amgen product. In addition, MTM could eliminate the need for thermocouples during development and facilitate troubleshooting in the commercial space (MTM could provide a record of product temperature during every cycle, a feature not currently available in commercial lyophilization).

Approach

The SFD was tested using two different protein solutions. Both solutions had the same formulation, but while one used a mimic protein (Bovine Serum Albumin, BSA) the other solution used an Amgen protein product, here referred to as AMG-Z (masked). Prior to the start of these experiments collapse temperature, T_C, was determined experimentally for both protein solutions using DSC and freeze drying microscopy.

All experiments were done using the FTS Lyostar II laboratory-scale lyophilizer with SFD software installed. Five lyophilization cycles were run in total, as detailed in **Table 2**. Freezing and secondary drying conditions were pre-set for all runs based on the most recent AMG-Z cycle. During "Smart" cycles, the SFD software determined appropriate primary drying conditions during the run as described above. During the "Auto" cycle, all freeze drying conditions were pre-set (SFD was not used during the run). A full tray of either 50cc or 20cc vials was used for all except the first run. Three calibrated TCs, placed at the bottom of vials at the front, center, and back of each tray, were used to measure product temperature during every run.

Run	Material	Vial Size / Count	Cycle	Description
1	AMG-Z mimic (BSA)	50cc / 48	Smart	Test SFD software functionality
2	AMG-Z	50cc / 70	Smart	SFD cycle
3	AMG-Z	50cc / 70	Auto	Repeat of SFD-determined cycle for sublimation rate determination
4	AMG-Z	20cc / 153	Smart	SFD cycle for comparison with current cycle and 50cc
5	AMG-Z	20cc / 150	Auto	Repeat of SFD-determined cycle with sublimation rate determination

Table 2: Set of five lyophilization cycles used to test SFD performance.

Both "Auto" cycles were used to verify the results of the preceding SFD runs. For these runs, primary drying conditions were set based on the cycle determined during the corresponding SFD run. Then, a total of six pre-weighed vials were removed from the freeze dryer at regular intervals during primary drying. The vials, sampled in groups of two, were weighed to determine their change in weight from the start of the cycle and, over several time points, the sublimation rate. Once sublimation rate was determined, vial heat transfer coefficient, ice and dry layer thickness, dry product resistance, and product temperature were calculated manually using the equations in the Appendix. These values were then compared with the SFD calculations for the corresponding SFD run. If MTM is accurate, manual calculations should match SFD calculations, since both are based on sublimation rate and both apply the same heat and mass transfer theory.

Following lyophilization, all vials were visually inspected for cake quality and any signs of collapse. At the end of each run a group of vials was reserved for product quality and moisture content testing; however, due to time constraints, these assays were not completed as part of this project.

Results

The first experimental run in this series was intended primarily to demonstrate the functionality of the SFD software. The lyophilizer controlled the cycle as expected, performing freezing according to the pre-set recipe before proceeding to primary drying. The first MTM measurement was taken once chamber temperature stabilized, and the SFD software automatically adjusted shelf temperature to maintain product temperature below collapse. MTM temperature was below the collapse temperature and 2-8°C less than the thermocouple temperature for most of the primary drying period. The SFD software transitioned to secondary drying following the significant drop in MTM temperatures that indicates the end of primary drying.

The second run used a full tray of vials to ensure sufficient sublimation surface area for accurate MTM measurement (Tang et al. suggest a minimum of 150cm^2 for this chamber volume; 70 50cc vials provide a sublimation surface area of 857.5cm^2)[44]. **Figure 12** shows the graphic results for this run. Both MTM and TC measurements were below the collapse temperature for the duration of primary drying. MTM measurements were 3-4°C less than TC measurements due at least in part to the temperature difference across the frozen layer. The SFD software calculates the temperature at

[44] (Tang, Nail, & Pikal – Part I, 2006)

the sublimation interface (T_P) from sublimation rate data and the temperature at the bottom of the vial (T_b) from product resistance for each MTM measurement; for this run, the SFD's T_P values were approximately 3°C lower than the calculated T_b values. Therefore, there is a discrepancy of ~1°C between TC and MTM values that cannot be accounted for by the temperature difference across the frozen layer.

Another interesting finding from this run is that shelf set point during primary drying was considerably higher than that used during experimental cycles for this product. Product quality was confirmed visually following the run: cake structure was good in all vials (no evidence of collapse). These results suggest that primary drying conditions can safely be more aggressive (leading to shorter cycles) than is typically assumed during development.

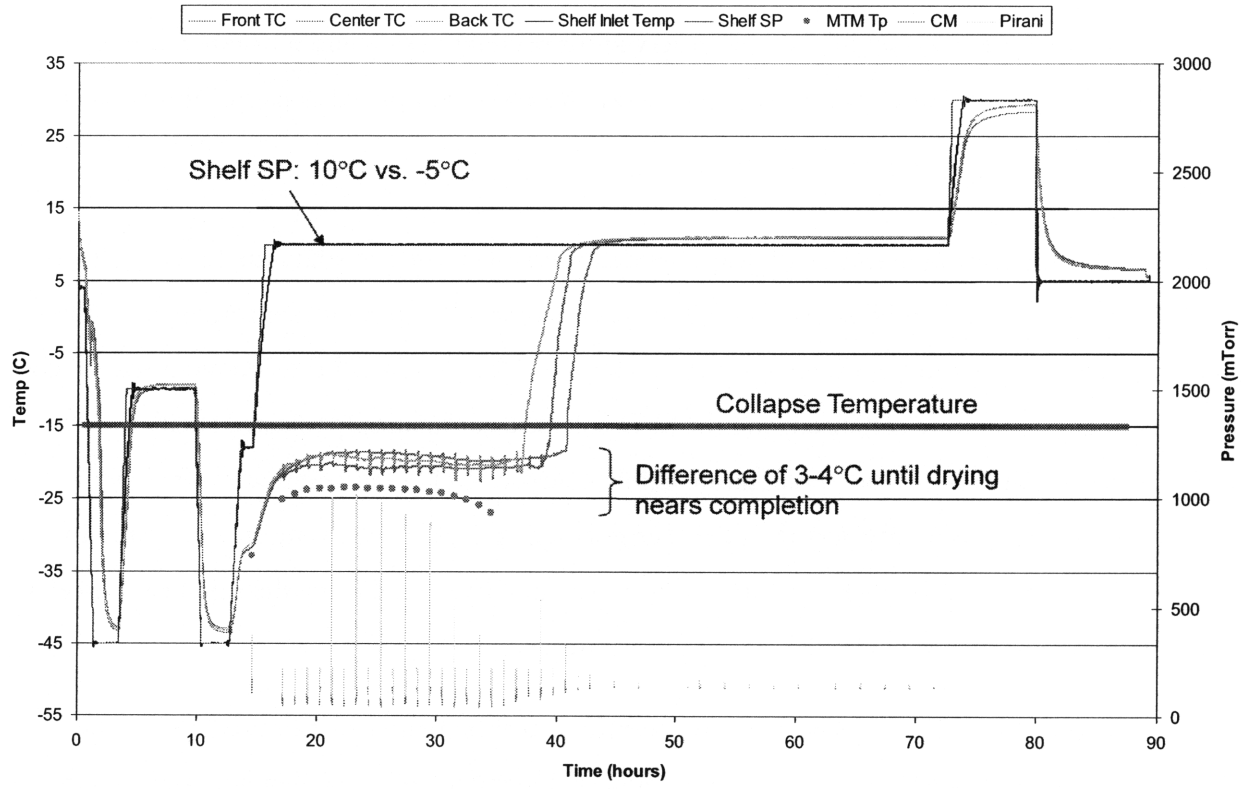

Figure 12: Lyophilization cycle data for Run #2. Compare MTM-determined product temperature (T_P) with thermocouple data at three different points on the tray (Front, Center, and Back TCs) as well as shelf temperature (Shelf Inlet Temp). [Chamber pressure data are also shown, measured with two different probes: a Pirani gauge (measures thermal conductivity) and a capacitance manometer (CM, based on physical displacement of a sensing diaphragm). Decline in the Pirani measurement to match the CM measurement typically signals the end of primary drying (complete

sublimation of unbound water). Both the Pirani and CM measurements show the chamber pressure interruption for each MTM measurement.]

The third run in this series was intended to confirm the results of the second run by manually measuring sublimation rate during primary drying and calculating product temperature and other key parameters using the relationships in the Appendix. However, the run was aborted immediately following the first sample due to an equipment malfunction. All of the pre-weighed vials were weighed again at the time the run ended, and an average sublimation rate between the start of primary drying and the point where the cycle stopped was determined. This value was used with the equations in the Appendix to provide the comparison in **Table 3**:

	MTM Calculation From Run #2	**Manual Calculation from Run #3**
Sublimation Rate (dm/dt)	0.46 g/hr/vial †	0.61 g/hr/vial
Product Temperature & Frozen Layer Difference (T / ΔT)	-23°C / 2.5°C	-22°C / 2.3°C
Vial Heat Transfer Coefficient (Kv)	2.9×10^{-4} cal/sec*cm^2*K ‡	3.0×10^{-4} cal/sec*cm^2*K
Product Resistance (Rp)	4.9 cm^2*Torr*hr/g ‡	9.3 cm^2*Torr*hr/g
Ice Thickness (L_{ice})	1.6 cm	1.5 cm

Table 3: Comparison of parameters calculated from MTM measurements during Run #2 with parameters calculated from manual sublimation rate determination (Run #3); values calculated based on time t=5h46min into primary drying, the point at which the cycle ended during Run #3. †Based on SFD-calculated change in mass at time t during Run #2 ‡Average of values collected between start of primary drying and t.

Some experimental error is likely for Run #3 given the equipment issues; however, the results are promising. Most of the parameters are comparable and some are quite close (e.g., frozen layer ΔT, and frozen layer thickness). While the frozen layer temperature difference is similar in both cases, the SFD-calculated product temperature is approximately 1°C cooler than the manually calculated product temperature. This matches the 1°C discrepancy between TC and MTM temperature data identified in Run #2. The comparison between SFD and manual calculations was repeated with experiments 4 and 5.

The fourth run in this series used 20cc vials rather than 50cc vials: the 20cc vial is a commonly used component, and it will ultimately be important to understand the impact of vial size on SFD performance (153 20cc vials provides a sublimation surface area of 889cm^2). **Figure 13** shows graphically the results of Run #4. As with the previous runs, the SFD software maintained MTM product temperature below collapse during primary drying. However, the MTM data were 4-5°C less than the TC data during that period. The temperature difference across the frozen layer calculated by the SFD for this run was 2-2.5°C, leaving a 2-2.5°C discrepancy with TC data. This discrepancy is greater than observed during Run #2 (approximately 1°C).

As with Run #2, drying conditions were more aggressive for this run than for the cycle currently being developed experimentally. Because higher temperatures were used, the duration of the cycle was 34% shorter than the fastest experimental cycle to date. Based on visual inspection following Run #4, product cakes were solid with no cracks, and there was no evidence of collapse.

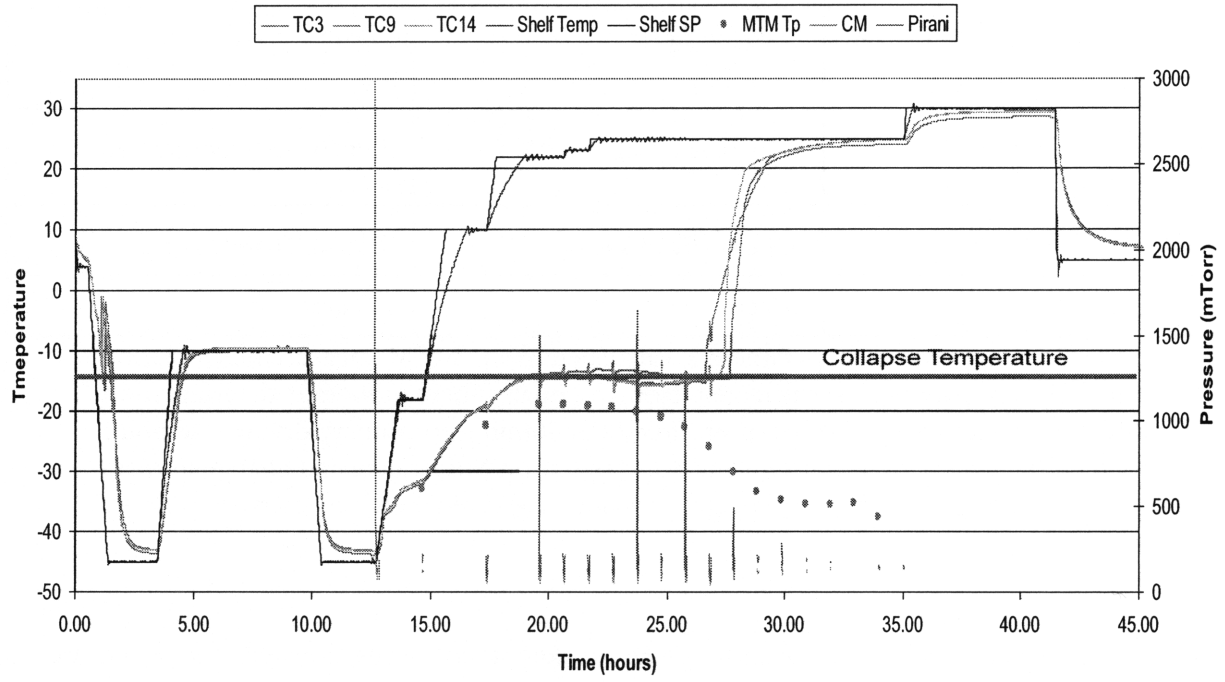

Figure 13: Lyophilization cycle data for Run #4. "TC3" was in a vial at the front of the tray; "TC9" and "TC14" were at the center and back of the tray, respectively.

The final run in this series was a verification of the MTM calculations for Run #4. As with Run #3, the lyophilizer was run in "Auto" mode using the primary drying conditions from the preceding

"Smart" cycle, Run #4. All pre-weighed vials were successfully removed at their respective timepoints, and a sublimation rate was estimated from their change in mass from the start of the cycle. The sublimation rate was used along with the equations in the Appendix to provide the comparison in **Table 4**.

	MTM Calculation From Run #4	**Manual Calculation from Run #5**
Sublimation Rate (dm/dt)	0.50 g/hr/vial	0.57 g/hr/vial
Product Temperature & Frozen Layer Difference (T / ΔT) †	-20.4°C / 1.9°C	-17.2°C / 1.3°C
Vial Heat Transfer Coefficient (Kv)	$3.2x10^{-4}$ cal/sec*cm^2*K	$4.6x10^{-4}$ cal/sec*cm^2*K
Product Resistance (Rp)	7.8 cm^2*Torr*hr/g	8.9 cm^2*Torr*hr/g
Ice Thickness (L_{icc}) †	0.86 cm	0.42 cm

Table 4: Comparison of parameters calculated from MTM measurements during Run #4 with parameters calculated from manual sublimation rate determination (Run #5). †At t=9.9hrs into primary drying.

Table 4 demonstrates that while the SFD-based calculations are once again comparable to the manual calculations, there are still some discrepancies that need to be resolved in order to improve the accuracy of MTM measurements. Most notably, the difference in the two product temperatures mirrors the 2-2.5°C discrepancy between TC and MTM values identified during Run #4 with the MTM temperature being lower than expected.

Discussion and Conclusions

Based on these preliminary studies, the SFD software is capable of predicting and controlling primary drying conditions to produce an elegant lyophilized product cake with no visual signs of collapse. SFD technology also has the potential to shorten lyophilization cycles by using more aggressive drying conditions. While it is certainly possible to use more aggressive drying conditions when developing a cycle by the traditional experimental method, the SFD provides a more direct path to the optimal cycle because it can adjust drying conditions real-time while monitoring actual

product temperature. While the traditional approach to lyophilization cycle development for a given Amgen SKU requires about ten experimental cycles, the SFD may ultimately reduce this number to one (plus a verification run). The result is an 80% reduction in resource and time requirements for this stage of process development. These savings agree with findings reported by Sesholtz and Mather at SP Industries.[45]

Although SFD technology is promising, this project demonstrated that the accuracy of MTM as performed on this particular set of equipment needs to be improved. Specifically, the differences between MTM and TC measurements are greater than expected. Sublimation surface area, chamber volume, and product resistance all fell within the limits established in the MTM literature, so other factors impacting MTM accuracy must be considered. The discrepancy could be due in large part to shelf-temperature heterogeneity. As Tang et al. described, MTM reflects the temperature of the coldest vials on the shelf.[46] So, if shelf temperature is uneven, the MTM reading would be lower than the average TC reading (when TC reading is corrected for the temperature differential across the frozen layer). This could explain why MTM values are consistently cooler than expected. Tang et al. observed a difference of up to 4°C over one similarly-sized shelf [47]; performing shelf-temperature mapping for the FTS Lyostar II should be helpful in resolving this issue. In addition, thermal shields could be applied to reduce edge effects for future SFD runs. Though less likely, other factors that may impact MTM accuracy include vial geometry and stopper resistance. These issues should also be investigated if decreasing vial temperature heterogeneity does not eliminate most of the error in MTM measurements.

SFD technology is one example of a PAT tool that can be applied during process development as a part of Quality by Design implementation. SFD can be used to better understand and optimize the lyophilization process for each SKU; it can also streamline the development process. SFD may have future applications in commercial production as well. If the software required for MTM could be installed in and validated for commercial-scale lyophilizers, it would allow real-time process monitoring of a critical process parameter, product temperature. Though this application is far from realization, it is one option to consider as regulatory expectations and quality systems evolve.

---

[45] (Sesholtz, Debra; Mather, Leslie, 2007)

[46] (Tang, Nail, & Pikal – Part I, 2006)

[47] (Tang, Nail, & Pikal – Part I, 2006)

Quality by Design in Process Development is focused on creating design space, a thorough understanding of the relationships between process parameters and product quality attributes. Design of Experiments and PAT tools such as SFD allow a more complete, systematic investigation of these relationships and streamline the process by which data is gathered. Knowledge gained during this stage of commercialization can be used to demonstrate process understanding to regulatory agencies, to enable operational excellence later in commercialization, and to make real-time quality (rather than post-mortem analytics and end-product inspection) possible. Process understanding can also be applied across the product pipeline, simplifying the development process for subsequent products. QbD in Process Development positively impacts the business with improvements in both cycle time and quality.

5.3 Technology Transfer

Technology Transfer is another element of commercialization that is impacted by QbD. The primary concern when transferring a process between scales and sites is ensuring the comparability of the product. Specifically, a manufacturer must demonstrate that the material produced at the commercial scale is comparable to the material produced at the clinical scale (supplying material for clinical trials) in order for the clinical trial data to be relevant for commercial product.

Various process parameters can change across sites and scales; these include batch size, equipment configuration and performance, and procedures. Differences are minimized wherever possible; where differences remain, however, the design space created during Process Development would allow for the prediction and minimization of any product impact. Hence, QbD has the potential to streamline technology transfer and ensure product comparability.

5.3.1 Applying QbD to Technology Transfer

An important element of QbD in Technology Transfer is understanding the differences in production equipment between scales and sites. Equipment design and performance can vary for a number of reasons; for instance, commercial equipment is likely to be different from pilot or clinical equipment because of the scale required for production. Also, costly equipment may be adopted for a given product based on its availability (e.g., in a lab or at a contract manufacturing site) rather than its design. In many cases identifying and closing scale-to-scale and site-to-site gaps in equipment (and procedures) are possible and can help streamline Technology Transfer. However, both the cost

of capital equipment and the cost of validating that equipment for drug manufacture often make upgrades prohibitively expensive. In these cases, QbD can be applied by thoroughly characterizing equipment and then applying that knowledge to create a scale-down model, which can be used to predict the impact of equipment differences on product quality (See Deep Dive #2, Section 5.3.2). In-depth knowledge of the various equipment and its limitations ultimately contribute to design space.[48]

QbD also allows a reassessment of the amount of site-specific work done during Technology Transfer, including process validation. Under the traditional approach to Technology Transfer, a variety of characterization and robustness studies would be performed at the receiving site (e.g., the commercial site) to confirm that the process functions within the required boundaries and is repeatable. These studies are typically done at full-scale, consuming considerably more raw materials, time, and resources (including equipment) than studies done at the pilot scale. The product from these development batches is typically not acceptable for commercial sale. Also consuming time and resources is process validation, which is a requirement for FDA approval and has in the past involved successfully producing three consecutive batches within specifications. Under Quality by Design, design space will allow enhanced prediction of the impact of scale-to-scale and site-to-site differences at the pilot scale with fewer commercial-scale studies. In fact, recent FDA guidance supports a new approach to validation complementary with QbD: the agency has shifted its focus from validation by testing at the commercial scale to validation through demonstrated process understanding and ongoing process control.[49] Consequently, it may be possible to eliminate much of the site-specific work done currently once QbD has been implemented.

The cost of applying QbD in Technology Transfer as described above is primarily the one-time cost of equipment characterization. The resulting knowledge, when incorporated into the design space created during Process Development, offers several benefits. First, because the impact of process parameters on critical quality attributes is well understood, the risk of the transfer to product quality is significantly reduced. Reduced risk translates into simplified comparability assessments with less regulatory oversight. In addition, QbD would help streamline Technology Transfer by reducing the

[48] (Nail & Searles, 2008)

[49] (Bush, 2008)

amount of site-specific work done, thereby providing a further reduction in material costs, resource requirements, and timelines.

Quality by Design can have further impact to Technology Transfer by enabling knowledge sharing and communication between stages of the commercialization process (knowledge management is discussed further in Section 5.5). Specifically, knowledge of equipment design, capability, and availability across the manufacturing network can help to guide decisions during Molecule Selection and Process Development, thereby simplifying later transfer of product and process into a commercial facility.

5.3.2 Example: Lyophilization Scale-Down Gap Assessment (Deep Dive #2)

The purpose of this deep-dive analysis is to evaluate the existing gaps in materials, equipment, and procedures for one unit operation, lyophilization, across several sites and scales. A thorough understanding of existing gaps is essential to creating an accurate scale-down model for Technology Transfer. This example also includes a retrospective case study estimating the potential impact of applying a scale-down model during transfer from clinical to commercial production.

5.3.2.1 Background: Scale-Down Models

Scale-down models (also referred to as scale-up models, depending on the application) integrate information from process development with in-depth knowledge of commercial equipment to determine how a change in scale impacts product quality. That model can in turn be used to determine appropriate measures for eliminating the impact following technology transfer. For instance, certain heat transfer characteristics such as vial heat transfer coefficient (K_V) and chamber wall emissivity (ε_{wall}) are unique to a set of lyophilization equipment and impact the performance of a lyophilization cycle. If the equipment-specific parameters are known for both the pilot lyophilizer and the commercial lyophilizer, then it is possible to simulate the commercial process by running the planned commercial cycle on the pilot lyophilizer and adjusting the results (including product temperatures) based on known heat and mass transfer relationships. Such studies require less material and fewer resources but provide much of the same information as characterization at the commercial scale. Consequently, they reduce the risk inherent in Technology Transfer and provide an opportunity to reduce the amount of site-specific development work.

Scale-down models are commonly used at Amgen in upstream (cell culture) and downstream (protein purification) process transfers, however they are not as widely used for fill/finish processes including lyophilization. This gap analysis could highlight areas of opportunity to improve the validity of scale-down models for lyophilization. Key business drivers for the gap analysis include enhanced process knowledge, enabling both QbD and Operational Excellence, and alignment of processes between sites and products to ensure consistency and quality.

5.3.2.2 Approach

The gap analysis focused on the lyophilization process, capturing as much data as possible relating to equipment design and performance, procedures, and raw materials at three different scales. Data were obtained through interviews, direct observation, and documentation (e.g., manuals, qualification reports, and technical reports). It was important to capture not only similarities and differences but also areas where data could not be obtained or did not exist. Results were compiled according to **Table 5** and **Table 6**.

	Pilot Scale	**Clinical Scale**	**Commercial Scale**
Raw Materials	(2 Lyophilizers)	(1 Lyophilizer)	(2 Contract Sites; 6+ Lyophilizers)
Components			
Equipment Design			
Equipment Performance			
Procedures			
Product Quality			

Table 5: Overview of data collected during gap analysis.

Category	Data Collected	Data Type
Raw Materials	supplier; source	material
Components	supplier; vial size and type; stopper size, type, and formulation	material
Equipment Design	physical specs; controls; equipment-specific parameters (e.g., K_V)	equipment
Equipment Performance	shelf temperature, condenser, and vacuum system performance	equipment
Procedures	cleaning & sterilization; stoppering	procedure
	loading; capping	equipment
Product Quality	spots & streaks; cake characteristics	material / procedure

Table 6: Data collected for each category; "Data Type" is included in order to simplify later analyses.

The gap analysis also included a case study relating to a historical Technology Transfer for one product between two sites. The case study was done based on interviews with and data provided by Amgen personnel directly involved with the transfer. The actual number of site-specific studies done was compared with the number of site-specific studies that would have been required if there had been an accurate scale-down model in place.

5.3.2.3 Results

In assessing the results of the gap analysis, it is valuable to divide the six data categories into two groups: material- and procedure-specific data and equipment-specific data, as in **Table 6**). Any discrepancies or gaps identified in the former group represent changes that could be controlled through alignment; although considerable effort would be required to ensure consistency in materials and procedures across sites and scales, alignment could be done in a step-wise, systematic fashion. Any discrepancies identified in equipment-specific data, however, are more difficult to resolve due to the high cost of capital equipment. Such issues could be addressed instead using scale-down models.

Material- and procedure-specific data were available for all scales; however the information was spread across a wide variety of sources (both individuals and functional groups) and was not

straightforward to access. As an added complication, components and procedures varied across products. Most of the gaps identified were between the pivotal (final clinical) and commercial scales and were related to components and procedures. Raw materials were generally consistent across scales, as they are governed by Amgen specifications. While alignment of all materials and procedures will ultimately help streamline Technology Transfer, the results of the gap analysis highlight two key material- and procedure-specific inputs to a scale-down model: components (e.g., vial size and stopper type) and procedures that can result in quality issues such as spots and streaks. These will be the most important gaps to close when improving the accuracy of the model.

Further knowledge gaps were found during the collection of equipment-specific data. Equipment characterization data were incomplete at all scales, but the greatest knowledge gaps were at the pilot and clinical scales. While commercial equipment is often characterized as part of validation efforts, pilot and clinical equipment undergo less formal characterization. Particularly at the pilot scale, equipment performance is learned experientially and not necessarily documented as products proceed through the pipeline. While the equipment varies almost unavoidably in design and performance across scales and sites, a key finding from the gap analysis is that validation and characterization methods and criteria also vary across sites. Standardizing the approach to characterization for non-commercial equipment and filling in the knowledge gaps identified in this analysis will ultimately streamline Technology Transfer, because an understanding of equipment design (e.g., size, capacity, heat transfer coefficients, and emissivity) and performance (e.g., temperature and pressure control) is necessary for valid scale-down models.

Much of the analysis described above focused on identifying the gaps that currently limit scale-down models for lyophilization. Another important aspect of this deep dive project was to identify business drivers for filling those gaps. The potential benefit of scale-down models was estimated through an evaluation of a historical technology transfer of the fill/finish process to a commercial-scale contract manufacturing facility. This particular transfer involved four different kinds of site-specific studies: machinability (testing that equipment physically handles product and vials correctly), validation (in this case, equipment verification), robustness (challenging process operating parameters) and engineering/shake-down ("rehearsing" for commercial production). Of these, robustness runs are the most flexible – they serve to mitigate risk, simply verifying that pilot-scale results also apply at the commercial scale. Since a validated scale-down model would serve the same

purpose, there is an opportunity to remove most of these robustness studies in a similar transfer in the future. According to subject matter experts, five robustness runs were carried out during the actual transfer; under QbD, with scale-down models in place, the same transfer would likely have required only one robustness run. Savings would be on the order of hundreds of thousands of dollars in resources and raw materials, and about one month would be removed from the transfer timeline.

5.3.2.4 Discussion & Conclusions

The lyophilization scale-down gap assessment demonstrated that the majority of current gaps are related to equipment, particularly knowledge gaps at the pilot scale. While it may be possible to align materials, components, and procedures to help streamline technology transfer, fully understanding differences in equipment will allow further streamlining by improving the accuracy of scale-down models. Because the same pilot scale equipment is used for a large number of products over the product pipeline, a one-time investment in equipment characterization can benefit multiple products.

Standardizing components and procedures as much as possible (e.g., through a platform), filling existing equipment knowledge gaps, standardizing equipment characterization procedures at all scales, and developing accurate scale-down models for the fill/finish process are very specific steps towards applying QbD principles to Technology Transfer. The result will be to simplify Process Development efforts through standardization and design space creation, improve scale-down models to reduce site-specific work, and improve homogeneity in CQAs across sites. Ultimately, when incorporated into the marketing application, proof of standardization and equipment characterization help demonstrate process understanding to regulators.

This deep dive analysis highlights just one area where steps are being taken to incorporate QbD principles into Technology Transfer. The example demonstrates some of the most important investment areas, specifically in equipment characterization, and some key operational and economic benefits, specifically more rapid and less expensive transfers. Similar benefits have already been achieved by applying QbD principles in the transfer of upstream (cell culture) and downstream (purification) processes. Overall, QbD in Technology Transfer positively impacts the business through faster cycle times and reduced costs.

5.4 Marketing Application & Commercial Production

The final stage of the commercialization process involves not only manufacturing product at the commercial scale but also demonstrating full product and process understanding and control to regulatory agencies in order to gain marketing approval for the drug. The marketing application (for biotech products, the biologic license application, BLA) is a compilation of the drug's clinical data as well as product and process characterization data. When regulators are confident that the drug itself is safe and can be made safely and reproducibly, the drug can be released to the market. It is during this phase of commercialization when much of the knowledge gained through the application of QbD can be employed to yield the most significant operational and economic benefits.

5.4.1 Applying QbD to Marketing Application & Commercial Production

The primary benefit of QbD in Marketing Application & Commercial Production is the creation of a robust and capable process through investments in product and process development made at earlier stages of commercialization. However, QbD principles can be applied during the final stage of commercialization as well.

Incorporating QbD principles into the BLA is one of the most obvious applications of QbD in this stage of commercialization, since regulatory requirements are a strong external driver for QbD. Without QbD the CMC section of the BLA would primarily describe and define the product and process, often including acceptable operating ranges but lacking a full exploration of interactions. Conversely, a QbD filing should include all of the data necessary to demonstrate full understanding of critical quality attributes and their relationships with process parameters. Under a comprehensive QbD program, a company might develop a standard filing template that captures and presents all of the necessary information to successfully demonstrate understanding. Participation in the FDA Office of Biotechnology Products' pilot program would be exceedingly helpful in determining what the template should look like, as it provides an opportunity to work directly with regulators and to help shape their expectations.

Another important application for QbD in Marketing Application & Commercial Production is the use of PAT in manufacturing. PAT tools have the potential to shift off-line, lab-based process assays to at-line or in-line measurements, allowing critical quality attributes to be monitored real-time. For instance, near-infrared spectroscopy (NIR) is being developed to measure biomass,

product titer, and nutrient levels during cell culture.[50] This and other advanced technologies are currently in development for a variety of bioprocess unit operations, and measurements will ideally be integrated into existing control systems. The overall result should be a shift from reactive, off-line, post-mortem analytics to real-time control.

Creating a "QbDed" filing template and applying PAT tools in Marketing Application & Commercial Production have a number of operational and strategic benefits. First, incorporating known relationships between CQAs and CPPs into the CMC section of the BLA in the form of design space will help to demonstrate process understanding to regulators (increasing the likelihood of marketing approval) and lead to greater process flexibility than is typical for this industry. Prior to QbD, a manufacturer would file "acceptable" operating ranges for each process parameter; ranges were relatively narrow, and regulatory approval would be required before a process parameter could be shifted outside of the filed "acceptable" range. With QbD, while the operating ranges for most parameters may remain relatively tight, only the design space, which is much broader, is filed in the BLA. As a result, a manufacturer should be able to shift the operating space anywhere within the design space without further regulatory approval. Hence, a QbD filing can provide the necessary flexibility to further optimize commercial processes and facilitate Operational Excellence.

Finally, the application of PAT tools in combination with risk management could significantly enhance product disposition performance. With design space in place, monitoring CPPs during production should be sufficient to ensure end-product quality: it may ultimately be possible to eliminate 100% end-product inspection and transition to real-time product release. Hence, QbD not only improves product quality through more well-understood processes, but it simplifies the operational demands of quality control.

5.4.2 Example: Multivariate Statistical Process Monitoring

Multivariate statistical process monitoring (MSPM) is one PAT tool finding increasing application in biopharmaceutical manufacturing. MSPM uses statistical software and historical process data to create a model that links process parameters to critical quality attributes and highlights those variables most likely to result in process deviations and product quality issues. MSPM is a means of efficiently monitoring multiple process variables at once, as it reduces a large number of variables to

[50] (Davies, 2006)

a few summary variables.[51] Once a model is in place, MSPM can be used to monitor batches in real-time, predicting outcomes and rapidly identifying any potential deviations.

Real-time data used for MSPM may come directly from installed equipment (e.g., existing pH and temperature sensors or newer optical cell density sensors). Real-time data may also be obtained through virtual sensors, or "soft sensors", which combine the measurements from installed hardware using the process model to predict parameters such as product titer. These data can all be monitored via summary variables during a batch; when a deviation is detected, one or two mouse clicks in the MSPM software are sufficient to dig down to the specific parameter causing the deviation.

MSPM is currently being implemented for upstream and downstream operations at more than one Amgen manufacturing site, making use of the abundant historical data available from long-running processes. Though implementation is still in early stages, the teams developing MSPM at Amgen have already demonstrated significant benefits to the technology. These benefits, summarized in Table 7, include enhanced process understanding, real-time prediction of process performance, earlier identification of any issues, and rapid troubleshooting. Planning for and implementation of MSPM does require an initial investment in resources and software; maintenance and licensing fees require a smaller, on-going investment. However, the total cost of MSPM over a 10-year period is less than $1M; with only a few examples of the benefits of MSPM (specifically Troubleshooting), Table 7 shows that MSPM can rapidly return that investment.

Benefit of MSPM	Example
Real-time prediction of process performance	Predicted product titers within 10% of actual
Earlier identification of process deviations	Contamination event identified 3 hours earlier than by operators
Rapid troubleshooting	Potential for multi-million dollar savings in lost product for identifying root cause of a series of low-yield batches (historical example)

Table 7: Benefits of MSPM in manufacturing; examples are only a small number of those identified by the team currently developing MSPM at one Amgen manufacturing site.

[51] (Undey, June 2-4, 2008)

MSPM is an incredibly flexible PAT tool. As process technology evolves, MSPM can include not only in-process data but also raw material data and other parameters critical to product quality. MSPM will ultimately provide a holistic view of the process. MSPM is also a critical element in the approach to process control under QbD. Linking MSPM back to the process through a control system will allow automatic feedback to the process in the event of a deviation; any issues can be identified and corrected before they impact the product. As shown in **Figure 14**, such an adjustable process can improve product consistency. Further, because MSPM can provide real-time assurance of product quality, it may ultimately support real-time release.

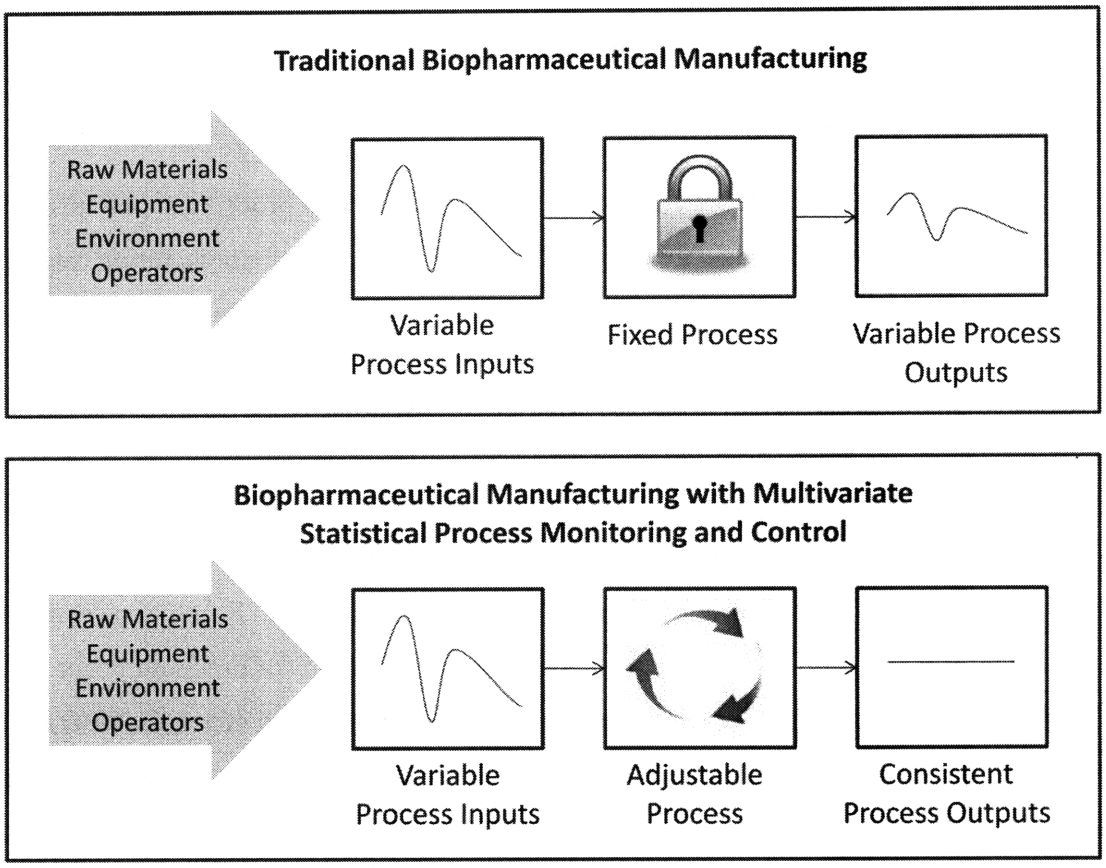

Figure 14: Impact of MSPM on biopharmaceutical manufacturing process (adapted from Undey, June 2-4, 2008).

MSPM is currently being applied locally at manufacturing sites with great success. However, additional value could be achieved through alignment with activity earlier in the product lifecycle, particularly in Process Development. Manufacturing can provide lessons learned and valuable process data, while development functions can expand process understanding and lead the

development of new process technologies. Thus, knowledge sharing between these two stages of commercialization will play a key role in both improving existing processes and enhancing process monitoring and control for future products.

5.4.3 Additional Benefits from QbD

During the course of the business case project, several additional areas where QbD is expected to have a measureable impact on Marketing Application & Commercial Production were identified. These particular topics are highlighted in the business case, because the impact of QbD for each has been debated both internally and externally; the goal of these analyses, though they are not exhaustive, is to help align expectations for QbD.

5.4.3.1 Reduction in Non-Conformances

In Operations, non-conformances (NCs) are deviations from established procedures or expected outcomes related to clinical or commercial product. NCs may result from manufacturing, supply chain, or laboratory activities (among others). For instance, out-of-specification (OOS) laboratory results, batch contaminations, and an operator's failure to follow standard procedures would all result in an NC.

NCs are classified according to the potential impact to the product. Class 1 NCs have little to no impact to the product and often simply must be documented. On the other end of the spectrum, Class 3 NCs have high product impact and often require a full investigation. Resolution of an NC involves a thorough investigation of the issue with a detailed justification for product impact determination. The cost of non-conformances increases as the classification increases; costs include administrative costs for documentation, resource costs for investigation and resolution (including laboratory work where necessary), and accumulation of inventory during NC resolution (product cannot be released until NCs are resolved and there is determined to be no product impact).

In theory, the number of NCs could be significantly reduced under QbD because of improved process control and the flexibility provided by design space. For instance, what may typically be considered an OOS process parameter may still fall within design space, and would therefore not require an NC (or would require an NC with a lower classification). The impact of QbD on the number of NCs was evaluated as a part of the business case. First, a detailed review of Class 2 and

Class 3 NCs for all products over the previous one-year period was performed. Class 1 NCs were not evaluated here primarily because of their comparatively low cost. Each NC was carefully evaluated for potential QbD impact based on the following set of assumptions:

- If an NC was due to a lack of process understanding, QbD would have had an impact.
- OOS results and process parameters *may* not have resulted in an NC under QbD if the data was within design space or if the issue could have been identified earlier.
- NCs with the root cause "Human Error", resulting from failure to follow standard procedures, could not have been prevented by QbD.
- Equipment malfunction/failure could not have been prevented under QbD.
- Contaminations may not have been prevented under QbD alone, but they may have been discovered more rapidly (less time spent continuing to process a contaminated batch).

Using these criteria, NCs were sorted into two categories: those with potential impact from QbD and those without. Those that may have been impacted by QbD were further divided into three subcategories:

- Type A: QbD would have prevented the event
- Type B: Event would have still occurred, but the result would have been within design space; NC classification could be reduced from Class 2 or Class 3 to Class 1
- Type C: Event would have still occurred and the NC classification would not change, but the overall impact of the event would be reduced

Potential cost avoidance was determined for Type A and Type B NCs based on an internal Cost of Quality model. Only NC process costs (administrative costs) were included; the costs of scrap and any studies required for resolution were much more difficult to estimate. Similarly, cost avoidance from Type C NCs could not be estimated as part of this analysis.

Results of the NC analysis are shown in Figure 15 below. Approximately 7% of the NCs evaluated represent events that could have been prevented under Quality by Design. Similarly, 8% of NCs could have been classified as Class 1 rather than Class 2 or Class 3.

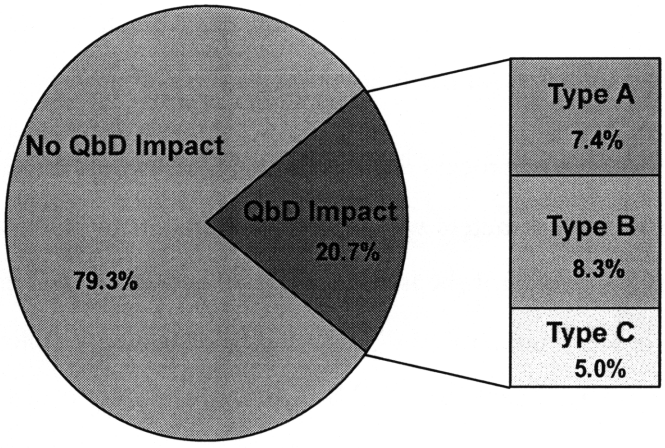

Figure 15: Analysis of Class 3 and Class 2 NCs from April 2007 to March 2008

Overall administrative cost avoidance for NCs under QbD was on the order of several hundred thousand dollars. These results, including the 7% overall reduction in NCs, are less than expected, however it is important to consider the potential savings that were not included in this analysis. The costs of scrap, inventory accumulation, and stability or comparability studies required for NC resolution, though difficult to estimate, are likely much higher than administrative NC costs. Additionally, better process understanding under QbD has the potential to simplify NC investigations, thereby reducing costs further.

Although the business case demonstrates that QbD should have some impact on the number of NCs annually, recent efforts by the Quality group to improve the NC process have had a far greater impact on reducing the number of NCs. However, the results of this analysis are important to the business case, because they help align expectations for QbD and focus attention on the areas that will see the greatest impact from QbD.

5.4.3.2 Reduction in Post-Marketing Regulatory Submissions

Thus far the business case has focused on one regulatory filing, the initial marketing application or BLA, in examining the Marketing Application & Commercial Production phase of commercialization. However, any changes made to the drug product or process after the BLA is approved must also be filed with the FDA. Changes filed for approval are generally known as post-

marketing regulatory submissions (here referred to as PMRSs). There are four types of PMRSs, which depend on the change the manufacturer plans to make and the magnitude (major, moderate, or minor) of the potential impact to product's identity, strength, quality, purity, or potency as they relate to product safety and effectiveness.[52] Each type of supplement is described in the United States Code of Federal Regulations, Title 21, Section 601.12, "Changes to an approved application" (21 CFR 601.12); these are summarized in **Table 8** below.

Type of Supplement	Description	Examples
Prior Approval Supplement (PAS)	For major changes; approval from the FDA must be obtained before product made with the change can be released.	• Changes in formulation • Changes that impact product sterility assurance • Changes requiring clinical trials • Changes in cell line
Changes Being Effected In 30 Days (CBE-30)	For moderate changes; supplement must be submitted at least 30 days prior to product release – if during this period FDA review deems the submission not in compliance, product cannot be distributed until the change is ultimately approved.	• Changes in production scale requiring different equipment • Replacement of equipment with similar but not identical equipment • Relaxation of acceptance criteria
Changes Being Effected (CBE)	For moderate changes; product may be released upon receipt of the submission by the FDA	• Addition of specifications to ensure product safety and effectiveness • Changes in labeling to include warnings or contraindications
Annual Report	For minor changes; changes are compiled in a single report submitted to the FDA annually on the anniversary of product approval	• Removal of an ingredient impacting product color only • Change in the closure system for a non-sterile product

Table 8: Types of post-marketing regulatory submissions as defined by the FDA.[53]

[52] (21CFR601.12, 2008)

[53] (21CFR601.12, 2008)

The current CFR already excepts certain types of changes from having to file a PMRS when the change has been provided for in the original BLA. Consequently, a manufacturer could achieve greater flexibility for changes by including design space in the original BLA. Additionally, to match its growing emphasis on QbD, the FDA may ultimately downgrade certain categories of changes from requiring FDA pre-approval to simply requiring FDA notification.[54] By eliminating the need to file or by downgrading certain changes, QbD has the potential to provide savings to drug manufacturers by shortening or eliminating a waiting period (and the resulting accumulated inventory), reducing the cost to file (including administrative work and any supporting studies), and accelerating change implementation (specifically with respect to process improvement).

The impact of QbD on post-marketing regulatory submissions was evaluated as a part of the business case. Rather than reviewing all Amgen PMRSs (several hundred), a single product was chosen that would be representative of other Amgen products as well as Amgen's PMRS process and provide a large pool of data. Only US (FDA) submissions were considered in this analysis due to time constraints; however, any process changes filed to one regulatory agency would need to be filed with all other regulatory agencies where the product is sold (for instance, changes to a product sold in Europe would require filing a submission with the European Medicines Agency, EMEA). It is important to note that additional costs are incurred when filing outside of the US, as many of these agencies charge a per-submission fee rather than the annual fee for submissions in the US.

All US submissions for the selected product between 2000 and 2008 were reviewed, and the potential impact of QbD on each was determined with the assistance of subject matter experts familiar with both the PMRS process and QbD principles. These historical PMRSs were sorted for QbD impact based on the type of change and whether or not the change may have been included in design space, had the original BLA included design space. Cost avoidance was estimated based on the cost to prepare a PMRS (cost per page). As with NCs, the costs of inventory accumulation and any supporting studies could not be estimated here, but they are likely to be significant. Results are summarized in Figure 16.

[54] (Wechsler, 2008)

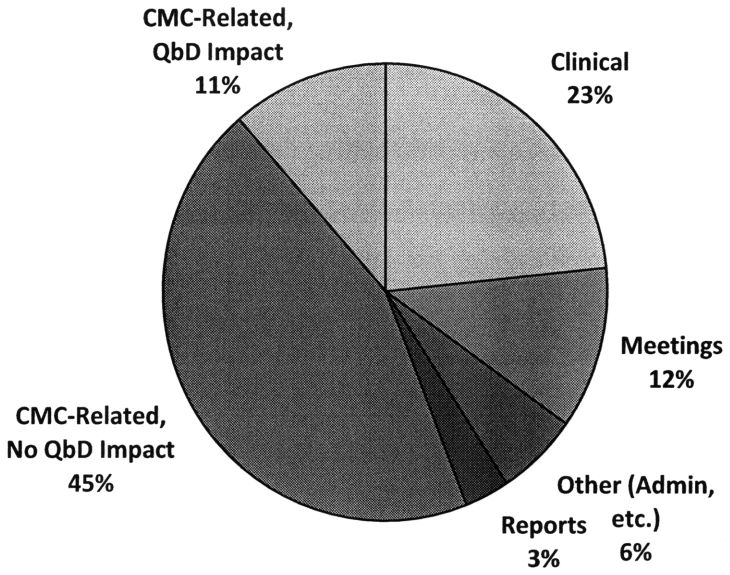

Figure 16: Classification of historical PMRS by QbD impact. Only those submissions related to the chemistry, manufacturing, and controls (CMC) section of the original marketing application were relevant for the QbD business case. The remaining submissions were related to clinical studies, meetings with the FDA, and other non-CMC activities monitored or mandated by the FDA.

Overall, when these results are extrapolated to include all products, 11% of US PMRSs could have been prevented with an approved design space. Administrative savings from preparing PMRSs would be on the order of several hundred thousand dollars, based on the per-page cost of submission preparation. Savings do not include the cost of accumulated inventory waiting for FDA approval for a change. Savings also do not include the costs of any stability or comparability studies that would need to be submitted to support certain types of changes. As with the NC analysis, the results of the PMRS analysis underestimate the overall financial impact of QbD, but they do provide an order-of-magnitude estimate around which the organization can align its expectations.

5.4.3.3 Reduction in Complaints

One final aspect of Marketing Application & Commercial Production likely to be impacted by QbD is product complaints. Quality by Design involves building quality into the product through the entire commercialization process, so complaints should decrease significantly as a result. Complaints from end users (e.g., patients and physicians) are tracked carefully at Amgen. At the time the business case was being developed, delivery systems (such as syringes) accounted for the

greatest fraction of total complaints. The analysis described below presumes that implementing QbD in development can eliminate nearly all delivery system failures.

To estimate the potential impact of QbD, a representative delivery system was selected, and all complaints related to that system since its launch were tabulated. The cost of complaints was estimated based on an internal Cost of Quality model. As with non-conformances, complaints are categorized by severity, and the cost of the complaint increases with severity (i.e., as investigation time increases).

The total cost of complaints for this particular delivery system since its launch was on the order of several million dollars. Amgen can realize these savings for its next delivery system by implementing a more systematic approach to device development, which would primarily involve adjusting existing business processes at minimal additional cost. Hence, while much of the focus for QbD in biopharmaceuticals is on guaranteeing drug quality, QbD can be applied in another arena to significantly reduce quality issues and their considerable costs.

The four examples described above (MSPM, NCs, PMRSs, and complaints) demonstrate how many of the benefits to applying Quality by Design earlier in the commercialization process are realized during Marketing Application & Commercial Production. Most importantly, QbD yields a robust process capable of delivering a high quality product. Additional operational and economic benefits can be achieved through modified regulatory filings and the application of PAT tools. Finally, specific measures of process robustness, flexibility, and quality such as NCs, PMRSs, and complaints will likely show measurable improvement under QbD. Together, these examples demonstrate QbD's broad impact to the business, including quality, cycle times, product supply, and economics, as summarized in Figure 20.

5.5 Alignment and Knowledge Management

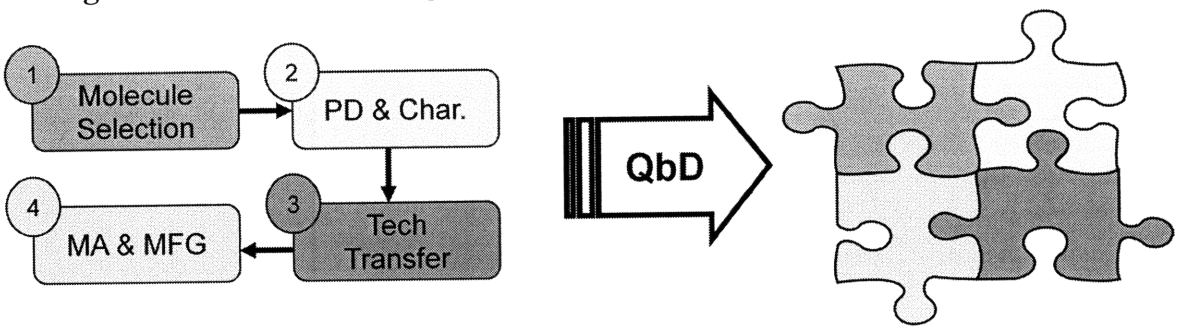

Figure 17: Quality by Design can provide a common philosophy for aligning the major elements of commercialization and ultimately yield an integrated product lifecycle.

Thus far, the business case has examined the impact of QbD in each of the four elements of commercialization defined in the conceptual framework. Though it is valuable to examine each stage of commercialization individually, QbD is fundamentally an integrated approach to product and process development; it relies upon the alignment and careful coordination of all activities involved in drug commercialization. Alignment can be achieved through business process re-design, enhanced communication across commercialization, and a comprehensive knowledge management system.

In order to make the most effective use of QbD principles, business processes should be designed to enable close collaboration between functions and across the product lifecycle. For instance, experiences gained and lessons learned in commercial manufacturing can aid early molecule selection and are critical for process development; hence, it is important for Marketing Application & Commercialization activities to be aligned with Molecule Selection and Process Development activities. Such interaction enables efficient organizational learning that can benefit both current products and pipeline products.

Additionally, communication between sites to share best practices will enable rapid progress towards a fully QbD state. For instance, advances in MSPM achieved at one manufacturing site could offer significant benefits when applied at another site. However, the incentives for knowledge sharing must be carefully structured to ensure continuous innovation through development and across the manufacturing network.

Knowledge management is another important aspect of QbD. Currently, product and process data are captured in a wide variety of systems and formats over the five or more years of commercialization activity for a given molecule. Consequently, significant time and resources are spent searching for, compiling, and sometimes replicating existing information. The concept of a knowledge base, a TELL & ASK information technology (IT) solution linking the network of data producers and consumers[55], offers one knowledge management solution.

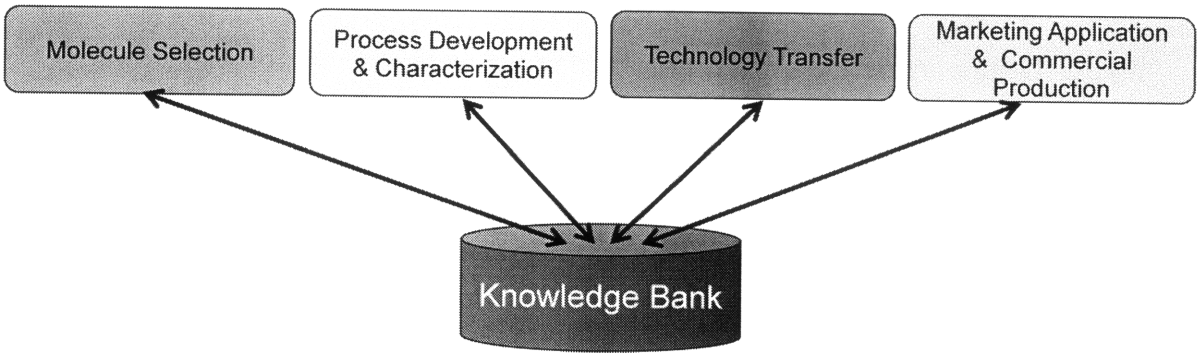

Figure 18: Knowledge base concept for a knowledge management system under QbD

With a central knowledge base, each element of commercialization could readily input (TELL) and retrieve (ASK) information, eliminating waste associated with searching for, translating, and recreating data. A single, broad knowledge management system would facilitate knowledge sharing and knowledge transfer in the earlier stages of development. The system would also provide considerable benefit in the preparation of regulatory filings, as all of the required information would be in one location and, if designed properly, in a format suitable for a QbD filing (i.e., including all elements necessary to define design space). Implementing such a knowledge management system would require a substantial information technology investment, and would necessarily be the product of collaboration among all groups involved in commercialization.

QbD emphasizes a strong link between product and process; this link should be reflected in commercialization practice. Alignment of commercialization processes under QbD and improving knowledge management adds value to the business from a product quality, operational, and economic perspective.

---

[55] (Ameri & Dutta, 2005)

6 Recommended Areas of Investment for QbD

The anticipated impact of QbD on product commercialization is outlined in Chapter 5. Further investment focused in three major areas, Science & Technology, Systems, and Business Processes, is required to realize the maximum benefit. Investment categories are described in greater detail below.

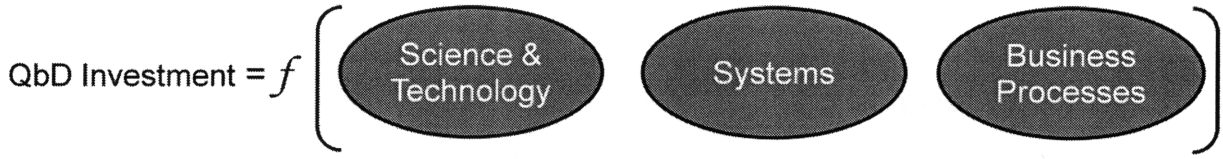

Figure 19: Three critical elements of a QbD investment strategy

6.1 Science & Technology

Science & Technology includes high-throughput analytical and development tools, PAT, design of experiments, risk analysis techniques, and any other tools that increase product knowledge and enhance process understanding and control. Amgen and others in the biopharmaceutical industry have already made considerable investments in this area.

Although the magnitude of investment in science and technology depends on available resources and long-term business strategy, the Science & Technology investment policy should be a distinct component of an organization's QbD strategy. A one-time, up-front investment in a particular new technology can offer benefits later in the commercialization process as well as across the product pipeline. However, a policy of on-going investment in Science & Technology will drive continuous innovation and improvement.

6.2 Systems

Here Systems refers specifically to knowledge management systems: how knowledge is captured and shared through the product lifecycle. A well-designed, integrated system can leverage organizational learning across the product pipeline. For instance, when design of experiments is used to determine

the impact of cell culture pH on titer for a particular product, the resulting data can be captured in a single location where it is accessible both to the group writing the marketing application for that product and to the group developing the manufacturing process for a similar product.

The monoclonal antibody (mAb) platform described in section 5.1.2 is one example of a knowledge management system. Ultimately, an IT solution may provide the link between the mAb platform and other similar data stores throughout the organization to create a fully-integrated knowledge management system (such as a Product Lifecycle Management, or PLM, system). While such a system would require a significant up-front investment, the benefits to commercialization efficiency would be tremendous.

6.3 Business Processes

The final area of investment for QbD is in reconfiguring the Business Processes that support commercialization. Business Processes designed for QbD ensure that the right data is captured at the right time, and that activities are aligned across functions and across the commercialization timeline. In this way, QbD is applied not just to the product and process, but also to the organization. The economic investment in Business Process re-design may be minimal compared to investments in Science & Technology and Systems. However, successful implementation of QbD requires changing the way that people think about how a drug is brought to market and likely involves a significant shift in organizational momentum. Investments in Business Processes should be undertaken with careful consideration of such organizational challenges.

7 Discussion

7.1 Overview of the Business Case

The business case is intended to highlight the most important areas of focus when considering QbD implementation. Results are summarized in Figure 20 below. While much of the investment in Science & Technology and Systems would be made relatively early in the commercialization process (i.e., in Molecule Selection and Process Development activities), the benefits are weighted towards the end of the process, primarily in Marketing Application & Commercial Production. Also, the magnitude of the benefits estimated in the business case is likely an underestimate of realizable savings due to the limited scope of the examples used.

	Business Impact	Summary of Benefits	Magnitude of Benefit*
1 Molecule Selection	Operational Cycle Time	More rapid advancement to commercialization Reduction in product attrition	26% reduction in cycle time to Tox release (Critical Path)
2 Process Development & Characterization	Operational Cycle Time & Quality	Optimal process conditions identified prior to launch Thorough process understanding for greater flexibility and control Learnings leveraged across pipeline	80% less cycle development time required per lyophilized SKU
3 Technology Transfer	Operational Cycle Time Economic	Reduction in risk Reduction in site-specific development work	80% less time required per Fill/Finish transfer $$ (per transfer)
4 Marketing App. & Commercial Production	Operational Cycle Time, Quality, and Supply Economic	Streamlined filing assembly through Knowledge Management In-control and capable processes Enhanced Operational Excellence	$$$ + (NPV)

***Based on examples evaluated in the business case.**

Figure 20: Summary of findings from the business case. [Magnitude of financial benefit (net cost avoidance and cost savings): **$** = up to $100K; **$$** = **$100K** to $1M; **$$$** = $1M to $10M]

Overall, the business case demonstrates that although the implementation of Quality by Design requires a considerable investment, both current and potential applications of these principles offer significant economic and operational benefits. So, although the primary driver for QbD in the biopharmaceutical industry is regulatory expectations ("the stick"), there are also some internal business incentives (the "carrot").

7.2 Internal Challenges for QbD Implementation

Amgen and other biopharmaceutical innovators have already begun to implement certain aspects of QbD. As QbD gains momentum, it will be important for each company to define a path forward to its target state. However, a number of internal challenges remain for the systematic implementation of the new paradigm. The first of these is related to the structure of the organization. In Amgen as in other biopharmaceutical companies, the groups responsible for carrying out the activities in the commercialization process are often divided by functional (organizational) and geographical boundaries. Part of the challenge with QbD is ensuring that goals are aligned between functions and sites through open communication and collaboration.

Another challenge to consider is the need to alter organizational momentum. QbD represents a paradigm shift in the approach to product and process development. Consequently, the individuals involved in bringing a drug to market will need to change the way that they think about the process as well as, in many cases, the specific work that they do. Business processes must be re-designed and communicated carefully.

Finally, the drivers for QbD implementation must be made clear. External, regulatory drivers, though certain, are somewhat slow to evolve as regulators are relying on industry to help define QbD for biotech products. On the other hand, recognition of internal benefits (such as those described in the business case) can help to accelerate implementation even though the establishment of clear regulatory expectations might lag behind. Identification and clear communication of both internal and external drivers is necessary to provide momentum for timely QbD implementation.

The four recommendations below are intended to help address these challenges:

- **Promote knowledge sharing across functions and sites.** Many groups have already begun to apply QbD principles and can share their learnings and successes to advance the entire organization more rapidly.

- **Identify leadership/champions to sustain momentum.** A champion for QbD integration is vital for sustaining the momentum of change and providing a vision for the future state of the enterprise.

- **Create a cross-functional team to develop an internal QbD roadmap based on the three key areas of investment.** Including input from all key stakeholders helps to put everyone on the same page and increase the likelihood of creating a fully integrated commercialization process.

- **Align internal and external efforts**. By continuing to collaborate with regulators and industry peers to define QbD for biotech products, the company will have the opportunity to shape expectations and will be better able to align internal efforts with those expectations.

7.3 Summary

The business case highlights the major areas across the biopharmaceutical commercialization process that are likely to be impacted by Quality by Design implementation. The results demonstrate that internal drivers do exist for QbD in a large biopharmaceutical company; considerable progress has already been made in applying QbD principles locally within specific functions and sites. Building on this progress, two of the most important tasks going forward will be to synchronize on-going activities under a comprehensive program and to ensure that the organizational structure and culture align with QbD principles.

As this new development paradigm gains momentum in the industry, innovators must define their QbD strategy and determine the appropriate magnitude and rate of investment based on resource availability and long-term business strategy. Through investments in Science & Technology, Systems, and Business Processes, the application of QbD principles will help to integrate the commercialization process, drive innovation and efficiency, bring more high-quality molecules to market faster, and lower the overall cost of quality.

BIBLIOGRAPHY

Ameri, F., & Dutta, D. (2005). Product Lifecycle Management: Closing the Knowledge Loops. *Computer-Aided Design & Applications , 2* (5), 577-590.

Amgen, Inc. (2009). *Company History.* Accessed on March 11, 2009 via http://www.amgen.com/about/company_history.html.

Amgen, Inc. (2009). *Fact Sheet: About Amgen.* Accessed March 11, 2009 via http://www.amgen.com/pdfs/Fact_Sheet_Amgen.pdf.

Bush, L. (2008, December 1). The New Era of Process Validation. *BioPharm International* , Accessed on March 12, 2009 via http://biopharminternational.findpharma.com/biopharm/Quality/The-New-Era-of-Process-Validation/ArticleStandard/Article/detail/568927?ref=25.

Conformia. (2008, July 28). Conformia and Leading Biotech Manufacturers to Collaborate in Unprecedented Effort of Advancing Application of Quality by Design Paradigm in Biotech Environment.

Davies, B. (2006, November 1). The Development of PAT in Biotech Manufacturing. *Pharmaceutical Technology* , Accessed on March 12, 2009 via http://www.ptemag.com/pharmtecheurope/Biopharmaceuticals/The-development-of-PAT-in-biotech-manufacturing/ArticleStandard/Article/detail/391530?contextCategoryId=37828&ref=25.

Drennen, J. K., & Cogdill, R. P. (2008, January 27). Making the Business Case for Process Improvement in Pharmaceutical Manufacturing. *IFPAC 2008* . Baltimore, MD.

Freeze Drying/Lyophilization Info Online. (2009). *Process - Freeze Drying.* Accessed March 13, 2009 via http://www.freezedryinginfo.com/Process.html.

Frost & Sullivan. (2008). *Strategic Analysis of the U.S. Biopharmaceuticals Market.*

Gieseler, H. (2006). PAT in the Laboratory: Case Studies in Testing SMART Freeze Dryer Technology. *IPT: Freeze Drying of Pharmaceuticals and Biologicals.* Accessed on March 14, 2009 via www.ftssystems.com/PDF/FTS_PAT_case_studies.pdf.

International Conference on Harmonization. (2008). *ICH Harmonised Tripartite Guideline: Pharmaceutical Development, Q8 (R1).*

International Conference on Harmonization. (2009). *Structure of ICH.* Accessed on March 12, 2009 via http://www.ich.org/.

Juran, J. (1992). *Juran on Quality by Design.* Simon and Schuster.

Karbhari, V. M. (1994). *JTEC Panel Report on Advanced Manufacturing Technology for Polymer Composite Structures in Japan: Product and Process Development Methods.* Accessed on March 12, 2009 via http://www.wtec.org/loyola/polymers/c7_s6.htm.

Korkmaz, B., Martin, A., & Undey, C. (2008, March). Getting Quality Down PAT. *In Tech* , Accessed on March 12, 2009 via http://www.isa.org/InTechTemplate.cfm?Section=Article_Index1&template=/ContentManagement/ContentDisplay.cfm&ContentID=68153.

Landers, P. (2003, December 8). Cost of Developing a New Drug Increases to About $1.3 Billion. *Wall Street Journal* .

Lasky, F. D., & Boser, R. B. (1997). Designing in Quality Through Design Control: A Manufacturer's Perspective. *Clinical Chemistry , 43* (5), 866-872.

Miller, H. I. (2009, February 5). The New Drug War: Congress vs. a NY-NJ Industry. *New York Post* .

Milton, N., Pikal, M., Roy, M., & Nail, S. (1997). Evaluation of Manometric Temperature Measurement as a Method of Monitoring Product Temperature During Lyophilization. *PDA Journal of Pharmaceutical Science and Technology , 51* (1), 7-16.

Nail, S. L., & Searles, J. A. (2008, January). Elements of Quality by Design in Development and Scale-Up of Freeze-Dried Parenterals. *BioPharm International* , 44-52.

Nasr, M. M. (2008, January 27). Strategic Implantation of PAT: FDA Perspective. *IFPAC 2008* . Baltimore, MD.

Noori, H. (1989). The Taguchi Methods: Achieving Design and Output Quality. *The Academy of Management Executive , 3* (4), 322-326.

Rader, R. A. (2008). (Re)defining Biopharmaceutical. *Nature Biotechnology , 26*, 743-751.

Rathore, A. S., & Winkle, H. (2009). Quality by Design for Biopharmaceuticals. *Nature Biotechnology , 27*, 26-34.

Seahorse Biosciences. (2009). *SimCell (TM) 200 Workstation Overview.* Accessed on March 13, 2009 via http://www.seahorsebio.com/products/SimCell/Simcell.html.

Sesholtz, Debra; Mather, Leslie. (2007). 'Smart' Freeze-Drying. *Innovations in Pharmaceutical Technology* , 87-90.

Submission of Quality Information for Biotechnology Products in the Office of Biotechnology Products; Notice of Pilot Program. (2008, July 2). *Federal Register* , pp. 37972-37974.

Tang, X. C., Nail, S. L., & Pikal, M. J. (2006). Evaluation of Manometric Temperature Measurement (MTM), a Process Analytical Technology Tool in Freeze Drying, Part III: Heat and Mass Transfer Measurement. *AAPS PharmSciTech , 7* (4, Article 97), E1-E7.

Tang, X. C., Nail, S. L., & Pikal, M. J. (2006). Evaluation of Manometric Temperature Measurement, a Process Analytical Technology Tool for Freeze-drying: Part II Measurement of Dry-layer Resistance. *AAPS PharmSciTech , 7* (4, Article 93), E1-E8.

Tang, X., Nail, S. L., & Pikal, M. J. (2006). Evaluation of Manometric Temperature Measurement, a Process Analytical Technology Tool for Freeze-Drying: Part I, Product Temperature Measurement. *AAPS PharmSciTech , 7* (1, Article 14), E1-E9.

Trappler, E. (2005). *Aseptic Pharmaceutical Manufacturing II.* (M. J. Groves, Ed.) CRC Press.

U.S. Food and Drug Administration, Department of Health and Human Services. (Latest revision 2008, April 1). 21CFR601.12: Changes to an Approved Application. *Code of Federal Regulations* . Accessed on March 14, 2009 via http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=601.12.

U.S. Food and Drug Administration, Department of Health and Human Services. (2004). *Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.*

U.S. Food and Drug Administration, Department of Health and Human Services. (2008). *Guide to Inspections of Lyophilization of Parenterals.* Accessed on March 14, 2009 via http://www.fda.gov/ora/inspect_ref/igs/lyophi.html.

U.S. Food and Drug Administration, Department of Health and Human Services. (2007). *Pharmaceutical Quality for the 21st Century: A Risk-Based Approach, Progress Report.*

Undey, C. (June 2-4, 2008). Are We There Yet? An Industrial Perspective of Evolution from Postmortem Data Analysis Towards Real-Time Multivariate Monitoring and Control of

Biologics Manufacturing Processes. *IBC's 5th Annual Process Quality Forum: Process Characterization and Control.* Cambridge, MA.

Van Arnum, P. (2007). ONDQA Director Addresses Pharmaceutical Quality for the 21st Century. *Pharmaceutical Technology* , Accessed on March 12, 2009 via http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=444420.

Wechsler, J. (2008, October 1). FDA Promotes QbD for Biotech Therapies. *BioPharm International* , Accessed on March 12, 2009 via http://biopharminternational.findpharma.com/biopharm/Quality/FDA-Promotes-QbD-for-Biotech-Therapies/ArticleStandard/Article/detail/557244.

APPENDIX

Key variables, constants and equations used in SFD calculation verification

Constants		
Concentration of Solution	c	0.029 g/g
Inner Area of Vial	A_v	5.81 cm^2 (20cc vials)
		12.25 cm^2 (50cc vials)
Density of Ice	ϱ_{ice}	0.918 g/cm^3
Density of Solute	ϱ_s	1.2 g/cm^3
Fill Volume	V_{fill}	8.1 cm^3 (20cc vials)
		20.88 cm^3 (50cc vials)
Volume Fraction of Ice	ε	0.962
Heat of Sublimation	ΔH_s	667 cal/g
Thermal Conductivity of Ice	κ_{ice}	0.006 cal/cm*sec*K
Variables		
Elapsed Time (since 1° Drying)	Δt	sec OR hours
Shelf Temperature	T_s	°C
Product Temperature (Thermocouple)	T_p	°C
Chamber Pressure	P_c	mTorr or Torr
Measured Values		
Sublimation Rate	dm/dt	0.57 g/hr/vial (20cc vials)
		0.61 g/hr/vial (50cc vials)

Thickness of ice, L_{ice}:

$$L_{ice} = \frac{V_{fill}}{\rho_{ice}}\left(1 - \frac{c * 0.082}{\rho_s}\right)$$

Dried layer thickness, ΔL:

$$\Delta L = \frac{\frac{dm}{dt} * \Delta t}{A_v * \rho_{ice} * \varepsilon}$$

Remaining ice thickness, L':

$$L' = L_{ice} - \Delta L$$

Temperature difference between sublimation interface and bottom of vial, ΔT:

$$\Delta T = \frac{\frac{dm}{dt} * \Delta H_s * L'}{\kappa_{ice} * A_v}$$

Vial heat transfer coefficient, K_v:

$$K_v = \frac{\frac{dm}{dt} * \Delta H_s}{A_v (T_s - T_p)}$$

Temperature at sublimation front, T_i:

$$T_i = \frac{\frac{-dm}{dt} * \Delta H_s}{A_v * K_v} + T_s - \Delta T$$

Vapor pressure of ice, P_0:

$$P_0 = 2.7 \times 10^{13} e^{\left(\frac{-6145}{T_i + 273.15}\right)}$$

Dry layer resistance, R_p (= Total resistance when stopper resistance, R_s, is negligible):

$$R_p = \frac{A_v (P_0 - P_c)}{\frac{dm}{dt}}$$