Improving Production Yields in Bio-pharmaceutical Filter Media

by

Jeremy Brian Rautenbach
B.Eng.(Mech), University of Pretoria, Pretoria, 2011

Submitted to the Department of Mechanical Engineering and the MIT Sloan School of Management in partial fulfillment of the requirements for the degrees of
Master of Science in Mechanical Engineering
and
Master of Business Administration
in conjunction with the Leaders for Global Operations Program at the
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
June
2017

Signature redacted

Author .....
Department of Mechanical Engineering and the MIT Sloan School of Management
May 12, 2017

Signature redacted

Certified by .....
Duane Boning, Thesis Supervisor
Clarence J. LeBel Professor, Electrical Engineering

Signature redacted

Certified by .....
Roy Welsch, Thesis Supervisor
Eastman Kodak Leaders for Global Operations Professor of Management

Signature redacted

Certified by .....
David Hardt, Thesis Reader
Ralph E. and Evelyn F. Cross Professor of Mechanical Engineering

Signature redacted

Approved by .....
Rohan Abeyaratne
Chair, Mechanical Engineering Graduate Program Committee

Signature redacted

Approved by .....
Maura Herson
Director, MBA Program, MIT Sloan School of Management

THIS PAGE INTENTIONALLY LEFT BLANK

Improving Production Yields in Bio-pharmaceutical Filter Media

by

Jeremy Brian Rautenbach

Submitted to the Department of Mechanical Engineering and the MIT Sloan School of Management on May 12, 2017, in partial fulfillment of the requirements for the degrees of
Master of Science in Mechanical Engineering
and
Master of Business Administration

Abstract

This thesis presents methods to identify sources of variation in rolled goods manufacturing by defining the critical input process parameters, and the application of statistical process control. Sources of variation are prioritized according to a process control hierarchy, and reduced or eliminated through iterative cycles of rapid experimentation. This work emphasizes the value of team work, breaking down the organizational barriers between departments, knowledge sharing and the importance of a scientific approach to problem solving.

FilterCo manufactures and assembles filter media catering to the ultrafiltration market growing at ~12% over the next five years. In a high growth scenario, production yield variability presents on-time delivery complications while below target yields drive significant scrap value. As FilterCo seeks to improve product lead time for its customers, while reducing WIP inventory, it must seek to maximize OEE with respect to product yield, equipment performance and availability. The variation identification, reduction and process control methodologies presented in this thesis are demonstrated to advance the goal of reducing production yield variation.

The impact of the work has been verified on three filter media grades and have shown ~40% reduction in production yield variation, and rolled throughput yield improvements of ~30%. These improvements on the three membrane grades alone have resulted in an annualized saving equivalent to 60% of the total 2015 scrapped membrane value.

Thesis Supervisor: Duane Boning
Title: Clarence J. LeBel Professor, Electrical Engineering

Thesis Supervisor: Roy Welsch
Title: Eastman Kodak Leaders for Global Operations Professor of Management

Thesis Reader: David Hardt
Title: Ralph E. and Evelyn F. Cross Professor of Mechanical Engineering

THIS PAGE INTENTIONALLY LEFT BLANK

Acknowledgments

First and foremost, I would like to thank Professor Duane Boning and Professor Roy Welsch for their support and guidance throughout this project. I am part of the privileged few to have worked with and learned from you both.

In addition, I would like to thank Matt, the project sponsor, for his time, direction and patience. I regard myself as fortunate to have been under your tutelage and I thank you for teaching me the practical aspects of statistical process control and process improvement.

To my first teachers, mom and dad, I thank you for your unwavering support and encouragement. Without your sacrifice and dedication, none of this would be possible, and I will never forget it. Lastly, I would like to convey my deepest gratitude to my wife, Dale, for her patience, love and encouragement these past two years. Thank you for the unforgettable journey thus far – I am excited for the future and look forward to our adventures together, wherever they may lead.

THIS PAGE INTENTIONALLY LEFT BLANK

The author wishes to acknowledge the Leaders for Global Operations Program for its support of this work.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

This chapter emphasizes the increasing demand for biopharmaceutical drug development and state-of-the-art manufacturing techniques, and highlights the need for using quality filtration products in the manufacture of biopharmaceutical treatments. The project goal of obtaining consistent and high yielding filter media manufacturing processes is defined from the perspective of high sales growth, and context provided by defining where FilterCo currently finds itself in its supply and quality journey. This chapter alludes to the business impact of the project, and concludes by providing insight into the project approach that allows for the development of a sustainable manufacturing control plan.

1.1 Filtration in Biopharmaceutical Manufacturing

Biopharmaceuticals constitute a significant portion of all pharmaceutical products and play an increasingly vital role in society. The development of vaccinations and treatments for a wide range of critical diseases, such as cancer, rheumatism and influenza, demand minimized drug side effects and high pharmaceutical efficacy. The manufacturing process includes chemical synthetic and biochemical synthetic procedures, which use the vital functions of living organisms such as microbes, mammalian cells and plant cells to construct the active pharmaceutical ingredient (API). Generally, this manufacturing process can be divided into three broad categories: cultivation, purification and formulation processes, where both cultivation

and purification processes are regarded as bioprocessing.

Filtration in bioprocessing plays an important role in purifying, concentrating and separating solutions and products. The use of appropriate filtration techniques are one of the ways in which biopharmaceutical manufacturers comply with the U.S. Food and Drug Administration (FDA) validation requirements ensuring product purity and consumer safety [1]. With a heightened focus on the development of protein-based therapeutics, demand for purification of monoclonal antibodies, plasma proteins and interleukins, for example, is rising [2]. This demand is satisfied through the use of membrane-based ultrafiltration (UF) products owing to their cost competitiveness, process reproducibility and scalability from development through to large scale manufacture [3]. Furthermore, the use of membranes in filtration systems is particularly well suited to biopharmaceuticals owing to their low operating temperatures and pressures, as well as ensuring no phase change during the action of filtration – all critical considerations that ensure high production yields of API's [4, 5]. The choice of membranes are dependent on the structure and size of the target API as well as the manufacturing process under consideration, and are manufactured in varying grades typically differentiated by their nominal pore size distribution.

In 2015, the annual UF membrane market was worth an estimated $3 billion, and the market growth rate is projected to be ~6% up to 2021 with the biopharmaceuticals segment – now a $300 million segment – projected to be growing at 11.8% over the same period [6]. This rapid growth is driven primarily due to a number of blockbuster drugs nearing the end of their patent term, resulting in a strong biologics pipeline for the foreseeable future. A host of pharmaceutical companies are now concerned with synthesizing these molecules, and their manufacture also necessitates adequate filtration techniques ensuring process sterility.

1.2 Business Context

FilterCo[1] is a global supplier of filtration and separation solutions catering to a broad range of industries and niche segments, including the life sciences. The journey to ensuring prolonged and continued success in supplying filtration products to biopharmaceutical manufac-

[1]The name of the actual filter company has been replaced with FilterCo.

turers starts at the beginning of the drug development process – pilot scale manufacturing. Biopharmaceutical drug companies are required to qualify their products as well as their manufacturing processes with the FDA. Manufacturing factors such as processing time and nominal filtration ranges are detailed, and highly dependent on the filtration products utilized. Significant deviation from these specified parameters is not tolerated by the FDA and, in order to produce a consistent product, drug manufacturers utilize the same filtration products over the drug's life cycle.

After successful qualification, the potential switching costs for drug manufacturers are significant, and the successful filter company could expect to supply the manufacturer for the drug's useful product life. At the same time, any significant process or raw material changes in the manufacturing of these filtration products would automatically require a re-qualification of the drug manufacturing process, thus dis-incentivizing filter manufacturers to implement breakthrough improvements on existing product lines for fear of losing business to its competitors.

Recently, FilterCo has realized an increase in demand for its biopharmaceutical filtration products utilizing product family X[2] membrane. Owing to continued industry growth and new product introductions, FilterCo has responded by increasing the frequency of production runs and, in turn, this manufacturing volume has resulted in significant membrane scrap values highlighting suboptimal production yield attainment. Simultaneously, as FilterCo has acted upon opportunities to reduce work in process (WIP) inventory while maintaining its on-time delivery (OTD) performance, production yield variability has been highlighted as an area of concern. Furthermore, as FilterCo seeks to differentiate itself from a growing number of entrants, it has introduced a number of new products to the market that make use of product family X. In a high demand scenario, below target production yields drive significant scrap values while yield variability impacts the supplier's ability to deliver product that is on-time.

FilterCo's future success is contingent on being able to supply a filter that is on-time, and meets the quality and performance expectations of the customer. Thus, the goal of the

[2]The name of the product family has been replaced with X.

project reduce production yield variability in order for FilterCo to ensure continued future success.

1.3 FilterCo's Supply and Quality Journey

In recent years, FilterCo prioritized operational excellence and developed a number of initiatives to drive improvements in key metrics such as OTD, back-order (BO), efficiency and stock holding. FilterCo started its supply chain journey by analyzing its demand profile and segmented its product offering by sales order frequency and sales volume. This provided a reasonable jump-off-point to develop stocking strategies for each of its product lines and would drive the initial inventory levels. The first phase of the strategy was, knowingly, sub-optimal, but enabled FilterCo to prioritize customer satisfaction through improved OTD and reduced BO, at the expense of reduced efficiencies and increased inventory levels.

Step two of the journey emphasized obtaining efficiency improvements and would be realized by characterizing the customer demand and scheduling production runs to suit. This initiative resulted in a level load design ensuring FilterCo would manufacture media X cognizant of the associated financial factors. This phase did not impact inventory levels and necessitated lead time optimization initiatives to be developed and implemented.

FilterCo is currently in step three of its journey and has started to look critically at lead time optimization. Success in this metric would result in reduced inventory levels and consists of increased product wheel speed, product portfolio optimization and improved overall equipment effectiveness (OEE). Using media X as an example, product wheel speed refers to the time between the manufacturing run of different media X grades, enabling scheduling more effectively and economically such that inventory levels are reduced.

As bio-pharmaceutical manufacturers progress through the various stages of the drug life cycle, demand for different filter products (e.g., nominal pore size and volumetric flow rate) varies. Increasing the frequency with which it analyzes and optimizes its product portfolio, FilterCo will be better positioned to cater to shifts in demand and, in doing so, maintain optimal inventory levels whilst not sacrificing performance in the areas of OTD and BO.

OEE is a function of availability, equipment performance and product yield, and all three metrics would need to be simultaneously impacted to drive noteworthy improvement.

1.4 Project Motivation

Media X production yield (both level and consistency) reflects the quality and reliability of FilterCo's manufacturing processes. Historically, yields of the media manufacturing line have been highly variable and standard deviations range from 7% to 42% depending on the grade of media manufactured. Furthermore, the average production yield to date has been 75% compared to a target of 85%. Facing increasing demand for the foreseeable future, production yield variability will impact FilterCo's ability to maintain its OTD promises, and below target yields will give rise to significant scrap value.

The basis of the third step in FilterCo's quality journey is aligned with Deming's chain reaction [7] where considerable effort is being focused on including quality principles into all business processes. Higher quality would result in decreased costs owing to fewer instances of rework, elimination of non-value added time (improved OTD and BO), and improved utilization of machine-time (OEE) and materials. These changes would automatically yield higher productivity metrics. The chain reaction continues on with capturing higher market share owing to price and quality competitiveness, ensuring continued success of the business.

Currently, FilterCo is experiencing strained WIP inventory levels owing to a spate of low yielding manufacturing runs. Almost automatically, the response has been to produce in higher quantities to alleviate the short-term pressure, but this "run faster" response only results in reduced productivity, increased scrap and decreased throughput all the while not focusing on the root cause of the problem. With the full intention to strive towards higher levels of quality, FilterCo management have highlighted the need to identify the root cause/s and develop a sustainable manufacturing control plan that ensures customer satisfaction through improved OTD and quality.

1.5 Project Approach

This work provides managerially relevant recommendations that address an enterprise specific problem by seeking multiple viewpoints from across the organization, and building a site-specific model grounded in iterative learning cycles. A research method proposed by Westbrook [8] is employed to develop a solution to the problem while comparing and contrasting its effects through practical observations. Research is conducted in such a way that the results are practically useful to managers and supervisors, and focuses on the entire system as opposed to a narrowed sub-set. In so-doing, we find that quality control methods can be highly effective in identifying, controlling and reducing variation if applied correctly and appropriately.

The journey of reducing production yield variability follows three distinct process control modes, and constitutes implementing statistical process control, conducting process optimization and installing feedback control. The approach consists of modelling the manufacturing process, identifying the equipment and material inputs, and defining the intended output in terms of geometry and material properties. Process understanding is formed by interacting with FilterCo specialists and experienced personnel, and hypotheses are formed based on the data analyses and observations made. Improvement opportunities are prioritized and acted upon according to a process control hierarchy of disturbance reduction, disturbance sensitivity reduction and disturbance counteraction.

Hypotheses are tested by initiating a number of mutually exclusive, collectively exhaustive pilot studies on a specific membrane grade. Data collected from these studies provide confidence in whether the change is successful, but more importantly whether it is sustainable. Initial success drives refinement through a process of iterative learning cycles. The learning from the pilot studies provides sufficient information and background to develop a comprehensive manufacturing control plan for FilterCo.

Planning of the pilot studies relies upon successful interaction with the research and development team as well as manufacturing and maintenance personnel. Knowledge is transferred through regularly scheduled meetings, as well as a comprehensive write-up that details the plan. Furthermore, it is important to train and educate FilterCo's associates on the im-

pact of the critical input variables and the necessary steps needed to ensure an "in-control" process.

1.6 Thesis Overview

This thesis is based on the findings and insights gathered as a result of action research conducted during a six-month internship project with FilterCo. The thesis highlights a set of data analyses and iterative cycles of experimentation to convey the impact of various methodological steps made in reducing production yield variability.

Chapter 2 provides background into the biopharmaceutical industry, highlighting its increasing importance in society and contextualizing the need for quality filtration. The process of manufacturing a filter membrane is described and specific process steps are emphasized to provide the necessary background for the discussions surrounding implementation. A novel framework for modeling a manufacturing process and implementing process control initiatives is presented and forms the foundation of Chapter 4.

Chapter 3 provides detail regarding the current state of the media X manufacturing line and presents the logic of focusing the scope of work such that business impact could be maximized. The reader is introduced to the typical components of variation present in rolled goods manufacturing, and provided with further reasoning for focusing on specific performance tests.

Chapter 4 develops a robust model for control of the manufacturing process, and highlights the importance of prioritizing variation reduction initiatives according to a process control hierarchy. A selection of variation reduction initiatives are presented followed by a brief discussion.

Chapter 5 presents the conclusions of the thesis and suggests recommendations for future work.

Chapter 2

Literature Review

Manufacturing products with a significant impact on human life drives the need for high quality consumables: one being high performance filter modules making use of anisotropic media. This chapter presents a summary of the literature detailing the manufacture of these membranes, and introduces a process modeling paradigm for the purposes of successful process control. The most critical step of the manufacturing process, phase inversion, and how it relates to the performance of the media is described herein. With this context, a number of relevant problem solving tools are presented that greatly assist in the goal of reducing yield variability.

2.1 Introduction

The current biopharmaceutical landscape offers a number of opportunities for the entire pharmaceutical value-chain; a number of drugs are nearing the end of their patent term, and many drug manufacturers have been granted authorization to develop similar drugs, or biosimilars, to that of their competitors. BCC Research [6] estimates the global biopharmaceutical UF membrane market to be worth $602 million by 2021, up from $312 million in 2015. This increase represents a compound annual growth rate of 11.8% and has been attributed to growing biopharmaceutical markets, especially in Asia-Pacific and other emerging countries, and also the shift to incorporating single-use technologies in downstream process-

ing [9]. As drug manufacturing processes become increasingly complex, the need for more sophisticated filtration products increases. Ultimately, it is the responsibility of the drug manufacturer to ensure purity and potency of their finished drug product/s, but the role of filter manufacturers and their control over the quality of their product plays a vital role in patient safety.

2.2 The Principle of Filtration

Filtration is a pressure-driven process by which particles are removed from fluid, air, or gas samples by passing through a permeable material. Typically, two modes of filtration exist today: normal flow filtration (NFF) and tangential flow filtration (TFF), most commonly differentiated by the direction of fluid flow in relation to the filtration interface.

Furthermore, filtration may be segmented into four distinct technology groups as summarized in Table 2.1. Microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO) constitute the filtration spectrum, and differ by the retention characteristics they provide such as nominal pore size and particle atomic mass separation. Additionally, these groups are also defined by the nominal pore size of the filter interface and the atomic mass of the particles to be separated (measured in Daltons, Da).

Table 2.1: Filtration Separation Spectrum

	MF	UF	NF	RO
Nominal Pore Size (μm)	>0.1	0.1 - 0.01	0.01-0.001	<0.001
Particle Atomic Mass (kDa)	>500	1 - 500	0.1 - 1	<0.1
Separation Targets	Colloids	Macro molecules	Small molecules	Ions
	Bacteria	Proteins	Organic Compounds	

A membrane may be described as an interface that moderates the flow of molecular and ionic species present in liquids and/or vapors [10, 11, 12]. Since the 1960's, membranes have become recognized as having the largest range of applications across a broad range of industries owing to their high filtration efficiency and low energy consumption [4, 5, 13].

The performance of a membrane is qualified by its selectivity and its flux parameters [13]. Flux refers to the volume flowing through the membrane per unit area and time whilst

selectivity refers to the ability of a membrane to separate solute from solvent. In the case of aqueous solutions, selectivity is typically expressed in terms of retention and expressed as the percentage difference in concentration before and after feed has passed through the membrane.

The biotechnology and post-genome science industries are concerned with developing novel therapeutic products to make great strides in the areas of gene therapy and cancer research. Ensuring sterility and high recovery rates of these high-value broths is an important requirement and robust purification steps are now demanded from the biopharmaceutical industry [14]. Furthermore, Guo et al. [15] notes that with the increased production of Monoclonal Antibodies (MAb), particularly for the bio-similar market, commercial success is now heavily reliant on bio-processing innovations in the areas of micro- and ultrafiltration, and filter manufacturers now face significant downward pressure on the cost of goods and higher quality demanded of products [3]. Low et al. [16] suspects that anti-body based therapies will be a major source of new therapies and highlights the considerable improvements that have been made in the upstream manufacturing processes. Many of these innovations (e.g., mammalian cell cultures titers, transgenics and microbial expressions) have proved large batch size manufacturing feasible and Low et al., note the significant cost pressures now faced by the existing downstream facilities, processes and consumables to achieve similar economies of scale [16].

Chromatography has been the "go-to" downstream process owing to its ability to provide high resolution in bioseparation. However, it has also become the single largest cost center in downstream processing in the past due to very low process throughput [3, 17]. Today, the challenge in purification is cost minimization whilst increasing throughput, and ultrafiltration is said to be a "natural born partner for the biotechnologist" [18] and "offers a simple yet elegant alternative" [3]. In ultrafiltration, downstream biopharmaceutical applications include fractionation, concentration and diafiltration, and are the most popular applications that make use of the TFF mode of operation [2, 4].

2.3 Tangential Flow Filtration

TFF or cross-flow filtration (CFF) is not a recent development; it was developed more than 40 years ago concurrent to the advancement of reverse osmosis technology. During the latter part of the 1960's, the TFF technique was used in the concentration and fractionation of macromolecules, also known as ultrafiltration [19].

Fundamentally, TFF is differentiated from NFF by the following three characteristics:

1. relative direction of flow
2. recirculation capability
3. the mechanisms employed to retain suspended solids

TFF filters exclusively utilize membranes whilst NFF filters could make use of membranes, paper or other special materials, depending on the feed stream to be processed [20].

In TFF, the solution is passed tangentially along the surface of the filter, and the constituents that are smaller than the membrane pore size are driven through the filter by means of a pressure gradient [20]. The use of the TFF method results in one feed generating two product streams; retentate and permeate as shown in Figure 2-1. The efficiency of TFF is largely dependent on high recirculation rates that help to ensure high tangential velocities along the surface of the membrane promoting turbulence and thus increasing the re-dispersion of retained solids in the bulk feed.

Conversely, in NFF, separation is achieved by applying a pressure gradient to the entire feed stock, and driving both the filtrate and feed concurrently along the length of the filter [19]. The result is a single product stream and a build-up of filtrate on the surface of the membrane that cannot be recirculated (Figure 2-1). The filtration rate (flux) in NFF decreases with increasing thickness of the filter cake layer or volume of feedstock filtered, as opposed to TFF where flux tends to approach an asymptotic limit owing to an equilibrium being reached between fouling and turbulence created on the surface of the membrane as depicted in Figure 2-2.

Operating in NFF mode, the per-pass recovery is close to 100%; however, employing

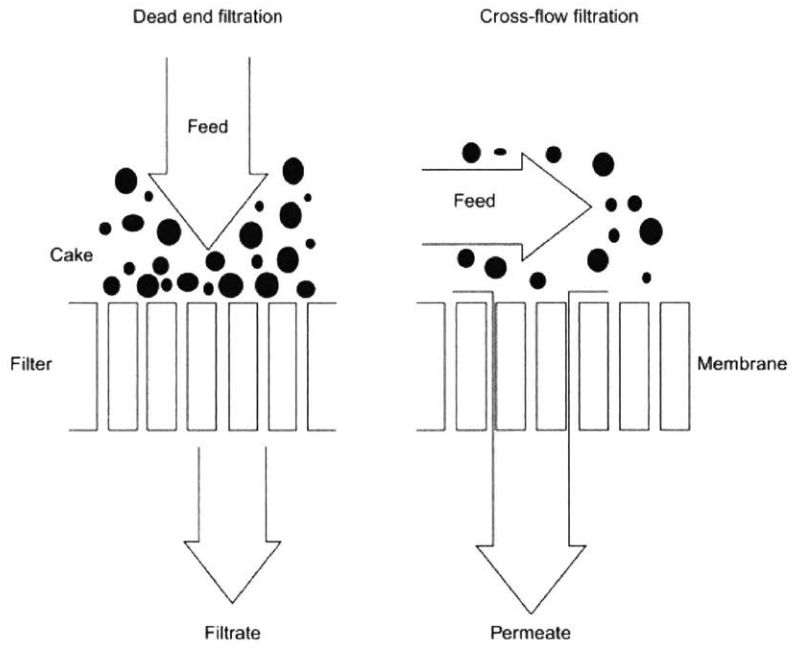

Figure 2-1: Two filter modes of operation highlighting the differences in flow direction and separation mechanisms [19].

TFF results in recoveries dropping off significantly to the 1-5% range [2, 19]. Depending on the control strategy employed, each NF filter possesses either a limiting flow or trans-membrane pressure that, when reached, necessitates the interruption of the filtration process to either clean or replace the membrane/filter cartridge. Selection of filter mode operation requires careful trade-off study comparing increased recirculation, driving energy consumption, and frequent discontinuities in modes of operation. Bhave [19] mentions that TFF is the preferred mode of operation when the particle size or molecular weight distribution is an important consideration, such as in the separation of enzymes, antibiotics and proteins and polysaccharides from microbial cell mass. Owing to the inherent behavior of biosuspensions, Kroner [18] highlights the limitations of traditional techniques such as centrifugation and NFF. Complexity in filtration arises when the feed stock is comprised of small particle size, wide particle distribution and high compressibility of the solids residues. TFF mode is also preferred when the feed stock has a high solids content and would otherwise foul a conventional NFF filter – rendering it inoperable much faster than TFF.

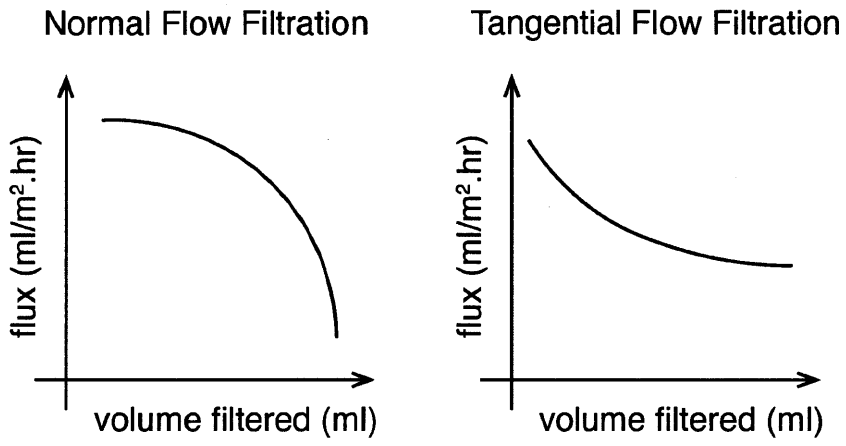

Figure 2-2: Flux characteristics heavily dependent on the filtration mode employed.

2.4 Membrane Manufacturing

Saxena et al. [10] report that membrane based processes are playing an ever increasing and critical role in the areas of separation and purification of biopharmaceuticals. New developments in membrane filtration technology have allowed for both high resolution and high-throughput separations with the potential for replacing traditional chromatography methods [17].

These recent advances, however, have only been made possible by two significant developments in the late 1960's: the ability to produce selective, highly permeable and defect free membranes on a large scale, and to construct an economical and compact membrane module that provides a high area-to-volume ratio [21]. The large diversity of commercially available membranes today requires the need for a robust classification system.

2.4.1 Classification of Filtration Membrane

Membranes can be classified according to their material composition, cross-section, preparation method employed and shape [11]. Ren et al. [22] offers a schematic diagram for membrane classification and is shown in Figure 2-3, and includes many of the distinctions proposed by Ulbricht [11] and Idris et al. [5]. Previously, UF membranes were manufactured

using cellulose and its derivatives because its hydrophilic nature proved advantageous in reducing membrane fouling [2]. However, due to the limited operating pH range, cellulose membranes are not suitable in biopharmaceutical manufacturing where sterilization is critical [2, 22]. Typical ultrafiltration membranes are thus manufactured using polymers since they provide good thermal and chemical stability, but do however require post-processing, since polymers tend to be hydrophobic in nature. Two of the most commonly used polymers in the manufacture of UF membranes are polysulfone and polyethersulfone [2, 5, 11, 19].

In an effort to continuously improve membrane capacity and performance, numerous materials have been utilized in their manufacture over the past five decades [5]. However, the majority of commercial grade membranes are synthetic and can be classified into either inorganic (ceramic or metal) or organic (polymeric). Today, polymeric and ceramic membranes are the most important synthetic membranes. Ulbricht [11] notes that the use of ceramics, although gaining importance, is still overshadowed by the use of polymers owing to the wide variability of barrier structures and properties that can be designed through their use [6].

Membranes can be manufactured to take on three basic forms – flat sheet, tubular or hollow fiber. In bio-pharmaceutical manufacturing, the flat sheet and hollow fiber forms are most commonly used [2], selection of which is highly dependent upon the application and feed stock to be separated. In its basic assembly, a flat sheet membrane module consists of a shallow channel with a sheet of membrane on one or both sides. The feed stock would typically be pumped in on one side of the channel and the retentate would be removed from the opposite side of the channel (Figure 2-4). By means of valve adjustment on the retentate side, the induced trans-membrane pressure would drive permeate through the membrane. It is common for several flat sheet membrane modules to be connected in series or parallel, and offer ease-of-cleaning, ability to accommodate a wide range of viscous suspensions and enables flexibility in changing out defective modules. The main drawback of flat sheet modules are the low area-to-volume ratios and high hold-up volume – which may be very costly when typical broths could be worth millions of dollars [2].

Anisotropic membranes are particularly well-suited to processing large volumes of feed stock owing to the thickness of the membrane and the inverse relationship between mem-

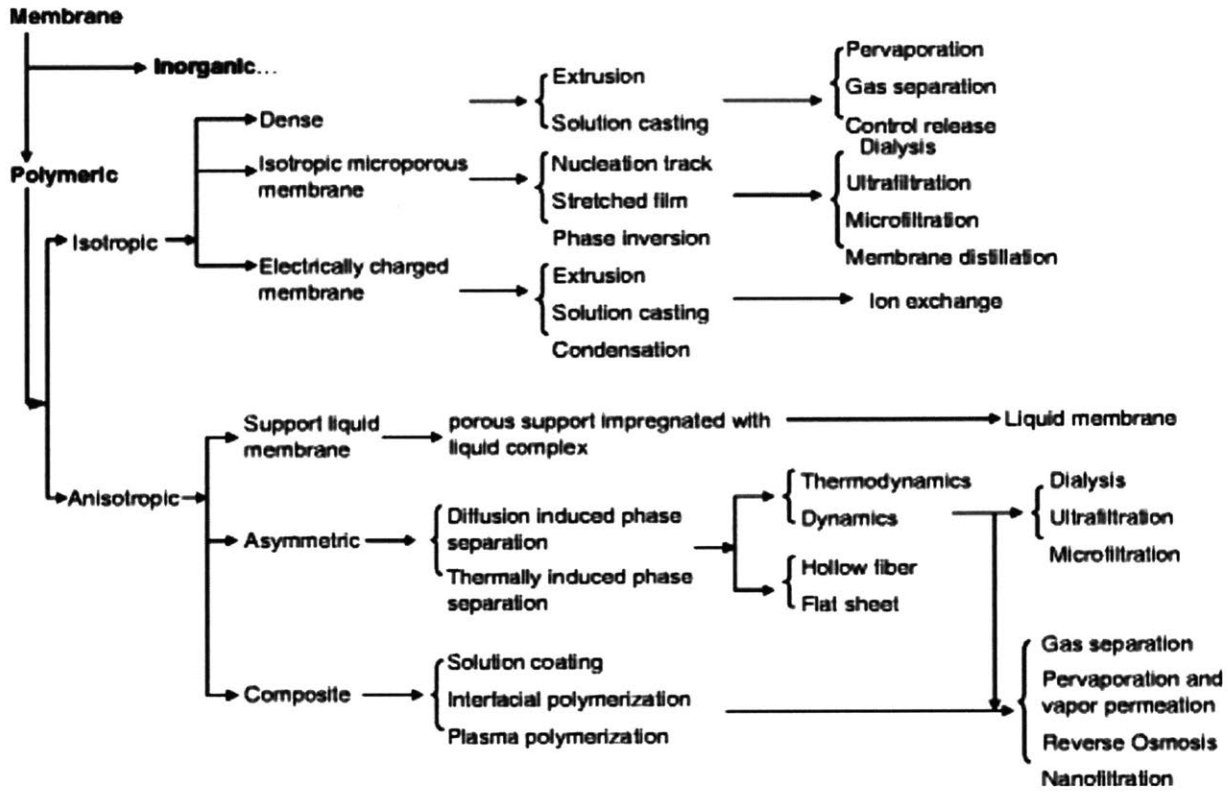

Figure 2-3: Polymeric membrane classification system proposed by [22].

brane thickness and membrane permeability. Regarded to be one of the major breakthroughs in the past four decades [12], anisotropic membranes consist of a thin surface layer and a thicker porous substructure. The surface layer, or skin layer, is the selective portion of the membrane while the porous substructure provides the mechanical strength of the membrane [22]. Prihandana et al. [23] provide a detailed cross-sectional view of an ultrafiltration membrane and highlight the two critical aspects of the membrane structure (Figure 2-5) where "diffusion layer" refers to the skin layer and "finger like structure" to the porous substructure. Mulder [13] remarks that anisotropic membranes offer the high selectivity of dense membranes with the high flux rates characteristic of thin membranes (Figure 2-6).

FilterCo's media X may be classified as a polymeric, anisotropic membrane that is manufactured in a flat sheet configuration. These sheets of membrane are stamped to take on the various layouts of the filter modules offered by FilterCo.

The membrane base materials, inorganic or polymeric, are selected based on the specific

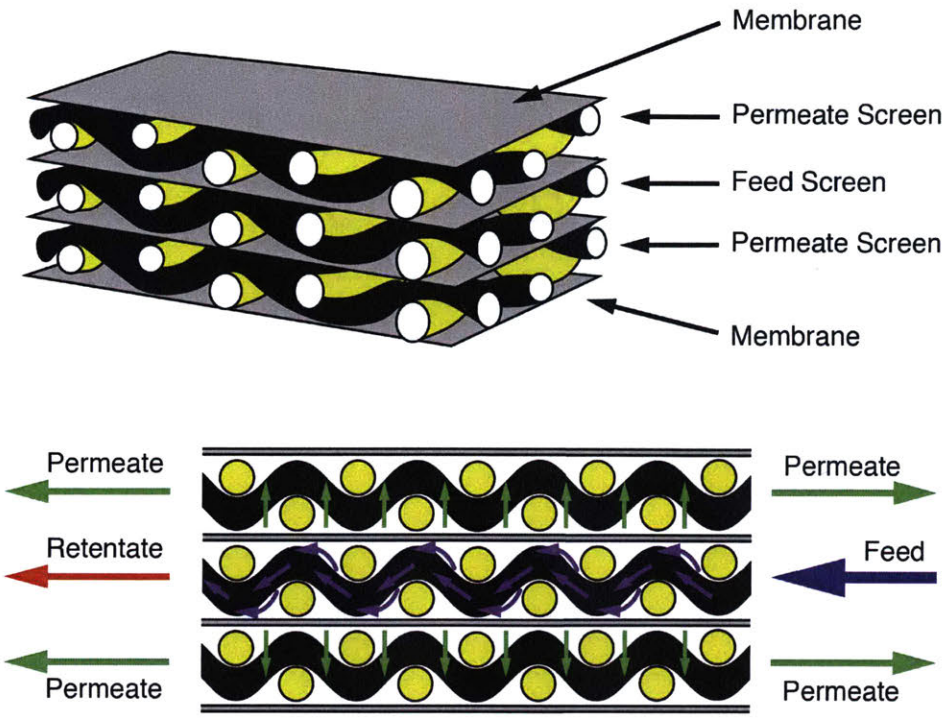

Figure 2-4: Stacked flat sheet membranes depicting filtration mechanism under trans-membrane pressure gradient.

separation application; their material properties limit the preparation techniques employed which ultimately impact the membrane morphology during the manufacturing process [13]. There are numerous techniques available to prepare and manufacture polymeric membranes, but the most popular and important manufacturing technique in commercial application is by way of phase inversion [22].

2.4.2 Phase Inversion Manufacturing Process

In the context of membrane manufacturing, phase inversion refers to the controlled precipitation of a polymeric solution. The process of manufacturing membrane by phase inversion starts off with the product formulation and typically consisting of a polymer resin, sol-

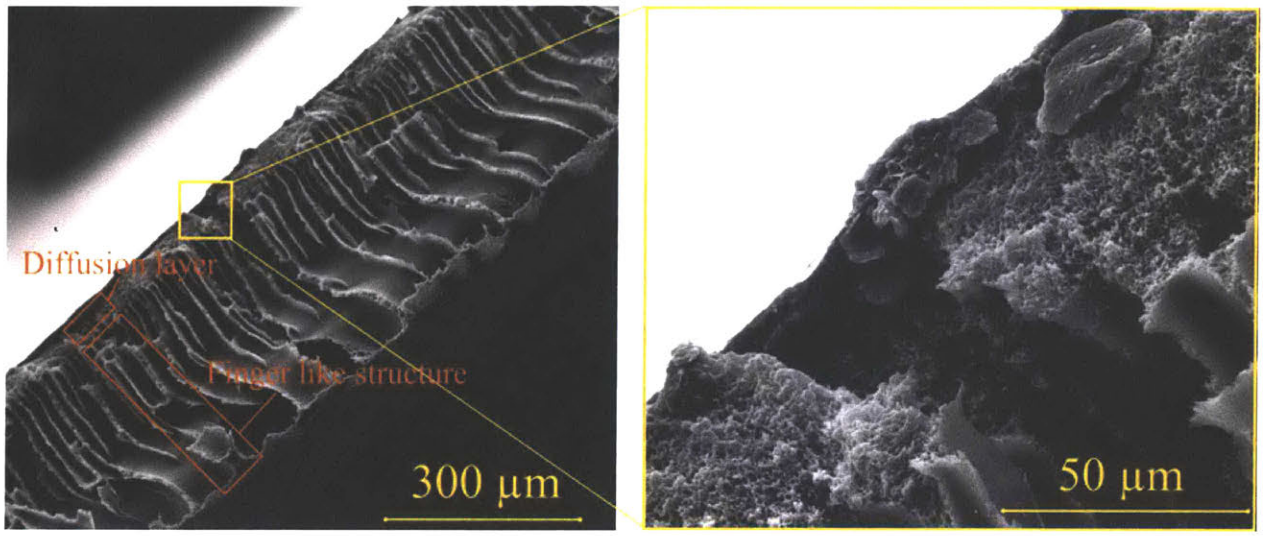

Figure 2-5: SEM cross section of anisotropic membrane [23] highlighting both the skin and macro-porous layers.

vent, non-solvent and additives. Additives are included in the formulation when specific membrane properties are desired and would otherwise not be supplied by the base polymer alone. The base polymer is initially in a solid phase and by dissolving it in a solvent, a stable homogeneous phase is created. Through a process of phase inversion, the solution enters a meta-stable state before completely separating into its solid and liquid phase constituents [5, 22].

Beyond the formulation, the most critical step in the manufacturing process is the phase inversion process itself. Mulder [13] provides a suitable depiction of the phase inversion step of a typical flat sheet manufacturing process and is shown in Figure 2-7. The polymer solution is cast directly onto a moving non-woven supporting fabric in variable thicknesses by means of a casting knife. This cast membrane is then immersed in a non-solvent bath (coagulation bath) where the polymer precipitates as a result of the gradient field between the non-solvent bath and the solvents contained in the polymer.

Furthermore, Ren et al. [22] offers a schematic diagram of the typical polymer application process (Figure 2-8) for illustrative purposes. The casting blade or knife is critical in controlling for an even distribution of polymer across the surface of the fabric. Once the dope solution or polymer is cast onto the fabric, the membrane is exposed to an air gap before undergoing quenching in the coagulation bath. Both the air gap and coagulation

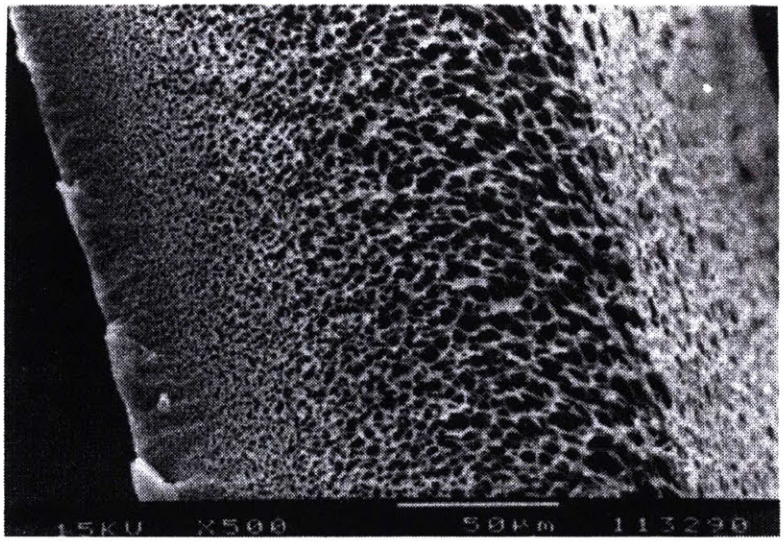

Figure 2-6: Cross section of anisotropic ultrafiltration membrane [13].

bath play an important role in the formation and solidification of the membrane, the cross-section of which is critical to membrane performance. Detailing the number of factors on the diagram, Ren et al. [22] emphasize the complicated nature of flat sheet manufacturing. Herein are a number of critical parameters that need to be closely monitored and controlled if the manufacturer is to ensure consistent and high product yield.

2.5 The Need for Quality Control in Biopharmaceutical Consumable Manufacturing

Linders [24] notes that the processes employed in biotechnology applications are highly sensitive to deviations in process parameters and contamination levels, thereby requiring the quality specifications on consumables (e.g., filtration products) be more stringent than those used for conventional small molecule pharmaceutical production. By way of example, the broth used for cell culture is dependent on many tightly controlled parameters including nutrient concentrations, temperature, pH, and chemical and microbiological impurities. Linders further comments that the need for high quality consumables is not specific to a particular process step and that even after the harvest of the API, great care needs to be taken in exposure to harmful molecules in solution.

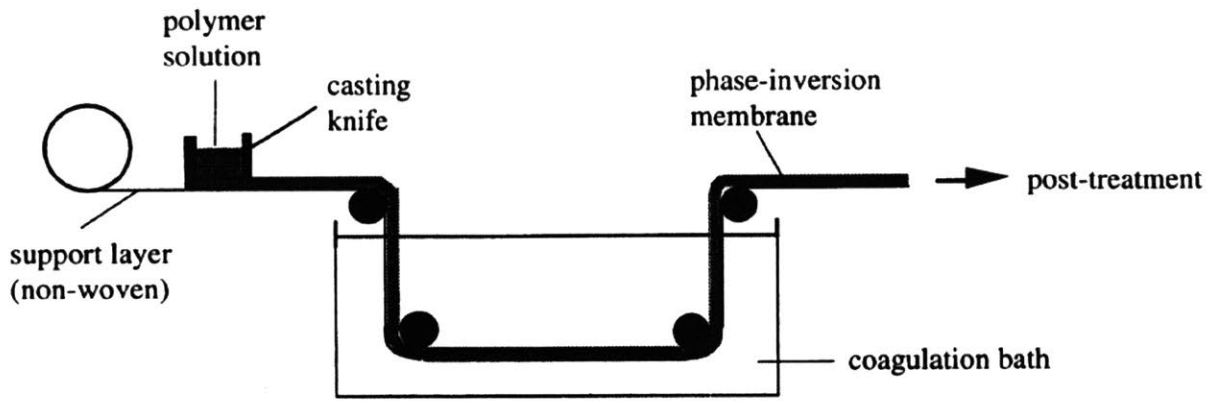

Figure 2-7: Schematic diagram of a typical phase inversion manufacturing line producing a flat sheet membrane [13].

All biopharmaceutical manufacturers are bound by the regulations set forth by the FDA, and as a result follow many guidelines so as to eliminate any potential for misinterpretation of the regulations. One such guideline was published in 2006 and titled *Quality System Approach to Pharmaceutical Current Good Manufacturing Practices* or CGMP [25]. This guideline forms part of a quality system and outlines the requirements necessary for the manufacture of drugs, medical devices, biologics, and food. This framework strives to control finished pharmaceutical processes so that the products meet the necessary standards of safety, efficacy, purity and stability [26].

In recent years, FilterCo has adopted this guideline and included the framework in all of its manufacturing processes. Ensuring the high quality standards, FilterCo's Quality Control laboratory performs two tests, Test A[1] and B to qualify the performance of its media. A large number of specimens are sampled from each media roll and subjected to both tests. These tests reveal the performance of the media specimens and enable inferences to be made regarding the entire media roll. Media rework is not possible and any media sheets found not meeting the specifications are scrapped.

The nature of flat sheet membrane manufacturing may be likened to rolled good manufacturing, and, owing to the width and length of the roll, there are two components of variation

[1]The names of the actual tests have been omitted.

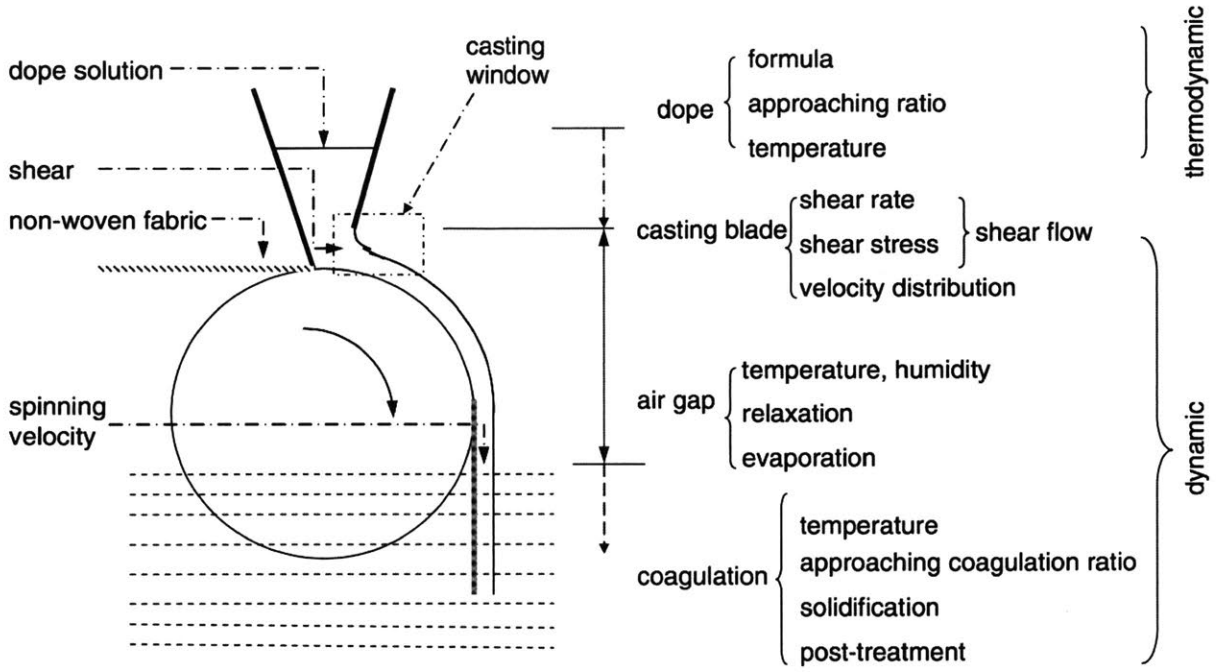

Figure 2-8: Cross-sectional view of generalized application technology utilized in flat sheet manufacturing [22].

manufacturers need to be mindful of: cross-web (left to right) and down-web (beginning to end). For this reason, additional specimens of media are sampled from a membrane roll in order to quantify any both components of variation.

Section 3 of the FDA guidance [25] emphasizes the significance of statistical process control (SPC) and recommends its adoption as "the information from trend analyses can be used to continually monitor quality, identify potential variances before they become problems, bolster data already collected for annual review, and facilitate improvement throughout the product life cycle."

2.6 Reducing Process Variation

Embarking on an initiative to reduce process variation may be fraught with difficulty without thoughtful analysis and thorough understanding of the process under consideration. Hardt [27, 28], defines a manufacturing process as an interaction of equipment and a ma-

terial whereby the material is transformed through the exchange of energy into the desired outputs.

Hardt asserts that process control can only be achieved through the control of the equipment itself since their inputs are the only accessible means of modulating the intensity and distribution of energy to the material, and presents a block model detailing these equipment and material interactions shown in Figure 2-9. Furthermore, Hardt states that all manufacturing processes have two outputs – geometry and properties – that completely define the product and govern the design specifications.

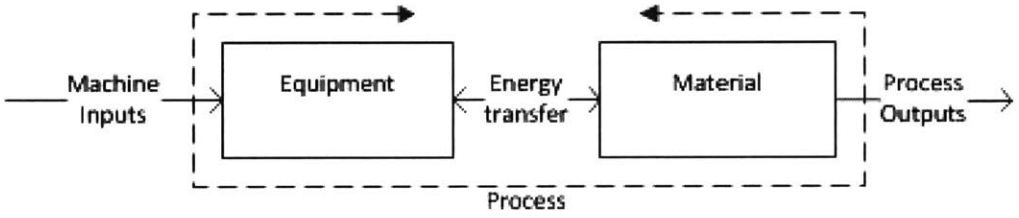

Figure 2-9: Interaction of equipment and material in a manufacturing process, adapted from [27].

The output ($\vec{Y}$) of any manufacturing process can be described by a functional relationship between the equipment inputs ($\vec{u}$) and other process parameters ($\vec{\alpha}$) defined in Equation 2.1.

$$\vec{Y} = \Phi(\vec{\alpha}, \vec{u}) \tag{2.1}$$

A distinction is made between equipment inputs and other process parameters because equipment inputs are accessible, critical to the conformance of the product and deterministic [27]. Process parameters ($\vec{\alpha}$) may be separated further into equipment and material parameters whose thermodynamic state and constitutive properties must be defined in order to understand the inherent physical variations, and predict their response to process changes.

With Equation 2.1 in mind, Hardt proposes that the variation in process output may be captured by a first-order differential equation defined in Equation 2.2 , and provides a strong basis from which to discuss the categories of process control initiatives.

$$\Delta\vec{Y} = \frac{\partial Y}{\partial \alpha}\Delta\vec{\alpha} + \frac{\partial Y}{\partial u}\Delta\vec{u} \tag{2.2}$$

Whereby the terms of Equation 2.2 are defined as follows:

$\Delta\vec{Y}$ is the variation of the output

$\frac{\partial Y}{\partial \alpha}$ refers to the disturbance sensitivity of the process

$\Delta\vec{\alpha}$ is the parameter disturbance vector

$\frac{\partial Y}{\partial u}$ reflects the process gain, and

$\Delta\vec{u}$ represents equipment input changes

The objective of process control is to reduce the effect of process parameter (equipment and material) disturbances on the process output such that the variation ($\Delta\vec{Y}$) is minimized. Considering the components of Equation 2.2 and assuming that machine inputs are held constant throughout the process, it is clear that there are three avenues available that, if acted upon correctly, could enable variation reduction.

1. The sensitivity of the process, $\frac{\partial Y}{\partial \alpha}$, relates to the parameter disturbances and could be reduced by designing and operating the manufacturing process in a manner that reduces their effects on the output.

2. Parameters variations, $\Delta\vec{\alpha}$, are correctly identified using SPC techniques and adequately minimized by way of robust problem solving frameworks and processes.

3. The machine inputs, $\Delta\vec{u}$, can be adjusted in order to compensate for parameter variations by way of feedback control.

The categories listed above represent a plethora of initiatives that can be undertaken to reduce process variation. These initiatives vary in complexity, depend on the operations strategy of company, and are heavily reliant on operator training. Embarking on a process variation reduction initiative would be futile without adequate consideration of these factors. Achieving superior process control, however, can only be achieved by following the process control hierarchy as proposed by Hardt [27]:

1. Reduce disturbances

2. Reduce sensitivity

3. Measure output and manipulate inputs

Reduction of process disturbances relies upon the successful roll-out of good housekeeping policies, standard operating procedures (SOPs), SPC and feedback control of machines. Once implemented, the sensitivity of the process to disturbances can be reduced by conducting numerous design of experiments (DOE). The most complex initiative, feedback control of outputs, can only be undertaken once the previous two initiatives have been fully implemented.

2.7 Problem Solving Tools

Developing a robust model provides a sound base from which to identify sources of variation as well as evaluate the impact of potential solutions. Implementation of the solutions though, requires a problem solving approach that is able to correctly identify the gap in performance between current and future state, and provides a method to develop solutions and implement sustainable countermeasures.

2.7.1 Problem Solving Processes

There have been many problem solving processes proposed over the years, most notably the Plan-Do-Check-Act (PDCA) process proposed by Shewhart [29] (Figure 2-10) in 1939, and later made famous by Deming [7] who altered it to the Plan-Do-Study-Act (PDSA) cycle. The PDSA cycle represents a flow diagram for continuous learning and describes the logic of the improvement process. Both Shewhart and Deming highlight the importance of the planning step as it defines the problem, generates the solution/s or ideas, predicts the outcome of the solution and defines the data necessary to make a data-driven decision.

In a similar manner, the Lean Six Sigma and Six Sigma philosophies propose the Define-Measure-Analyze-Improve-Control or DMAIC improvement cycle that is grounded in the

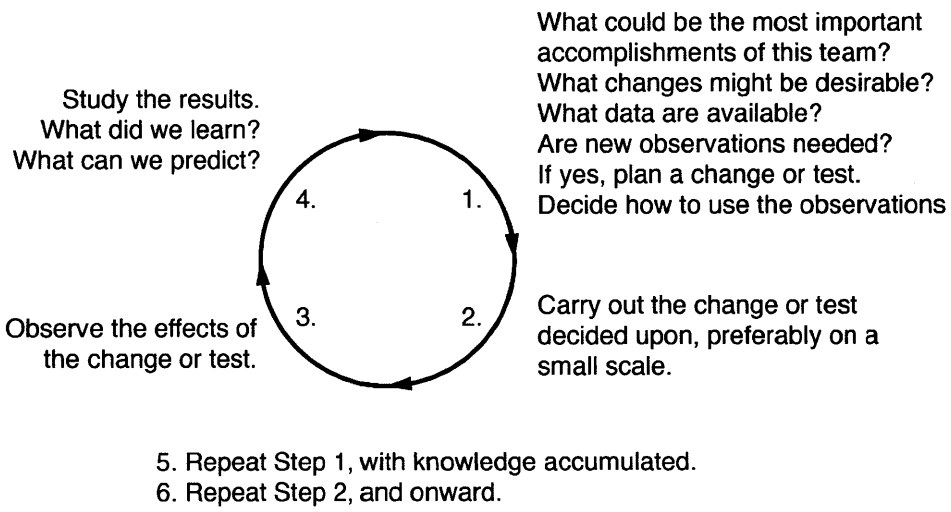

Figure 2-10: Plan-Do-Check-Act continuous improvement cycle [7].

PDSA logic. It differs from the PDSA in that it caters to both process improvement and process design/redesign efforts as opposed to solely process improvement. DMAIC provides a clear definition of the problem and is explicit in the need to *go to Gemba* or the place where the work is conducted to do so. The power of the DMAIC and PDSA processes is that they emphasize that problems are solved on the shop-floor with the input of the associates as opposed to managers solving ambiguous problems behind closed doors.

During the *analyze* phase effort must be spent discerning symptom from cause, and avoid doing unnecessary work or treating too many causes simultaneously. Breaking down the problem from point of recognition to point of occurrence and, finally, to point of cause is enabled through the development of a robust process model.

The *improve* phase considers development of the solutions to remove the root causes and measuring them against a set of standardized metrics. A large component of the improve phase is the evaluation of the various ideas with respect to ease of implementation and impact on the overall process. The *control* phase is typically regarded as a verification step that ensures the sustainability of the countermeasures while identifying additional opportunities for further process improvement.

SPC involves the measurement and evaluation of variation in a process, and plays a critical role in both the DMAIC and PDSA processes. Correct implementation of SPC

allows for the identification of a problem, portray the benefits of the countermeasures and reveal the sustainability of the solutions.

2.7.2 Statistical Process Control

The American Society of Quality defines SPC as a procedure to help monitor process behavior [30]. Quantifying the process behavior allows for conclusions to be drawn about whether the process is "in control" – the state in which only sources of natural process variability are present. It is in this state that the process is said to be operating at a stable level and the process is considered to be producing reproducible product [31].

The control chart is the primary tool of SPC and was developed by Shewhart in the 1920's who sought to determine if a sequence of data may be used for predictions of what will occur in the future. With a reasonable amount of historical data, appropriate limits are determined and as future observations continue to fall within these limits, the process is said to be predictable or in-control. At the point when these observations are inconsistent with the established limits, it is a signal that action needs to be taken to identify and control assignable causes of variability.

UF media is manufactured in web product form and, as such, requires a more specialized application of conventional SPC techniques. According to Frost and Gutoff [31], SPC was originally developed for piece part manufacturing and the techniques have not traditionally been applied to continuous roll product manufacturing owing to the reliance on inspection techniques, lack of motivation in applying it in a difficult setting and ineffectively translating SPC from piece part to roll products.

The effectiveness of SPC in achieving high quality standards has been proven time and again, and in the life sciences industry where products impact human health, the use of SPC is especially important. In many instances, the FDA has compelled companies to include SPC as part of their quality system approach within their manufacturing environments. So often though, SPC efforts are focused on the downstream processes (i.e., final inspection) and does not improve nor guarantee quality. By rather focusing on the upstream activities, ensuring a state of statistical control, quality can be guaranteed every time [7]. As proclaimed

by Harold F. Dodge, "Quality can not be inspected into a product; it must be built into the product" suggesting that SPC is a reactionary measure of quality, and merely applying it to the particular process, does not ensure compliance nor control.

2.8 Conclusion

The increasing costs of healthcare and improvements in the scientific understanding of biotechnology has led to an increase in manufacturing of biotechnology related drugs. While innovations like biosimilars promise to have comparable quality, safety and efficacy as the original drugs they have been designed to replicate, the necessary processes required for their manufacture are complicated. High quality and cost effective consumables are critical in ensuring that therapeutic drugs are manufactured to the correct purity, potency and cost.

These market drivers have fueled advancements in materials and manufacturing practices associated with membrane filtration products. The high resolution and high throughput filtration capabilities of ultrafiltration membranes allow them to compete with conventional high cost methods.

However, complexity arises in ultrafiltration polymeric media manufacturing owing to the large number of variables over multiple process steps. With the highest quality standards demanded, the manufacturing processes require the strict control of critical parameters, and the correct application of process control techniques to enable reduction in production yield variability.

Chapter 3

Current State Analysis

Chapter 3 provides an overview of the current state of FilterCo's membrane manufacturing and testing processes, and highlights the key findings of analyses used in the distillation of the project scope. Numerous process improvements have been made in the past, however, it is noted that yield variability has not been regarded as an avenue for improvement until the recent implementation of a initiative seeking to reduce WIP inventory. Financial impact and customer satisfaction are maximized by focusing on the membrane grades responsible for the largest historical scrap value as well as present sales volume. As a first step, the components of variation are defined, mapped, and quantified through careful analysis of quality control test data – establishing a road-map for the process variation reduction initiatives detailed in Chapter 4.

3.1 Introduction

Over the years, FilterCo acquired a number of manufacturing companies that aligned well with its business interests. These acquisitions were either in support of its organic growth strategy and represented "bolt-on" acquisitions or were as a result of FilterCo entering a new market. FilterCo's media X manufacturing line is a result of an acquisition made 20 years ago, and many of the original components are still in use today. Conversations with long time FilterCo employees reveal that the current manufacturing processes and procedures repre-

sent a significant improvement over what was originally received and recommissioned at the facility. A number of standard work processes have been implemented, some even as simple as not changing the lacquer recipe owing to the season of the year. Manufacturing yields have improved considerably over the years, but as FilterCo seeks to improve its operational efficiency, considerable emphasis is now placed on media scrap and yield variability.

Yield variability, however, is not a recent occurrence. As buffer inventory levels have been decreased to reduce inventory holding costs and obsolescence, the impact of yield variability on the value chain has been exposed. Regular stock-outs and OTD misses have highlighted the need for a manufacturing control plan that identifies the sources of variation and provides sustainable countermeasures that limit their effects on the process.

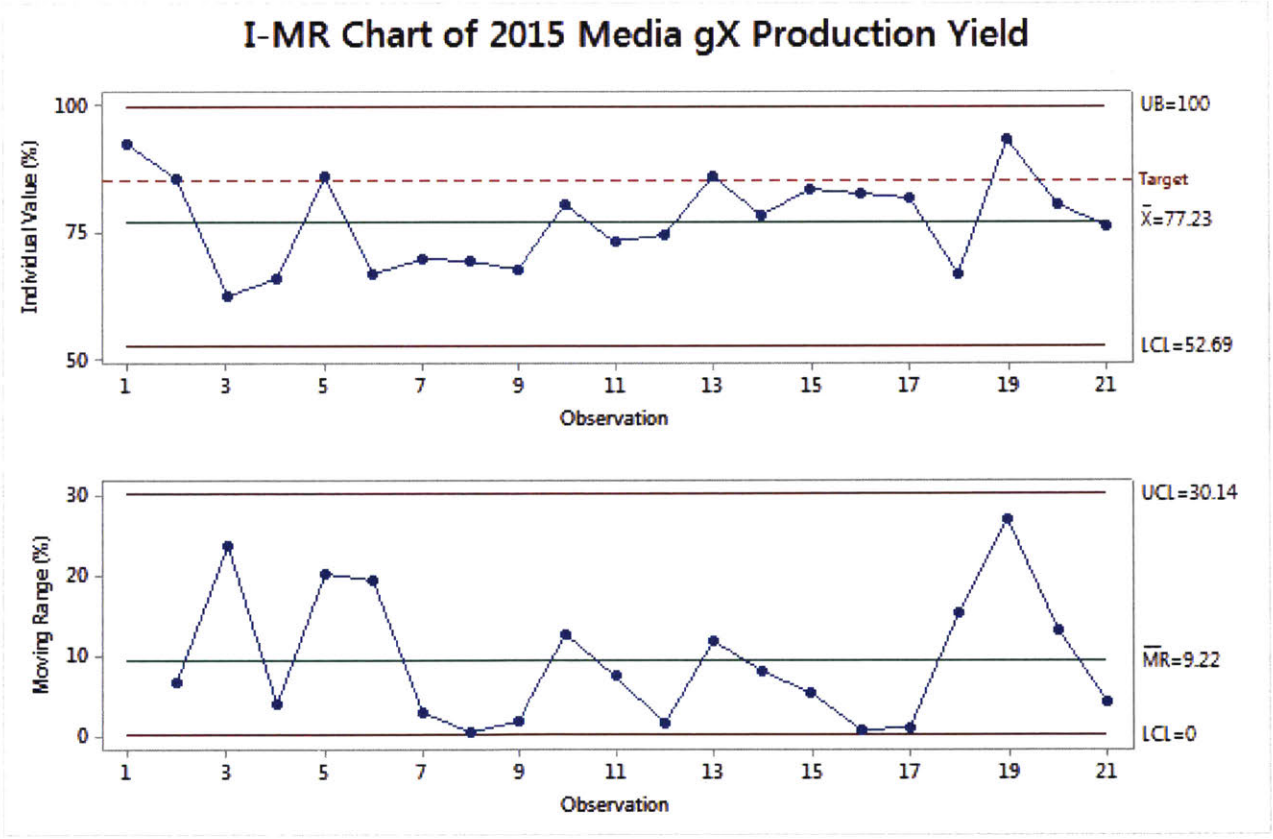

Figure 3-1: Prevalence of production yield variability as shown by historical data.

Figure 3-1 depicts media gX[1] production yield data in an individual-moving range (I-MR) chart and represents the typical performance of media production yields for 2015. Average

[1]The grades designation of media X has been altered.

production yield for 2015 was determined to be 77% compared to a target of 85%. Of greater concern to FilterCo is the yield variability whereby the upper control limit is calculated to be 30% – negatively impacting production scheduling and cost control.

3.2 Media Scrap Analysis

The first step in the development of the manufacturing control plan is to understand the current state of the process, and identify where focused efforts would lead to maximum business impact. While FilterCo manufactures over twenty-five grades of Membrane X, attempting to monitor and drive simultaneous improvement on all grades would present an unreasonable task.

Providing FilterCo with the maximum business impact is achieved by focusing on the "critical few" that represent the highest financial impact and customer satisfaction potential. The historical financial performance of the manufacturing process is established by analyzing historical scrapped media data. A Pareto chart as shown in Figure 3-2 reveals that 83.1% of the total scrapped value is attributable to six grades. Grades nX, kX, gX, sX and fX were frequently manufactured whereas oX only represents one lot of media, and will thus be excluded from further analyses owing to scarcity of data.

Analyzing the current year-to-date (YTD) media sales data (Figure 3-3) reveals that these five grades are responsible for 74.7% of the volume and, in particular, grade kX is responsible for 45.5% of the output. Thus, developing and implementing robust manufacturing processes aimed at improving the production yields of grade kX have the greatest short-term business impact. Furthermore, ensuring high production yields of grade kX would substantially improve the supply of media to the filter assembly department and, in turn, reduce the current OTD gap by 35%[2].

Forecasting demand, however, proves to be a difficult task for FilterCo management, as it is strictly dependent on the biopharmaceutical manufacturer and where that manufacturer finds itself in the life-cycle of the drug. During the drug development phase, small filter

[2]Calculated based on YTD yield and sales data.

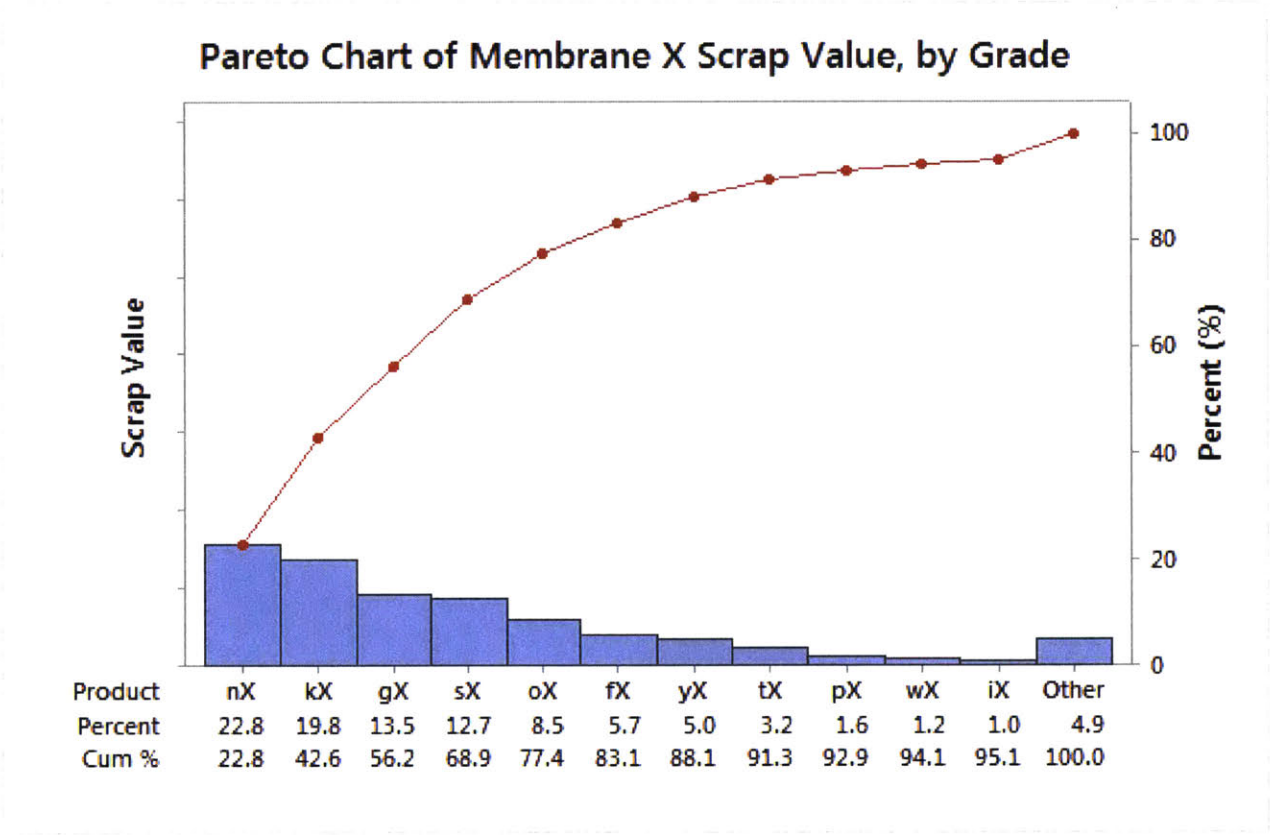

Figure 3-2: Pareto chart of 2015 membrane X scrap.

modules that utilize a fewer number of media sheets are demanded, as opposed to large scale manufacture requiring multiple large filter blocks/modules. Thus, FilterCo experiences a number of "demand shocks" throughout the year, and focusing on improvement efforts on membrane kX proves to be reactionary as opposed to preventative.

3.3 Quality Control of Membrane X

A typical manufacturing lot consists of multiple media rolls and, once manufactured, the media rolls are tested in the quality control laboratory before being delivered to the filter assembly department. Two tests, Test A and B, are performed within the laboratory and, depending on the results, media rolls are released to the filter assembly department in full or in part. Typically, this media is not used immediately and would serve to increase the buffer inventory levels, unless media yields of previously manufacturing lots have yielded low

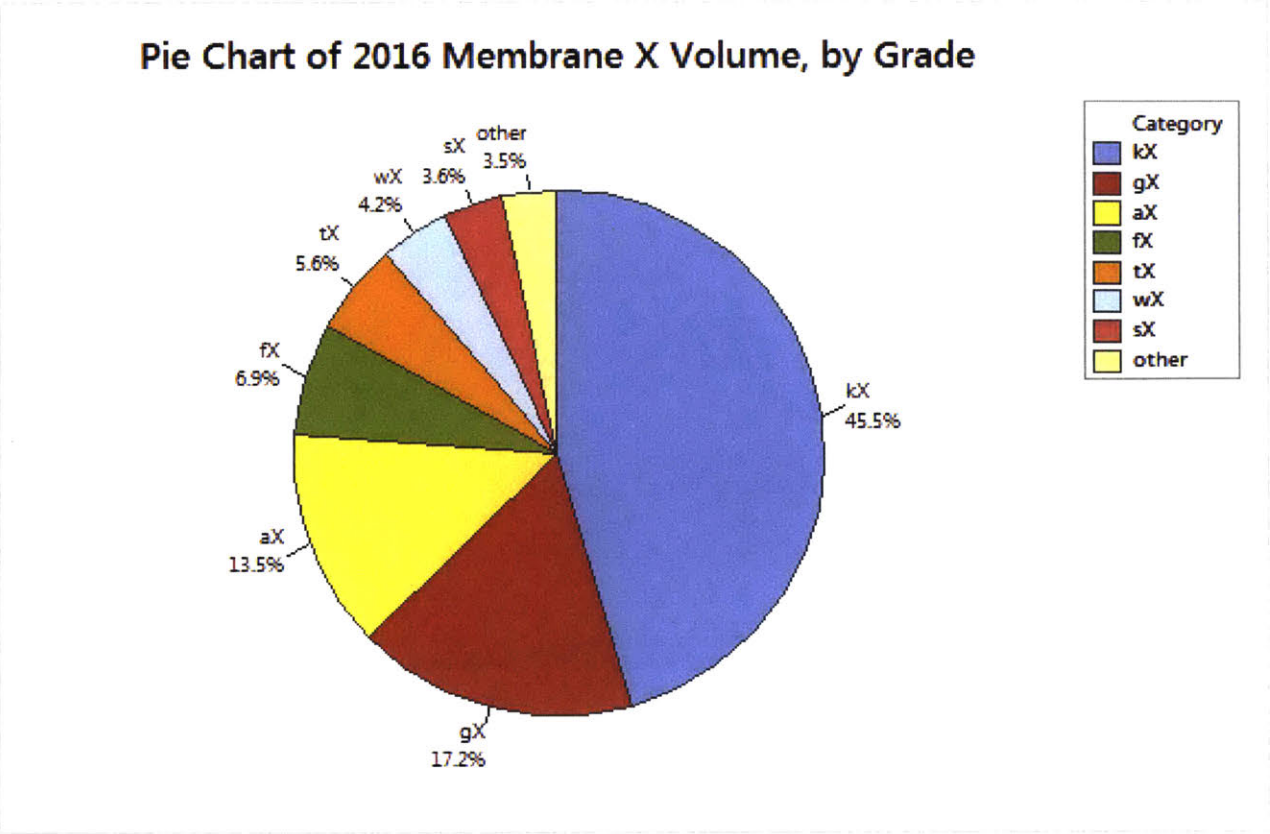

Figure 3-3: 2016 membrane X sales data, by media grade.

media.

The time consuming nature of the tests combined with current scheduling practices influenced by yield variability, however, do not allow for efficient and timely feedback to be incorporated in the next manufacturing run. The average cycle time, from manufacture through to laboratory results, of a media lot is *three weeks*. Current scheduling practices, however, allow for multiple media grade lots to be manufactured in a successive fashion and devalues the opportunity to analyze QC results and incorporate learning into the process. Furthermore, the filter assembly department does not draw from the inventory in a first-in first-out basis, thus further increasing the complexity for fault finding when the problem relates to a media lot manufactured, for example, six months prior. In the face of a rising backlog, a typical response to a spate of low yielding lots is to schedule more manufacturing runs in a shorter period of time, in the hope that a sufficient volume media will pass through QC, irrespective of yield. This practice of "running faster" is contrary to building a quality

organization; it prioritizes managing outcomes instead of managing the system [7].

3.3.1 Membrane X Yield Data Analysis

For budgetary purposes, FilterCo expects all manufacturing runs to achieve a minimum of 85% yield. In order to provide some context of manufacturing performance, 2015 QC yield data are gathered and analyzed based on the yield expectation. Figure 3-4 reveals that Media grades gX, kX and nX were the most frequently manufactured grades during 2015, while close to 50% of these runs are below the 85% threshold suggesting that the process is currently not capable of achieving the target.

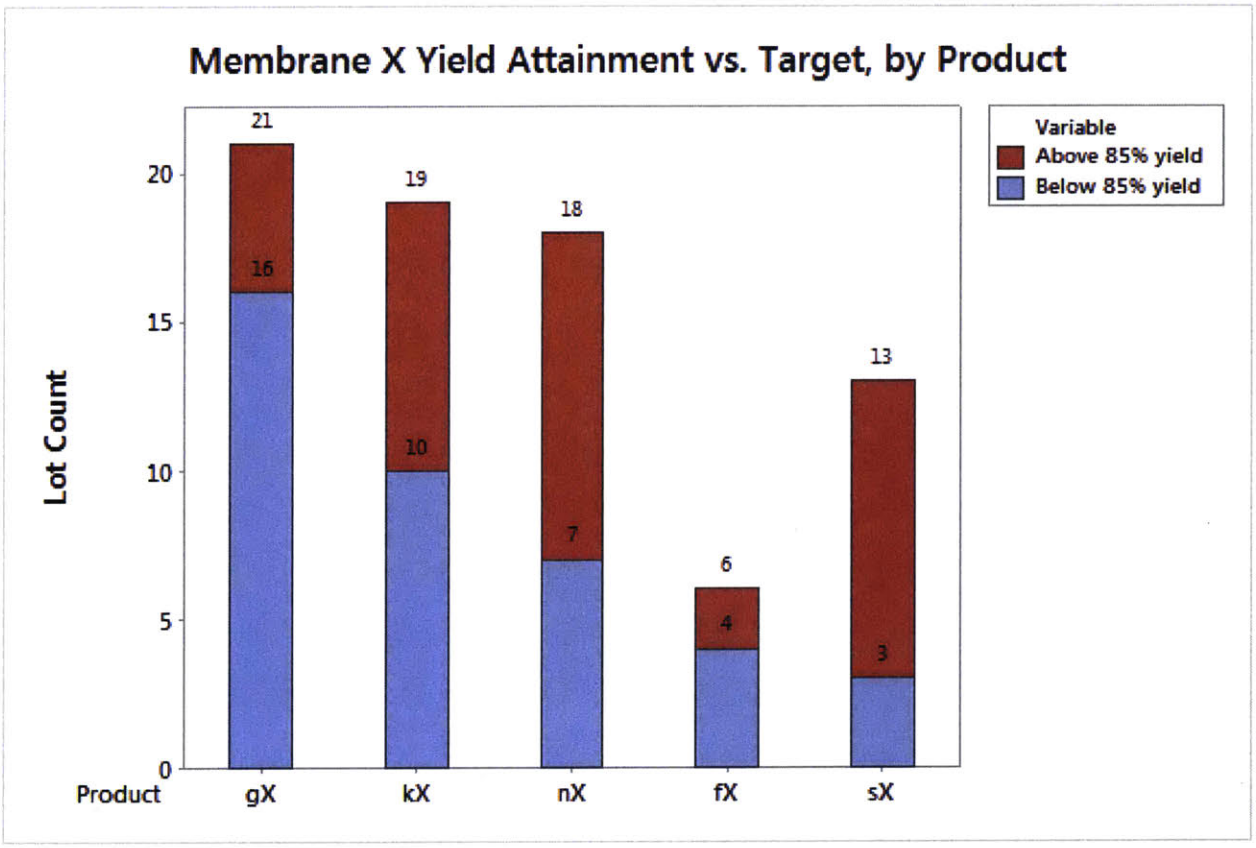

Figure 3-4: 2015 yield attainment of high volume membrane X grades.

The sampling plan of a media roll is cognizant of the two components of variability, and the trends observed in both tests do allow for root cause analysis to be conducted in the event of non-conformance. Typically, 12 specimens are removed from each media roll and subjected to both Test A and B procedures. A general sampling pattern consists of

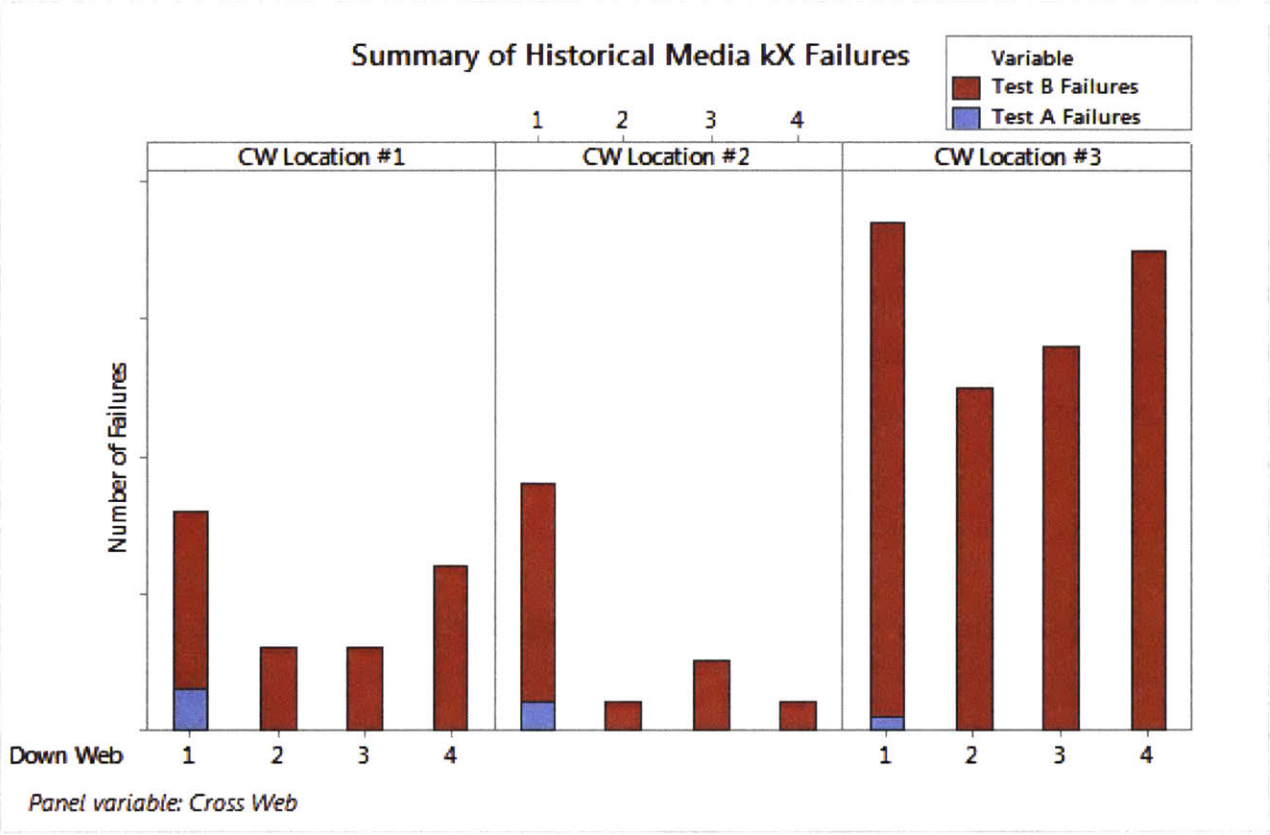

Figure 3-5: Historical media kX failures highlighting significantly more Test B failures than Test A, particularly in Location #3.

extracting three cross-web specimens at four down-web locations. This sampling plan was developed to strike a balance between the time consuming nature of the tests and providing sufficient resolution in terms of spatial variation.

The historical test data specific to media grade kX is analyzed and shown in Figure 3-5, and structured such that it depicts both CW and DW results. It is apparent that there are significantly more (30X) Test B failures when compared to Test A, and 67% of all Test B failures occur within Location #3 of the media. The frequency of these failures are relatively consistent down the media web and suggest special cause variation in the manufacturing process.

FilterCo employs stringent policies to ensure final product quality, and its release criteria of media is based upon the individual specimen results as well as the media roll average. Individual and average values for both Test A and B are specified for each media grade. The

location of an individual specimen failure (Test A or B, or both) within a media roll has the potential to trigger significant scrap of the roll. For example, an individual failure of any of the CW specimens in DW#3 would result in sections DW#2 and DW#4 being questioned. FilterCo argues that without further testing, it is not certain where the problem may have occurred and so 75% of the media roll would be scrapped.

3.4 Conclusion

In FilterCo's pursuit to become more operationally efficient, a number of initiatives have been implemented upstream of the manufacturing department. Reducing WIP inventory levels has exposed the impact of yield variability on the system: increasing the output of media, at the expense of increased scrap, has proven to be an ineffective countermeasure and prompts a formal investigation into the root causes of the variability.

The scope of the project is defined by two key insights revealed by means of data analysis:

1. Over 80% of media scrap is attributable to six of the twenty-five membrane grades.

2. Of these six, three membrane grades responsible for 70% of the current sales volume

Analyzing QC laboratory test results reveals that the ratio of Test B to Test A failures approximates 30, whilst the majority of the Test B failures occur in location # 3 of the media – twice as many as the other CW locations combined. In order to deliver maximum business impact, the project is to initially focus on media grade kX, considering factors that influence Test B performance in a cross-web manner.

Chapter 4

Reducing Process Variability

> A state of virtually uniform product can be achieved only through the careful study of the sources of variation in a process, and through action by the management to control the sources of extraneous or excessive variation.
>
> *Donald J. Wheeler* [32]

This chapter highlights the importance of on-going experimentation for the purposes of continuous improvement, and describes how the current manufacturing system does not promote learning owing to process design limitations and suboptimal reactions to poor yielding production runs. The chapter portrays how having a robust process model that relates machine inputs and process parameters to the output allows for experimental feedback, and how the application of hierarchical process control methods leads to yield variation reduction. The chapter concludes by showcasing yield improvements of up to 100% and, most importantly, yield variability reduction of 60% that amounts to 60% of the 2015 scrap media value.

4.1 Introduction

The yield of a particular media roll is determined by comparing the results of Test A and B to the FilterCo engineering specifications. From the results, the media is classified as either meeting or failing the specifications. This binary approach to manufacturing has not reinforced the importance of process discovery and continuous improvement, and institutes considerable complexity in identifying the factors driving the non-conformance. This method of manufacturing has reduced media manufacturing to a sequence consisting of "fabrication, inspection and [scrap]" [32].

To date, the root causes of poor yielding media lots have not been identified with certainty owing to the design of the manufacturing process with regards to the material, people and information flows. Where a single media lot would require a minimum of three weeks before yield data are received, media of the same grade would have been scheduled for manufacture during this time. The task of identifying the exact factor/s driving the yield non-conformance in a multiple-step, multiple-variable process is, understandably, overwhelming. Currently, the identification of root causes is conducted by means of a slow process of elimination in combination with speculative reasoning, commensurate with the production downtime time provided to conduct a thorough study.

This thesis focuses on reducing process variation by implementing hierarchical process control changes through a cycle of observation, hypothesis formulation and rapid experimentation. These rapid trialing events are grounded in scientific reasoning and understanding of the process mechanisms. The speed with which ideas are actioned enable success (or failure) to be revealed immediately, and provide some measure of sustainability which may spur further refinement or abandonment of the solution. This process of rapid trialing is rooted in the philosophies encapsulated in the PDSA cycle [7, 29] and relies heavily on building consensus within the department and drawing upon the practical experience of the associates. The cycle is initiated by planning a change (or test) with the explicit intent of process improvement. This plan is carried out, preferably on a small scale, and the results are recorded and studied. Once all of the learnings have been extracted from the results, a decision is made to either adopt, abandon or repeat under different conditions that will

prove or disprove a refined hypothesis.

4.2 Understanding the Manufacturing Process

Hardt [28] states that the goal of any process can be categorized into quality, flexibility and rate, and highlights the similarities between conventional operations objectives and the intent of classical feedback systems. He distills operational excellence as being concerned with minimizing production variation, increasing process flexibility and maximizing productivity. Feedback control is utilized to match output to input regardless of process disturbances, provide a high bandwidth response to new inputs and maximize the stable bandwidth of the process. Hardt discusses the complexity in implementing control methods to a broad range of manufacturing processes, but highlights the pitfalls of not appreciating the physical constraints imposed on the system by the process itself.

The benefits of feedback control are well documented in the literature; however, the implementation of control theory suggests that all prior hierarchical process control steps have successfully been implemented (Section 2.6). This work is centered around achieving operational excellence by developing and successfully implementing the parameter disturbance and sensitivity reduction initiatives that would ultimately allow for more sophisticated feedback control systems to be employed.

The process model as described in [27] is applied to the current media manufacturing process, and is depicted in Figure 4-1 where $\vec{\alpha}$ and $\vec{u}$ represent the sub-process step parameters and machine inputs, respectively. Figure 4-1 reflects the serial nature of the entire media manufacturing process, and reemphasizes the importance of output conformance of the individual sub-process steps since media performance feedback is only received at process step #5 ($\vec{Y}_5$).

Prior to the commencement of this work, FilterCo management had conducted a variability reduction workshop focusing on process step #1. This workshop comprised of technical and non-technical personnel, and generated many ideas aimed at reducing process variation. Many of these actions had been implemented and it was only logical to continue the varia-

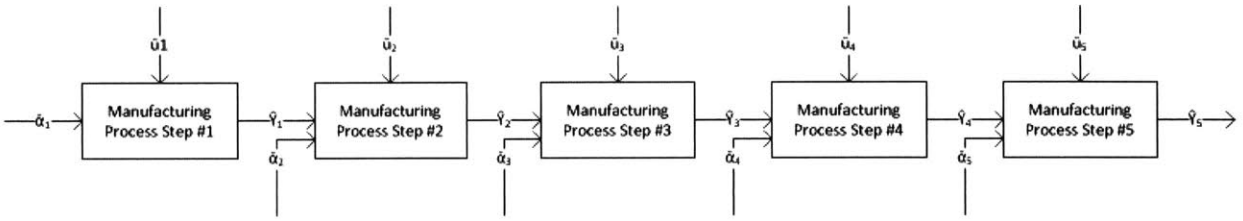

Figure 4-1: Media X manufacturing process model.

tion reduction process in step #2. Through independent research [13] and formal discussions with both the R&D and manufacturing teams, consensus was that process step #2 is the most important step in ensuring media conformance, and any successful variation reduction initiatives would greatly impact the output yield of the entire process.

Gaining expert knowledge such that a robust process model can be developed would only be achieved through hands-on, practical experience. Time spent with FilterCo associates learning, asking questions and identifying the critical activities of the process proved invaluable. Observing the manufacturing tasks being carried out while comparing to that of the SOPs provided insight into what the design engineers and scientists had initially intended for the process. All of these factors, combined with the framework provided by Hardt, enabled Figure 4-2 to be compiled.

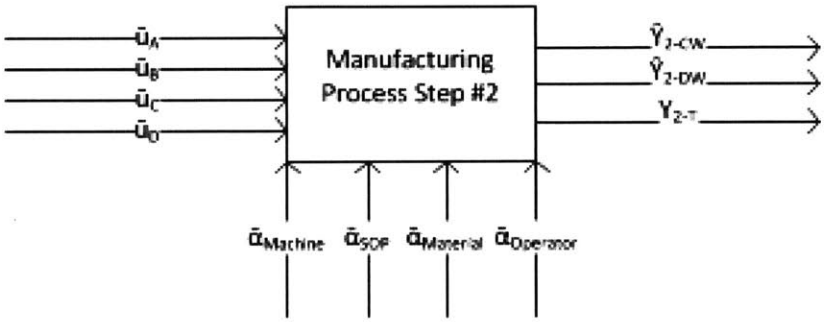

Figure 4-2: Detailed block diagram of media X manufacturing process step #2.

In the past, the importance of process step #2 warranted the addition of numerous sensors to the equipment. In aggregate, over thirty separate data streams are gathered and monitored over the course of a manufacturing run, collecting down-web, cross-web and point measurements. Most importantly, there are four pieces of equipment that are critical to

the manufacturing process, and their inputs are depicted separately by $\vec{u}_A$, $\vec{u}_B$, $\vec{u}_C$ and $\vec{u}_D$, and will be discussed in sections to follow. Furthermore, other parameters pertinent to the process are shown as $\vec{\alpha}_{Machine}$, $\vec{\alpha}_{Material}$, $\vec{\alpha}_{SOP}$ and $\vec{\alpha}_{Operator}$. Process step #2 produces three outputs, $\vec{Y}_{2-DW}$, $\vec{Y}_{2-CW}$ and Y_{2-T}, and are all critical in the performance of the media as well as assembly of the filter cartridges. Y_{2-T} refers to the thickness of the media and is the only immediately measurable output from the second process step and is used to make adjustments during the manufacturing process. Figure 4-2 in conjunction with the first-order variation equation, repeated here as Equation 4.1 for convenience, will form the basis for discussion regarding the variability reduction initiatives.

$$\Delta\vec{Y} = \frac{\partial Y}{\partial \alpha}\Delta\vec{\alpha} + \frac{\partial Y}{\partial u}\Delta\vec{u} \tag{4.1}$$

4.3 Reducing Process Disturbances

The first step in the process control hierarchy is the reduction of parameter disturbances, and consists of adherence to good housekeeping practices and the roll-out of relevant standard operating procedures. Once implemented, more advanced techniques are applied to the process, including SPC as well as appropriate feedback control of the equipment. While SPC is only a low-bandwidth diagnostic tool of the process output, it does reveal the presence of non-random disturbances. Once the presence of special cause variation has been identified, it is the responsibility of management to critically reflect upon the process and, in consultation with the manufacturing associates, determine the root cause of this non-random disturbance through a formalized problem solving approach.

4.3.1 The Connected and Critical Few

As noted previously, thirty process parameters are "monitored" during a typical manufacturing run and detail both down-web and cross-web changes. All of these parameters are neatly displayed on two monitors, and associates are expected to be mindful of all parameters whilst maintaining operational discipline during the manufacturing run. Initial conversations with

the associates concluded that all parameters are vital to the success of the media run, whilst no obvious priority could be assigned.

Interfacing with the R&D and maintenance personnel, it was quickly established that certain parameters within each process category needed to be prioritized higher than others. These conversations sparked a thorough analysis of the building infrastructure, the sources of supply to the equipment, and critical review of the modes of operation the equipment utilized in process step #2. With the assistance of the facility maintenance personnel, the process inputs are formally mapped (Figure 4-3) in order to allow for a systems approach to implementing variation reduction initiatives.

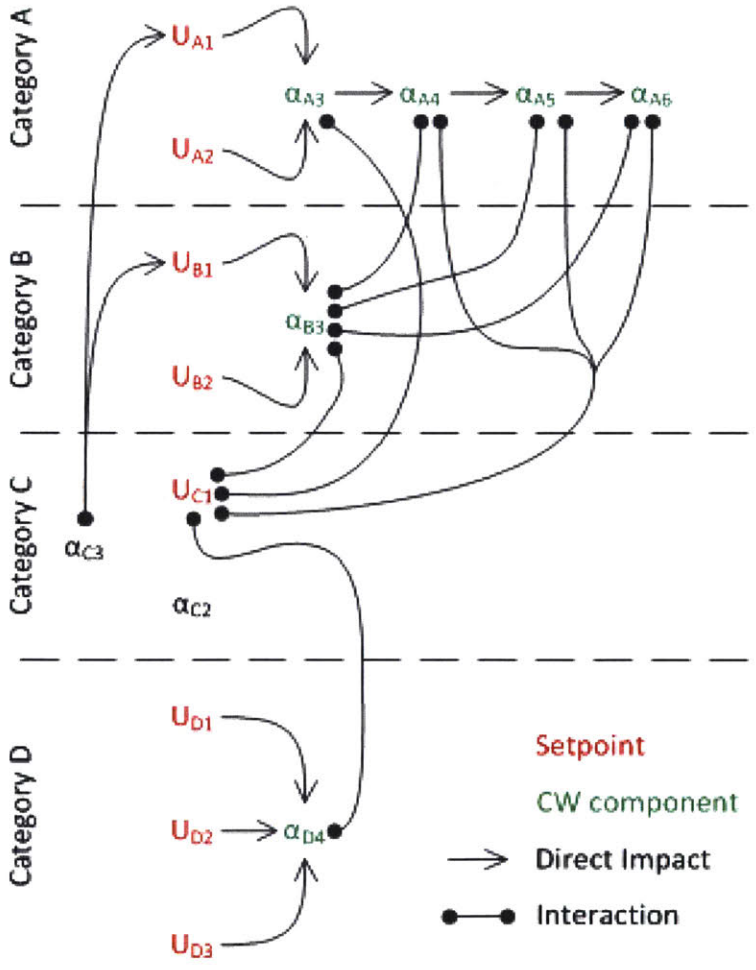

Figure 4-3: Parameter mapping of process step #2 depicting dependencies and interactions.

The thirty measured parameters are grouped into the four categories corresponding to

the pieces of equipment utilized. This approach reveals that only eight of the parameters monitored have machine set-points, whilst the remainder of the parameters are a direct consequence of the inputs and interactions. Furthermore, this analytical approach enables the parameters with cross-web components to be identified, and highlight the critical interactions of the parameters. Formally mapping the parameters provides valuable insight into the governing mechanisms of process step # 2, but more importantly is able to distill the thirty measured parameters into the critical few parameters that play a pivotal role in the success of the process, namely α_{C3}, u_{A1}, u_{A2}, u_{B1}, u_{B2}, u_{C1}, u_{D1}, u_{D2} and u_{D3}.

4.3.2 Cross Web Variability Reduction

With the main objective of reducing cross web performance variability in the media (see Section 3.3.1), it is a logical progression to identify parameters with cross web components and develop initiatives to reduce their cross-web variability. The formal parameter mapping process (Figure 4-3) highlights which parameters have cross-web components, and includes the following parameters: α_{A3}, α_{A4}, α_{A5}, α_{A6}, α_{B3} and α_{D4}.

Interestingly, two key parameter interactions are identified based on the analysis of the equipment:

1. The influence of u_{C1} on all parameters identified with CW components, and;
2. The interaction between parameter α_{B3} and parameters α_{A4}, α_{A5} and α_{A6}.

While the latter interaction proves to be more complex to solve without major equipment redesign, reducing the effects of the first interaction is achievable within a reasonable amount of time.

FilterCo is an established UF media manufacturer in the market whose presence and success over time has enabled it to make significant investment in research and development. Much of this research investment has been applied to the development of manufacturing equipment to be utilized in the processing of next generation media, seeking to improve upon current equipment and processes. Conversations with long-standing personnel reveals

the existence of another UF media manufacturing line whose design is based on that of media X. Describing the prevalence of parameter u_{C1} and its interaction with the other parameters to an engineer revealed prior knowledge of the problem and how it had been resolved on the newer manufacturing line.

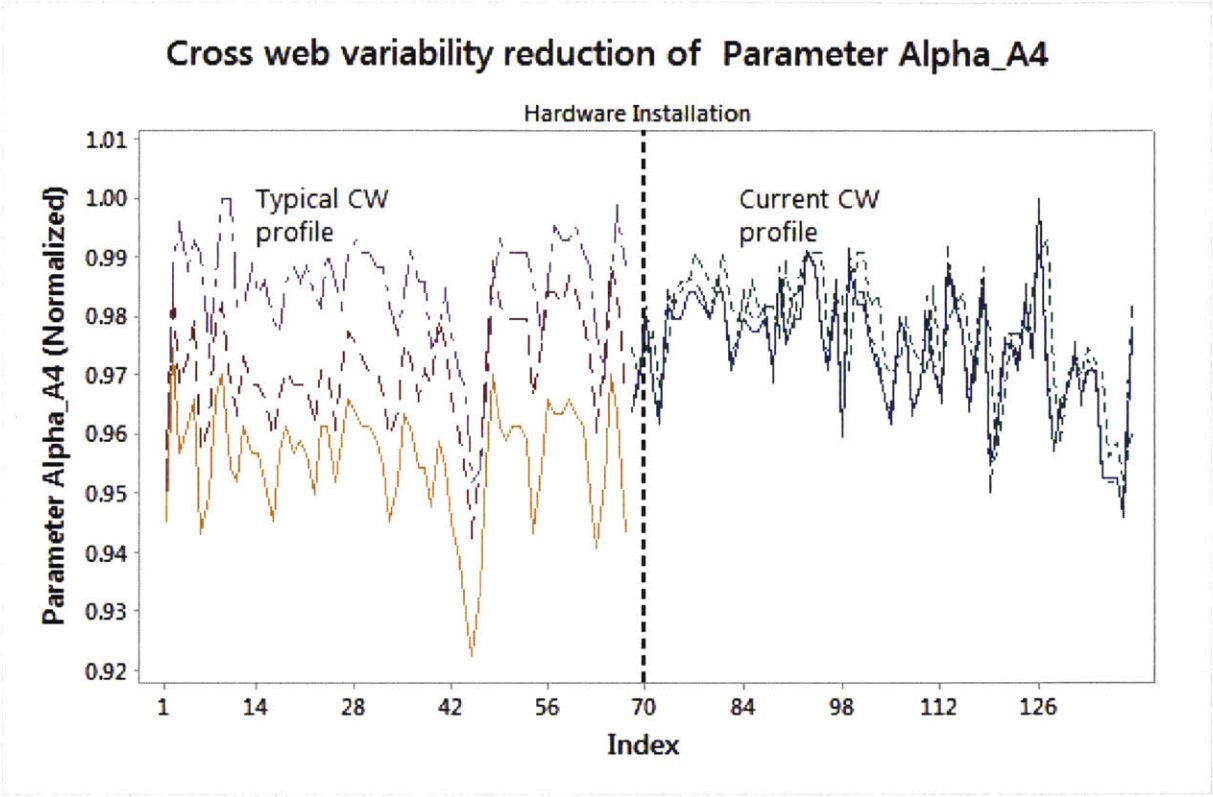

Figure 4-4: Immediate reduction in variability and absolute differences between CW locations by implementing known solution within FilterCo

Installing similar hardware on the media X manufacturing line results in an immediate reduction in the effect of the gradient field, shown in Figure 4-4 after index 70. The average absolute difference of parameter α_{A4} across the three cross-web locations is reduced by 3X whilst the within-run standard deviation is reduced by half. Similar reductions in absolute differences and variability are observed across all other parameters. Although the cross-web profiles are impacted, it is noted that there is clear evidence that the parameters are still not stable over time and the root cause of the instability remains to be investigated.

The methodology for reducing cross-web variability highlights the importance of open communication and breaking down barriers between departments and staff areas. Had a

team-based approach been instituted previously to solve this particular problem, it would have likely been solved much sooner with, potentially, a reduced number of non-conforming media lots. The implementation of the over-the-counter hardware is a relatively minor change to the manufacturing line, but possibly lead to higher yields through the Quality Control department and, ultimately, could result in producing a more uniform product for the customer. As part of FilterCo's daily management, supervisors from the respective areas walk around the facility and share their performance of the previous day with their colleagues. Although the intention of the exercise is valuable, the discussions have mainly circled around the symptoms and not solutions to the root causes of the problem. Rather, this form of daily management must be a team-based activity held with regular cadence to ensure quality process discipline and drive improvements around the area's critical performance metrics. Evidence of special cause variation must be addressed by the *team*, by applying a formal problem solving framework and taking urgency in eliminating the root cause.

4.3.3 Variable Supply Equals Variable Output

A first-hand account of a particular manufacturing run highlights the erratic nature of inputs u_{A1} and u_{B1}. Building infrastructure schematics show that both parameters are directly connected to α_{C3} (Figure 4-3) and are subject to fluctuations owing to the upstream activities within the facility also utilizing α_{C3}. The unpredictable nature of the upstream activities means that the media X manufacturing line could experience a disruption at any moment, which ultimately impacts the performance of the media. It was clear that these disruptions had been accepted for so long that the reactionary tasks necessary to maintain "control" had become second nature and could now be regarded, informally, as SOP. In the past, ideas to reduce the impact of α_{C3} had been put forth to management, but had not been acted upon owing to the financial costs involved, excessive downtime required for implementation and unproven nature of the ideas.

As part of this work, an idea was developed in conjunction with the associates, presented to management and accepted. Following the rapid trialing methodology, a high level risk assessment is conducted with input received from the associates on the manufacturing floor,

maintenance personnel and the quality team, and concludes that the trial be conducted on one roll of media during the manufacturing run so as not to impact the media team's ability to deliver product to the customer (filter assembly department).

The idea is to decouple parameter α_{C3} from the entire media manufacturing process thereby reducing its impact on inputs u_{A1} and u_{B1}. The idea can be regarded as a mechanical buffer whereby variable supply is received, and uniform supply is provided to the equipment. A majority of the hardware required is sourced from within the maintenance department and the remainder sourced from external suppliers. The solution is designed such that assembly can be done on-site and within the maintenance workshop thereby reducing downtime of the manufacturing line. FilterCo incurs minimal financial cost owing to the simplicity and appropriateness of the design.

The solution is found to have an immediate and significant impact on inputs u_{A1} and u_{B1}, and reduces within-run parameter standard deviation by 25X and 5X, respectively. The results of the trial are presented in Figure 4-5, and include the before and after parameter responses as a function of a time increment (index). It is noted that a number of experimental errors are observed in both figures and are a result of the associates not having adequate experience with the trial equipment.

The first rapid trial proved successful, but also identified opportunities for ergonomic refinement. With the changes made, it is believed that α_{C3}'s impact on u_{A1} and u_{B1} has been reduced as much as reasonably practical through the decoupling initiative. The success of the trial warrants that the equipment continue to be used while a final solution be developed in conjunction with the Advanced Engineering department. Training of the associates ensures their familiarity with the new equipment.

A failure of the past was to assume that an unproven idea needed to be judged on the basis of a full-scale design, thus demanding a complex and costly prototype for proof-of-concept. Instead, the power of rapid trialing is to prove the validity of an idea and whether its impact is in the *direction* intended. The idea is refined through a number of rapid trialing cycles and leads to a final proven design that can be built for full-scale roll-out. Spear [33] offers that *Toyota-like* operational excellence can be achieved by developing and nurturing

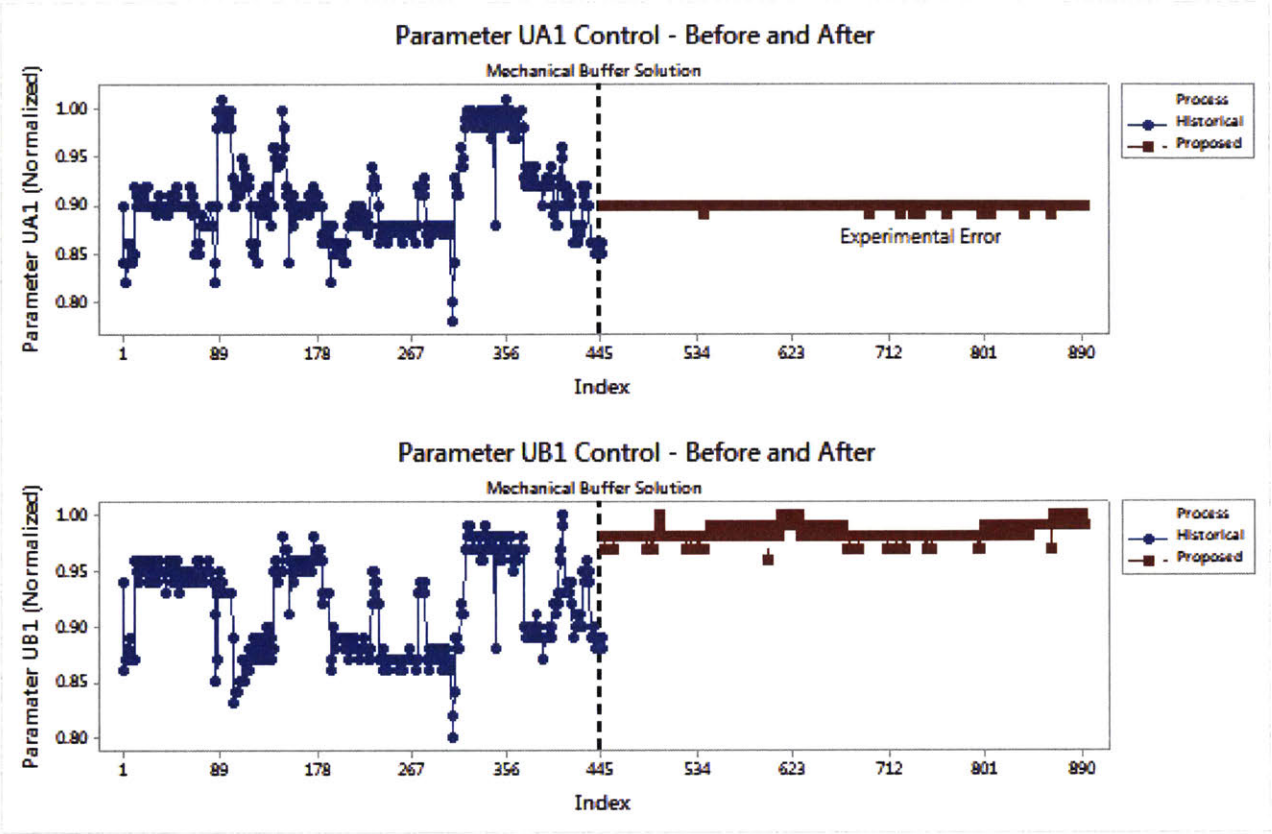

Figure 4-5: Reducing output variability of u_{A1} and u_{B1} through the implementation of a mechanical buffer solution.

the following four basic organizational capabilities:

1. Work is designed as a series of ongoing experiments that immediately reveal problems
2. Problems are addressed immediately through rapid experimentation
3. Solutions are disseminated adaptively through collaborative experimentation
4. People at all level of the organization are taught to become experimentalists

By instituting these four organizational qualities, FilterCo would enable its associates to succeed in their daily tasks, reduce the occurrence of inefficient work-arounds, ensure that its workforce builds upon localized insights that can be applied throughout the organization, and most importantly build an exceptionally adaptive and self-renewing organization.

4.3.4 Controlling the Machine Inputs

Establishing the state of the current process involves mapping the process with respect to movements related to material, information and people. This visual representation of the process, or "spaghetti diagram", is part of a suite of Lean conversion tools that assist in identifying opportunities to reduce waste. Successfully addressing unnecessary transportation, motion and waiting time contribute towards achieving a leaner process.

Closely observing the activities and tasks necessary to manufacture one roll of media, a spaghetti diagram is constructed for the process step #2. Figure 4-6 conveys the movements of the associate and does not include material and information flow for clarity purposes. The movements are depicted in colored lines corresponding to the piece of equipment that triggers that specific movement.

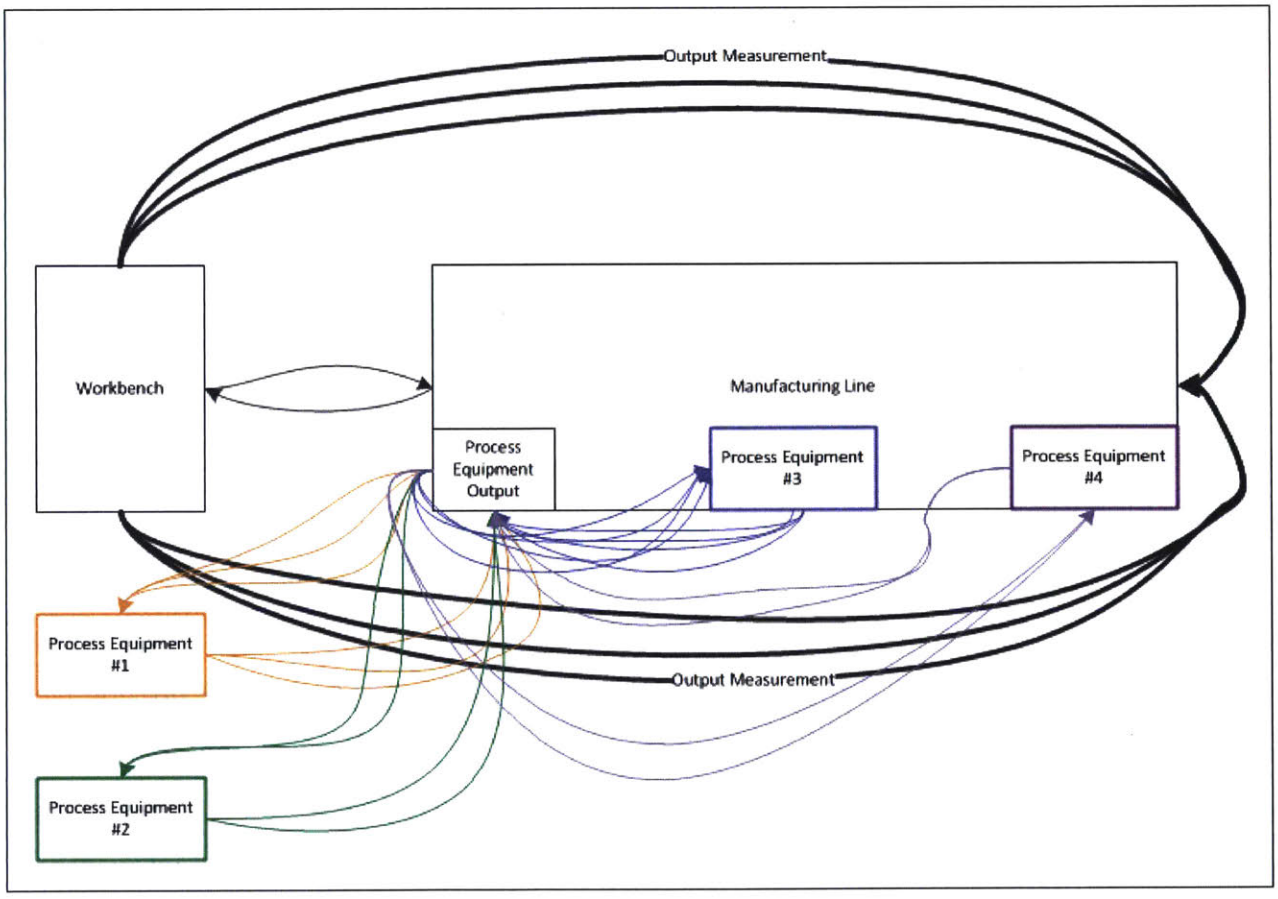

Figure 4-6: Large number of equipment adjustments made by the manufacturing associate.

The thick black lines depict the necessary movements of the associate when measuring

the cross-web thickness of the media. These values are then recorded on the workbench and the necessary adjustments, if any, are made to the process. Media thickness is the only recordable output that has been defined for this step in the manufacturing process, while all other movements should be regarded as wasteful.

In a natural conversational approach, the associate was questioned as to the reason for the movements between the various pieces of equipment, and what he had noticed on the display (*Process Equipment Output*) that had triggered these movements. The conversation revealed that the associate had noticed variability in the process output and had taken it upon himself to ensure that the process was "in-control" by adjusting the set points on the equipment. In this way, he would be correcting the behavior of the machines ensuring that he was making the best possible quality product.

Joining the associate at the display, he revealed the triggers and shared his thought process about how he compensates for this behavior by adjusting the input parameters. His experience had also taught him that changing parameters on one piece of equipment would typically affect other outputs too, and so he needed to compensate for those changes as well. This "trigger" would ultimately lead to multiple changes across different pieces of equipment, only to be repeated when the next trigger appears on the monitor.

It was clear that there was a tendency to assume that all the variation observed on the screen had a specific cause which led the associate to make the adjustments. Further dialogue suggests that the distinction between common and special cause variation had never been explained, and his best intentions had only exacerbated the variability owing to a lack of training. In most environments, the implicit assumption is that the implementation of SPC, and the calculation of control limits, automatically reduces the tendency or motivation to tamper with the process. There is no argument here that the control limits provide clear criteria for identifying the presence of special cause variation, but this is only evident to a person who has been sufficiently trained. Furthermore, it should not be the responsibility of the associates to compensate for an unstable system, but rather only *report* instances of out-of-control behavior. Policies and frameworks reflecting management's commitment to quality should necessitate that manufacturing cease until the root cause of the special

cause is investigated *by management*, and removed or reduced. It is the responsibility of management to provide assistance in removing problems connected with the malfunction of machinery [7].

The difference between special and common cause variation was explained to the associates, and the value in comparing the data points to the control limits was emphasized. In the event the data points fall outside the control limits, it is requested that manufacturing cease until management investigates the root cause. Reduced "tampering" of the process was found to greatly reduce the waste of continually moving around the manufacturing line, and associates are now able to focus on media thickness – the only output within their control.

4.3.5 When Workarounds become Standard Operating Practice

The decoupling initiative discussed in Section 4.3.3, greatly reduces the within-run variability of u_{B1}, but contrasted to the results of u_{A1}, it is evident that additional dynamics are being introduced into the system, and at regular intervals (Figure 4-5). The typical response of u_{B1} after the decoupling initiative was completed is shown in Figure 4-7, and plotted against a time increment (index). Visual analysis suggests that the disturbances are approximately periodic in nature and result in $\sim$10% increase in u_{B1} during the interval under consideration. In the pursuit of continuous of improvement, further investigation is performed including discussions with the associates as well as thorough observation of the manufacturing process.

As noted previously in Section 3.3, a number of rolls of media are manufactured in a given run. Once each of these are manufactured, the entire media line is stopped while the roll is manually handled and moved to the next step in the process. It is at this instant that parameter u_{B1} is affected by the associate in order to make the handling of the roll easier. What was not understood is the impact on the equipment's ability to maintain control over the parameter as well as its impact (albeit delayed) on another critical parameter α_{B3}. The original design of the manufacturing line did not consider the ergonomics involved in removing the roll from the line and a simple "work-around" had been implemented and passed on from operator to operator, embedding itself in the SOP.

A solution is developed that considered the ergonomics of the media roll removal process

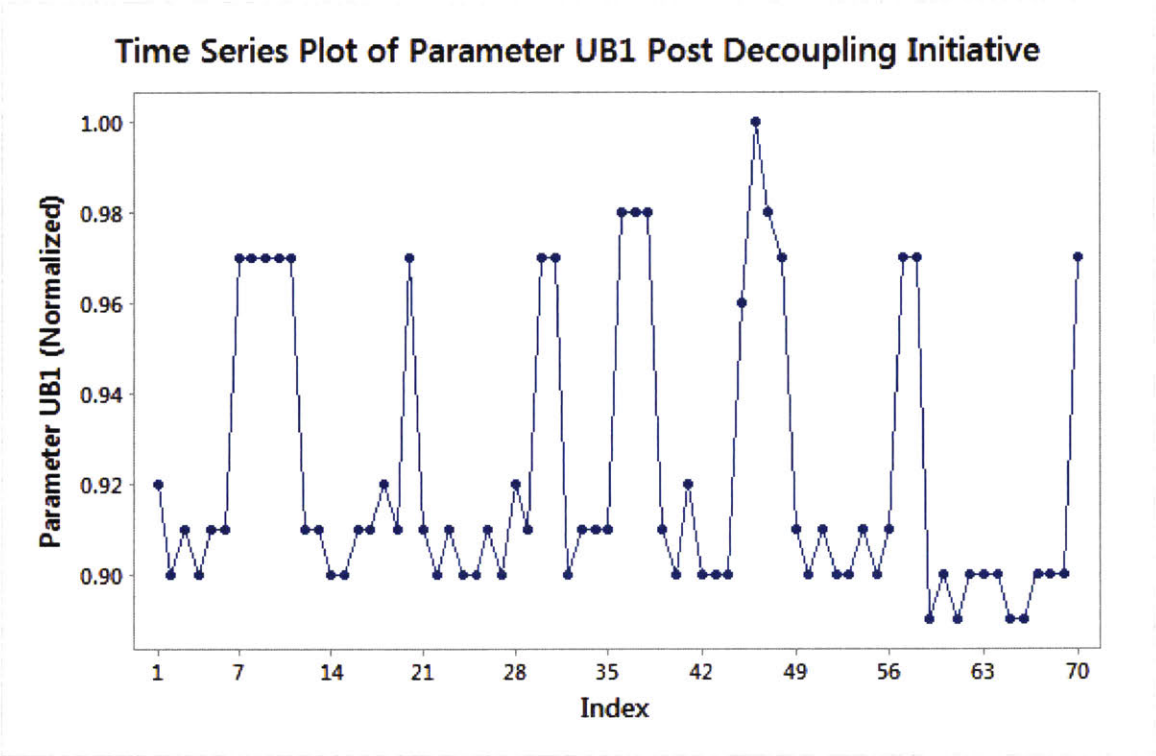

Figure 4-7: Parameter u_{B1} disturbances as a result of media roll handling work-around.

as well as the interaction of parameters u_{B1} and α_{B3}. By means of a device installed on the equipment, the disturbance on parameter u_{B1} is reduced whilst enabling fast and efficient removal of the media roll as depicted in Figure 4-8. The hardware was located within the facility's maintenance locker with the help of the maintenance personnel, and installed with minimal disruption to the manufacturing line.

Associates will always attempt to do the best they can, in the easiest way possible based on the constraints presented to them. The design of the manufacturing process and the equipment is the responsibility of management, and associates will operate within the confines of the system by applying their best efforts. In many instances, as is shown, an employee's best efforts do not result in creating value since the impact of their actions on the system have not been studied nor adequately explained.

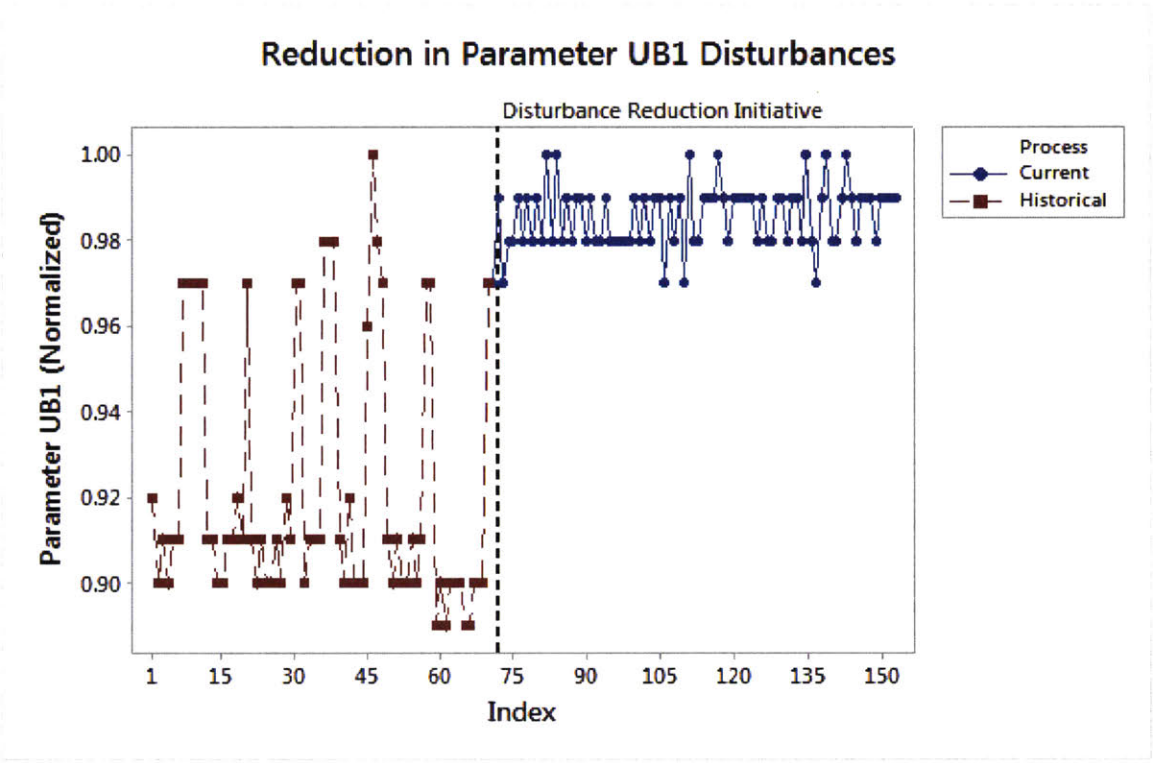

Figure 4-8: Reduction in process disturbance amplitude following successful hardware installation.

4.3.6 Enabling Feedback Control of Equipment

Almost all of the machines installed on the manufacturing line are equipped with feedback control capable of comparing the machine output with the set-point, and making adjustments accordingly. A majority of these are the original machines purchased during the 1990's and, on many occasions, their age have been called into question regarding their capability, particularly during instances of bad yielding media lots. By today's standards, these machines would be regarded as rudimentary, and they merely carry out their intended task based on the input (set-point) they receive. Owing to their continued service for the last 20 years, during times of good yielding and bad yielding lots, it is hard to conclude that their capability is stochastic – assuming that they have been maintained in *as good as new condition.*

The success of the previous initiatives generated sufficient inter-departmental momentum, enabling more problems to be highlighted and discussed, as opposed to being worked around or ignored. Furthermore, the basic control chart training was now being applied in the

associates' daily operation, and feedback was received that parameter u_{A2} was exhibiting strange behavior during the course of a manufacturing run. This behavior could be described as α_{A3} oscillating around a negative sloping mean, and the drift tending to increase over time. For clarity purposes, a brief snapshot of parameter α_{A3}'s behavior is depicted in Figure 4-9, plotted against a time increment, index. It is observed that the machine's control system is attempting to compensate for this behavior with an initial over-correction, stabilizing around the set-point, and then reverting to the same downward trend after only a few time increments.

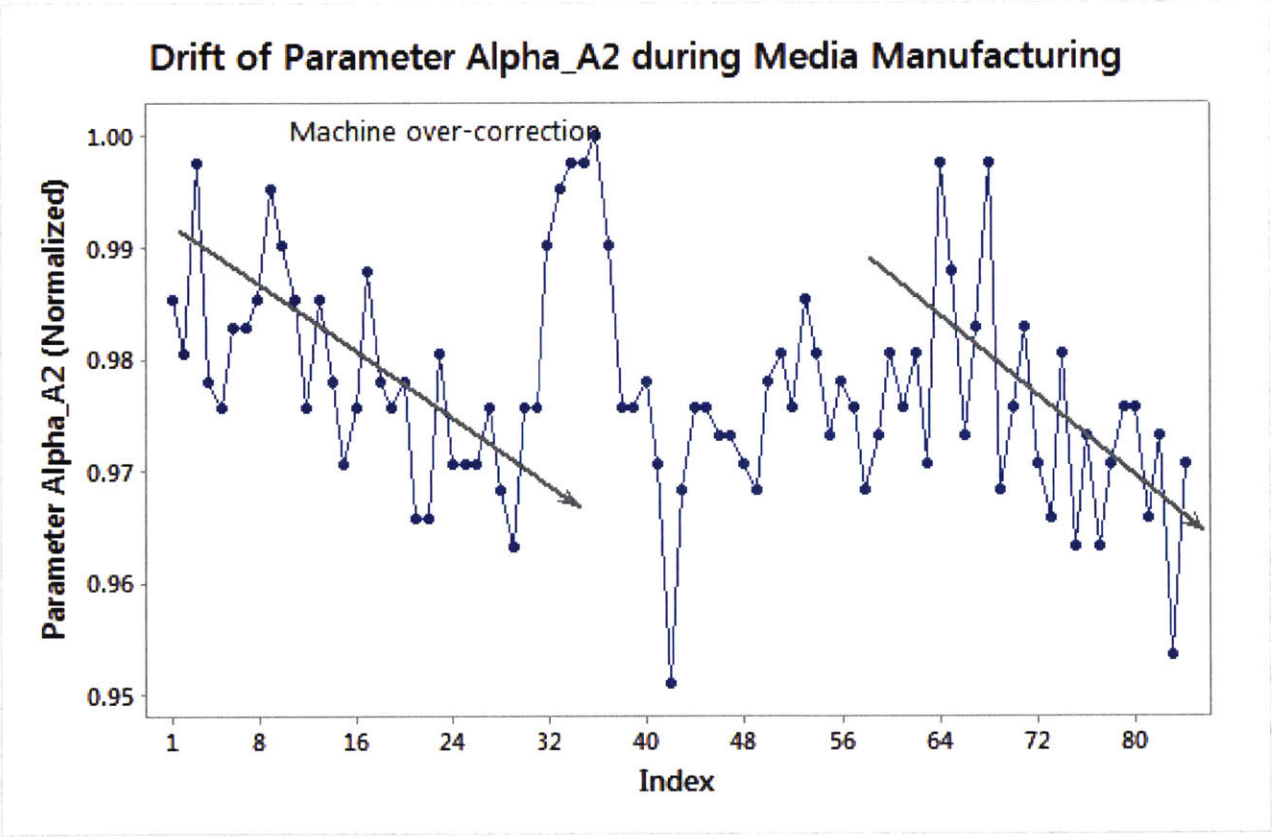

Figure 4-9: Presence of drift in parameter α_{A3}.

Based on the process model developed in Section 4.3.1, α_{A3} could only be influenced by two inputs, namely u_{A1} and u_{A2}. Owing to the improvements made to u_{A1}, instabilities in u_{A2} are the only logical explanation for the trends observed in α_{A3}. The initial hypotheses are that (1) the machine's control system is either receiving poor feedback from the sensors on the manufacturing line driving poor compensation; or (2) that the downward trend in

parameter α_{A3} is evidence of an imminent failure of an electrical component within the machine.

Process step #2 maintenance logbooks reflect recent calibration checks of all the sensors supplying information to the machine, and rule out the first hypothesis. Under the supervision of the maintenance supervisor and electrical engineer, the electrical panels of the machine were opened and contact points tested for continuity, resistance and voltage. In addition, the panels were also inspected for any obvious signs of wear. Small piles of black dust were observed to have collected directly below the electrical contactors at the base of the panels. The black dust is evidence of arcing between the surfaces of the contacts and a clear indication that the contactors had reached the end of their useful life owing to the high frequency of switching performed daily.

Wear of the electrical contacts means that any input received from the machine controller results in a delayed response from the contactors. Over time, the drift in parameter α_{A3} becomes so far out of the limits that when the contactors were finally able to close, the input signal from the controller had been so large (over-correction) that parameter α_{A3} reflects a spike in its output value. Replacing all of the electrical contactors had an immediate effect on the control of parameter α_{A3} and also actions their future frequent inspection on the maintenance logs as per the instructions of the electrical engineer.

Figure 4-10 reflects the improved control over parameter α_{A3} immediately after the replacement of the contactors. While the controllers are set to the original set-points, it is clear that they are no longer relevant, and do not provide the mean level required. Factoring for a set-point change during the run, the reader is advised to consider the range and trend of current and original set-point groupings individually.

Deming [7] states that new machinery and gadgets are not always the answer to reversing trends in poor quality and low productivity – such poor quality and low productivity may be because associates (management included) have not learned to effectively use [or maintained] the machines on hand. The capital cost of new machines can only be justified through statistical evidence that the operating requirement is outside of the machine's capability.

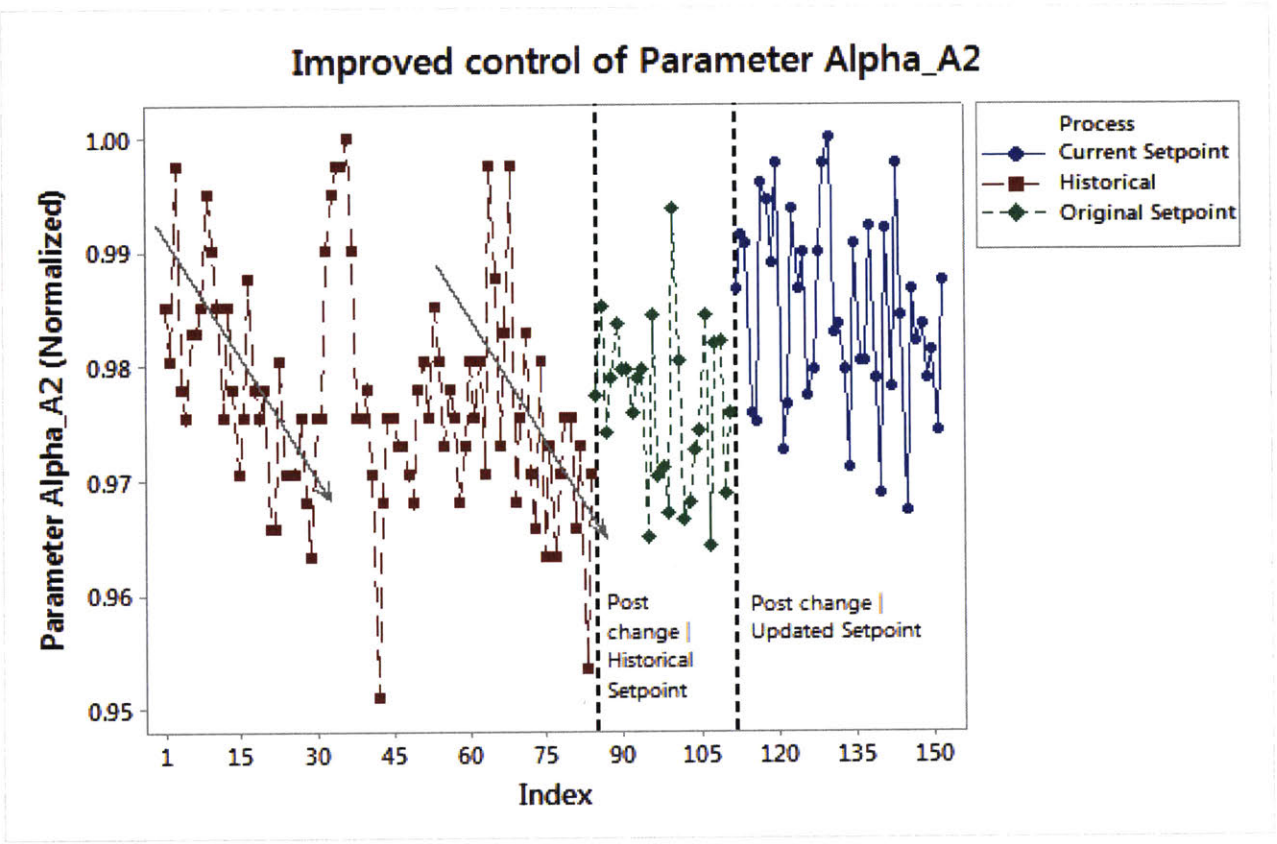

Figure 4-10: Improved control of parameter α_{A3} after replacing the electrical contactors.

4.4 Preliminary Test B Improvements

Variation awareness training of the associates combined with the process disturbance reduction initiatives discussed thus far have a tangible positive effect on the process. This combination has translated into the improved conformance of Quality Control Test B results, particularly in location #1 and #2 of the cross-web profile, and shown in Figure 4-11.

Figure 4-11 is an indicative example of media kX Test B results before and after the roll-out of the initiatives discussed. As can be seen, a marked decrease in the number of outliers in location #2 as well as a reduction in the inter-quartile range of location #3 are achieved. The inter-quartile range of location #1 appears to have increased when comparing before and after, but appears to be more consistent with location #2, and the majority of results are still significantly below the upper specification limit (USL).

Although the box-plot provides a good indication of the process improvement, it does

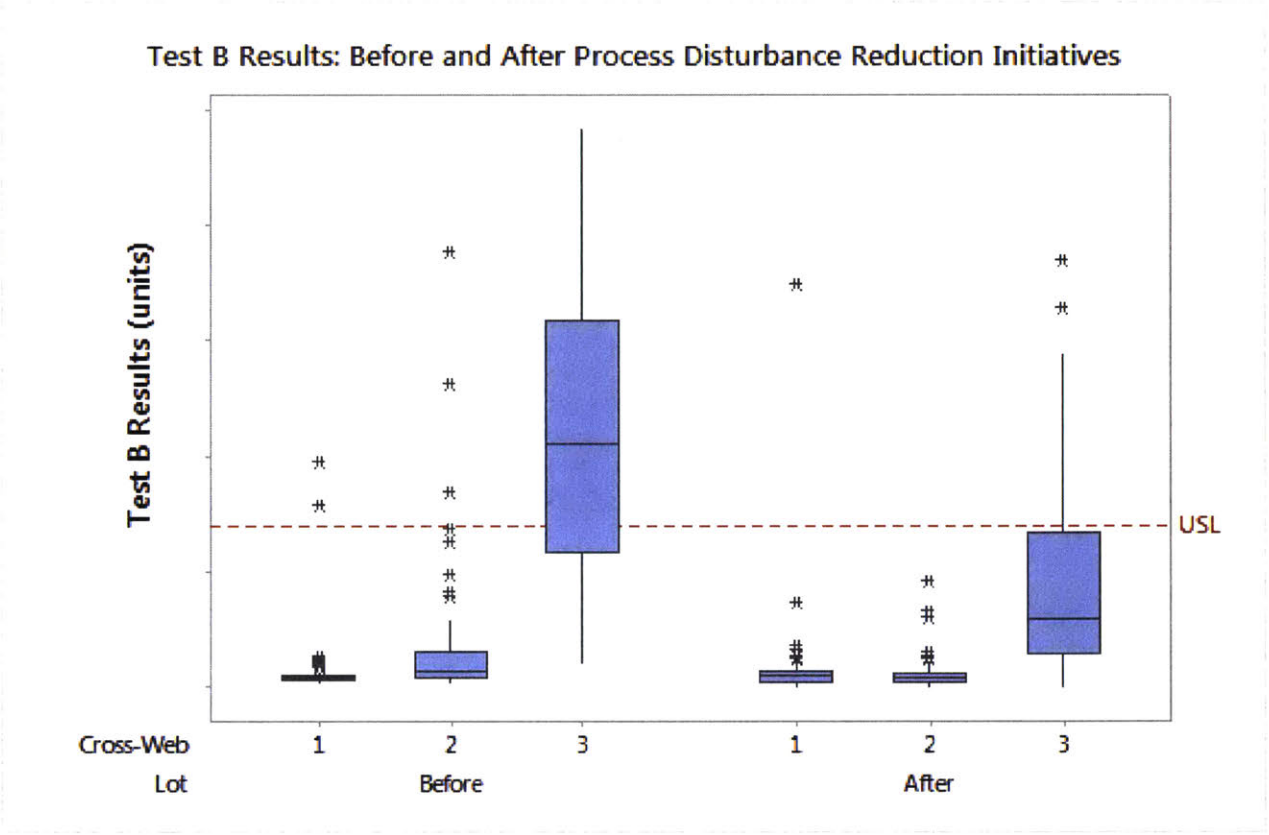

Figure 4-11: Impact of process disturbance reduction initiatives on Test B result outliers.

not provide a measure of the variance components in a nested variance application. When collecting data in batch sub-groups, the overall process variation may be due to random error as well as between-sample variation. Furthermore, within-sample variation (e.g., location effects) may also be a leading contributor of the overall process variation. By not accounting for these effects, and assuming the presence of purely random variation effects, the upper and lower control limits would be much wider than reality. In this situation, many of the points would be close to the center-line and within range – providing a misleading indication of an in-control process.

In media manufacturing, overall process variation will be a result of random error, batch, cross-web and down-web effects. Wheeler [32] recommends the use of the *three-way chart* or the *individual-moving range-range (I-MR-R/S) chart* in situations where additional variation drivers exist. An I-MR-R/S chart is compiled and shown in Figure 4-12; the sub-group (down-web) means are plotted on an individual chart where the moving range is utilized

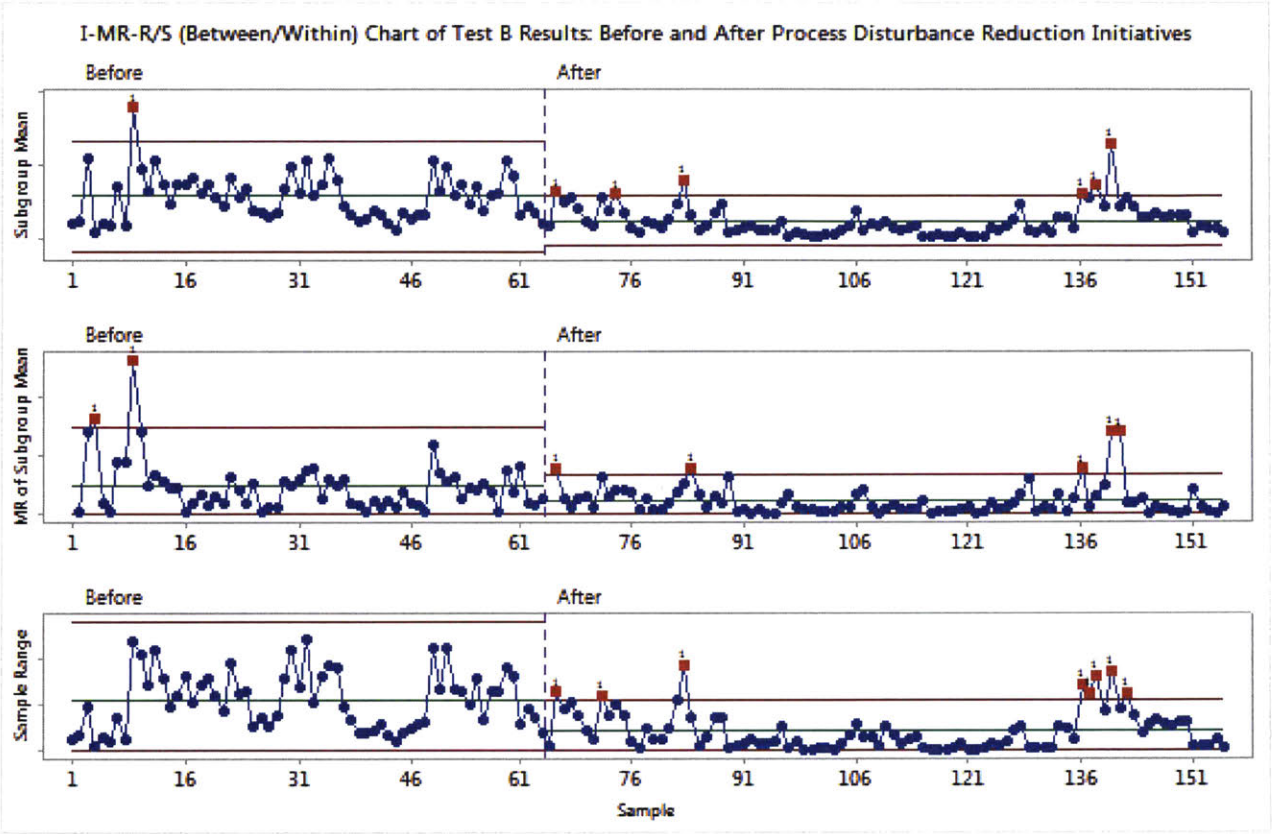

Figure 4-12: Three-way chart highlighting Test B results before and after process disturbance reduction initiatives.

to determine the control limits. In the case of media manufacturing, the polymer is mixed thoroughly enough such that homogeneity may be assumed and, as such, utilizing the moving range enables the random error to be estimated without incorporating the within-sample variation. The moving range chart provides a measure of the between-sample (down-web) variation whereas the range chart would indicate the presence of a significant within-sample (cross-web) variation component.

Thus, the combination of the three charts provides a method of assessing the stability of the manufacturing process based on location, the between-sample component of variation, and the within-sample component of variation. Figure 4-12 reveals manufacturing process improvement (tightening of control limits in all three charts) owing to the improvement initiatives, while also indicating the presence of special cause variation (points 66-83 and 135-143) throughout the improved run. Further analysis reveals that the majority of the outliers are present in location #3 of the media, requiring further analysis of the manufacturing

process.

4.5 Reducing Process Sensitivity

The implemented process and machine changes proved successful in reducing the number of parameter disturbances, and any further reduction in process step #2 disturbances would only be achieved through the installation of new equipment with the latest control system architecture, and other major equipment upgrades to reduce the interaction between $\vec{\alpha}_{B3}$ and $\vec{\alpha}_{A4}$, $\vec{\alpha}_{A5}$ and $\vec{\alpha}_{A6}$. The trade-off between equipment downtime, capital cost and machine control would need to be made by FilterCo management, and this process could only be initiated once the resolution or impact of machine control has been specified and justified.

Reducing the sensitivity of the process is to design and operate the process such that it is minimally affected by process disturbances [28]. By quantifying the effect of the parameter variations on the outputs, the process can be "tuned" so as to minimize these sensitivity functions [27]. Since there is no direct feedback loop, disturbances in $\vec{\alpha}$ cannot be compensated for directly, but their effects only minimized. This feedback loop may extend to include raw materials, whereby it is not always feasible or practical to request process improvements from the supplier. It is then the responsibility of the process owners to reduce the disturbance sensitivity by creatively changing tooling, modifying procedures, or choosing operating points in a manner that reflects scientific understanding.

4.5.1 The Confluence of Three Small Issues

With the process disturbance reduction initiatives discussed up to this point fully implemented, it is hypothesized that Test B failures are due to the media suffering mechanical damage during its manufacture. The inconsistency of Test B failures across the media web, as discussed in Section 4.4, particularly the gross failures in location #3 can no longer be explained by the presence of CW gradient fields, and necessitates a visual investigation of the testing samples.

In line with the CGMP policies and frameworks presented in Section 2.5, FilterCo retains

several sheets of each roll of media that is manufactured. In this way, should any external customer queries arise, FilterCo is in a position to conduct further testing. Visually inspecting the retained sheets reveals extensive mechanical damage in the form of small indentations on the surface of the media as seen in Figure 4-13, while the intensity of the indentations increases in the direction of location #3 (Figure 4-14).

Figure 4-13: Media indentations observed on the location #3 samples and subjecting the substrate to Test B markers.

Figure 4-13 represents two magnified samples of the media surface extracted from location #3, but at different down-web increments along the roll. Furthermore, it is known that Test B provides a measure of the selectivity of the media, and this performance characteristic is wholly dependent on the surface structure of the membrane (or "skin" layer). At greater magnification of the indentations, the substrate is observed which suggests that the source has penetrated the "skin" layer and, as a result, the media is reflecting gross failures when subjected to Test B procedures. The consistency in the patterning suggests that the indentations are a result of regular manufacturing processing, and might be easily identifiable if the individual process steps are critical reviewed.

The constituents of the polymeric solution used to manufacture the media rolls are high in solvent content, and the media is not sufficiently immersed during the phase inversion

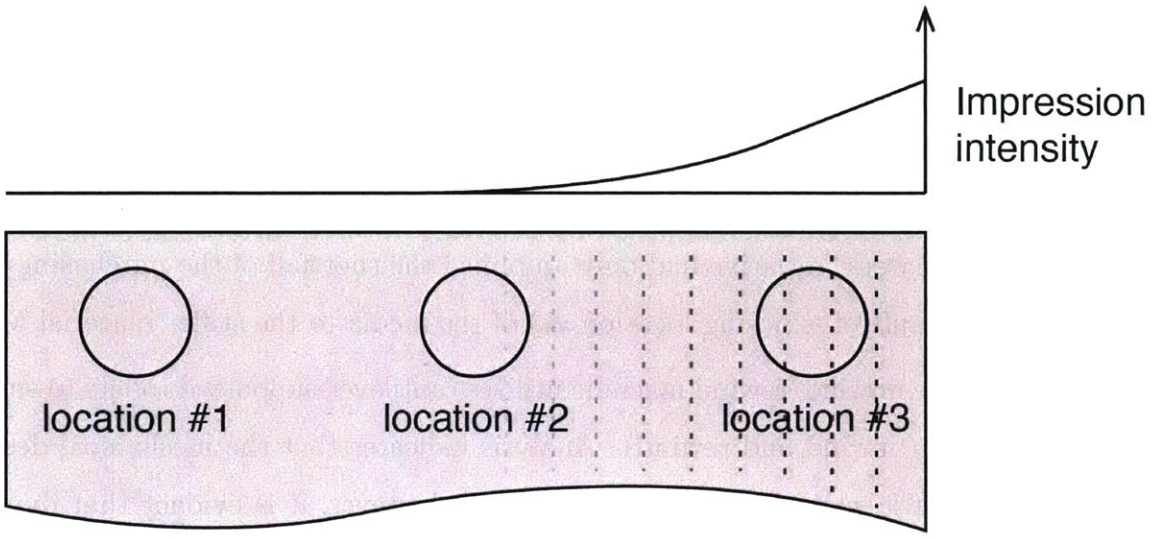

Figure 4-14: Indentation intensity observed across the surface of media sheets.

process to rid the media of excess solvents. As a result, the media rolls must be post treated in a separate process that allows for the efficient removal of the solvents. The physical output of process step #2 takes the form of a tightly wound media roll and, by design, traps a significant portion of the solvent between the surfaces of the wound media. Process step #3, however, is concerned with unwinding and rewinding the media roll to include two additional materials (material M#1 and M#2) separating the media surfaces from one another such that the excess solvents can be removed in process step #4. With the assistance of the associates, material M#1 is identified as the source of the indentations, confirmed by measurements having the same pitch spacing as observed on the surface of the media.

Further research regarding the process indicates that material M#2 specified in the unwind/rewind procedure is utilized in order to provide a protective interface between material M#1 and the surface of the media. However, measuring the width of the material M#2, it is determined that it is only be able to protect 90% of the media surface from the material M#1. Reviewing the purchasing specification confirms that the width of the protective material, and rules out any fault of the external supplier. Requesting further information about the source of the specification, none could be provided, with indications that "it has always

been this way."

A conversation with the associate responsible for process step #3 reveals that both material M#1 and M#2 were aligned with the location #1 media edge. While the SOP does not specify the alignment, the associate was concerned with ensuring that his work is reproducible and repeatable, and had taken it upon himself to ensure his consistency. The associate's standard work initiative had only amplified the shortfall of the purchasing specification, with the result of exposing location #3 of the media to the stiffer material M#1.

Furthermore, the unwind/rewind machine utilizes cantilever-supported rollers to suspend both rolls of media (unwind and rewind). Analysis indicates that the mechanical design is adequate for the static suspension of the media rolls; however, it is evident that dynamics were not considered in the design. Thus, the weight and number of media rolls over the length of the supporting roller result in a run-out in the direction of location #3 across the web of the media, as confirmed with a laser alignment system.

The media indentation could have resulted from any of the factors acting alone but did not; rather media indentations manifest into a significant non-conformance driver owing to the combination of all three factors.

Of particular interest is FilterCo's media gX and its use of a single material in the unwind/rewind procedure. Being exposed to the same phase inversion process, media gX also requires unwind/rewind processing, yet the SOP specifies the use of a different material (material M#3) to separate the surfaces of the media roll. Purchasing specifications of material M#3 are such that it is wider than a typical media roll. With the same polymer constituents, no technical background could be provided as to why media gX specifies a different material besides "it has been like this for years." With no clear risks associated with altering the material, an experiment is proposed to manufacture one media kX roll and utilize only material M#3 in the unwind/rewind process. This roll is to be processed as standard media kX, but not released to the customer.

Test B results of the experimental media kX roll are revealed in Figure 4-15 alongside the results of the previous parameter disturbance reduction initiatives, where the material M#3 countermeasure constitutes the sensitivity reduction initiative. It is noted that fewer data

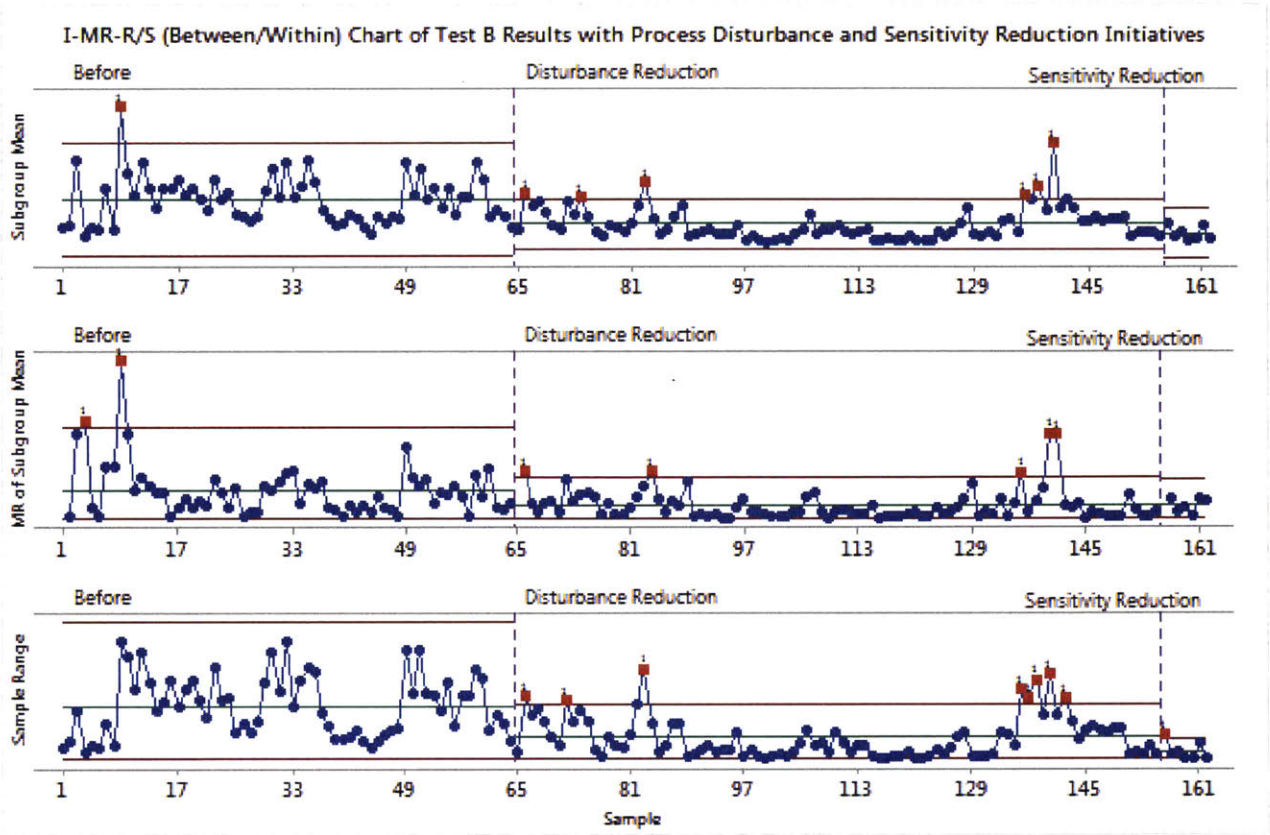

Figure 4-15: Three-way chart of Test B results before and after disturbance and sensitivity reduction initiatives.

points are represented in the sensitivity reduction portion of the figure owing to the outcome of the risk assessment to only manufacture one roll of experimental media. The sensitivity reduction initiative does not significantly affect the control limits of the subgroup mean nor the moving range of the subgroup mean; however, the sensitivity reduction initiative has a significant impact on the sample range. Reducing the upper control limit by 63%, the trial proves the feasibility of using material M#3 in the manufacturing of media kX and shows that high CW uniformity is achievable.

This sensitivity reduction initiative would not have been possible without the prior implementation of the various parameter disturbance reduction initiatives. From Figure 4-15, it is not initially evident that the media is suffering mechanical damage in the process owing to the large control limits. This sensitivity reduction change is only enabled by a systems approach to improve the process, and by following the process control hierarchy such that the root cause of the CW variation could be identified. The successful completion of each

hierarchical level reduced the upper control limit of the process and enabled further problems to be highlighted. Furthermore, close interaction with the associates on the manufacturing line revealed knowledge of the process problems, yet lack of engagement and empowerment had led to years of non-conforming product. Accepting specifications and processes without questioning their basis contributed to the continued use of a purchasing specification that was never adequate in protecting the media. It is clear that the associates take a great deal of pride in their work and implemented measures to be as consistent as possible, yet their efforts were poorly managed and only exacerbated the underlying root cause.

4.5.2 Reassembling the Equipment, Correctly

Media thickness is an important consideration in both its impact on flux and selectivity performance, but also on the overall height of the filter modules (stacked media sheets). Molds having a predetermined dimension only cater to small variations sheet thickness, and any excessive adjustment in media manufacturing will negatively affect the assembly process.

Based on the manufacturing process design, the Quality Control department is able to make statistical inferences regarding the performance of the media based on the sampling strategy. The department, however, is not able to visually inspect the individual media sheets due to the inspection time required and the resource availability. The media passing the performance tests are qualified and placed in inventory to be used by the Filter Assembly department. Assembly procedures dictate that every sheet must be inspected prior to being installed into a filter cartridge, ensuring the highest quality of the filter and reducing the wasteful allocation of assembly resources. In some instances, as much as 20% of an inventoried media roll could be scrapped owing to visual defects. The two major contributors of scrap are termed "tiger stripes" and "bald spots."

Tiger stripes are shown in Figure 4-16, where the darker sections of the media represent the sub-optimal application of the polymeric solution on the substrate. The thicknesses of these areas are substantially larger than the target thickness of the manufacturing run, and result in gross failures when subjected to the QC performance tests. Further complicating the problem is the infrequent occurrence of the tiger stripes in the media. The initial hypothesis

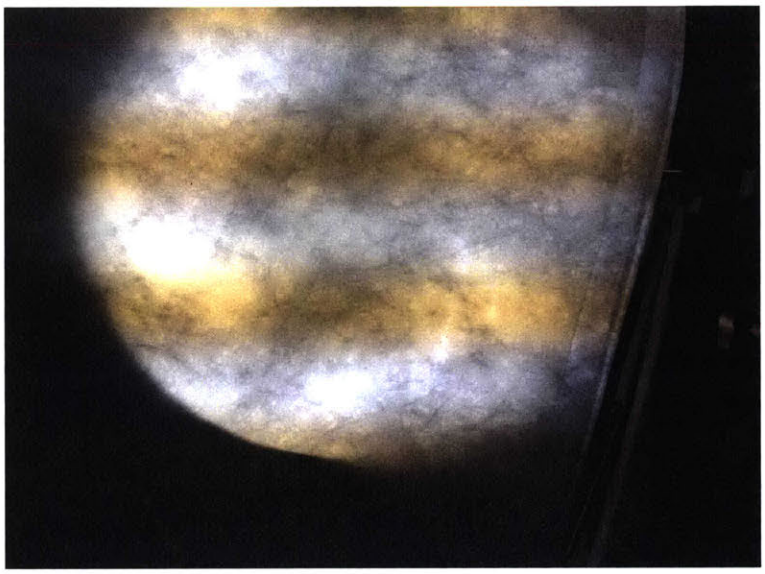

Figure 4-16: *Tiger stripes* present in the manufactured media

suggested that the visual defects are a result of poor quality material received from the substrate supplier; although the supplier had been notified, confidence was low amongst FilterCo management that the problem would be rectified based on previous experience.

Closer observation of the polymer application process reveals significant lateral movement of the web as it is unwound from the substrate roll. In instances where the lateral movement does not "stabilize", the substrate roll is shifted by the associate to ensure the web center aligns with the center of the casting die. During a typical manufacturing run, seeing the misalignment of the web would be due to pure chance, as such observations are not included in the SOP. Upon further inspection, it is determined that instances of web misalignment give rise to the tiger stripes.

Figure 4-17 represents the front-view of a casting die and emphasizes the casting die support brackets. From the design of the brackets, it is evident that the original designers envisioned web alignment disturbances and provisioned for it in the design by removing material from the bracket to provide a larger gap. However, current bracket installation practices had negated the efficacy of this sensitivity reduction measure – during periods of web drift, there was insufficient space for the substrate to move and leading to the formation in peaks and valleys within the flexible substrate. As the polymeric solution is cast onto the substrate, excess solution collects in the valleys of the substrate and leads to the formation

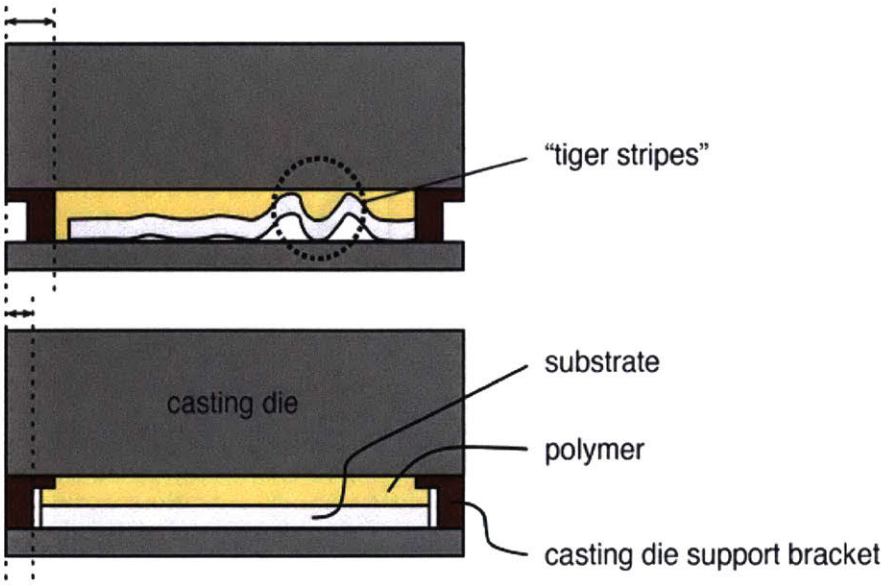

Figure 4-17: Importance of orienting the casting die brackets correctly to reduce sensitivity towards raw material variations.

of tiger stripes. Although the root cause of the web drift is attributed to misalignment of the substrate roll during its specific manufacturing process, installing the casting die brackets as per the original design results in reduced the sensitivity of the casting process to web drift and, in turn, reduces the frequency of tiger stripes.

4.5.3 Raw Material Variability

Another visual defect often seen in the media is what is termed as "bald spots", or areas of no polymer, that occur predominantly in the thinnest polymer add-on target media grades. As with the indentation marks discussed previously in Section 4.5.1, these bald spots lead to gross failures seen in both Test A and Test B results since the substrate does not possess any filtration properties in the presence of these bald spots, and thus would not present any resistance in flux or selectivity. Similar to the issues regarding tiger stripes, the sampling strategy does not allow for every sheet to be tested, and based on the release criteria, sheets with bald spots may be inventoried for use and later scrapped when inspected for visual defects.

Referring to Figure 4-18, overall or target thickness (h) is a critical parameter affecting

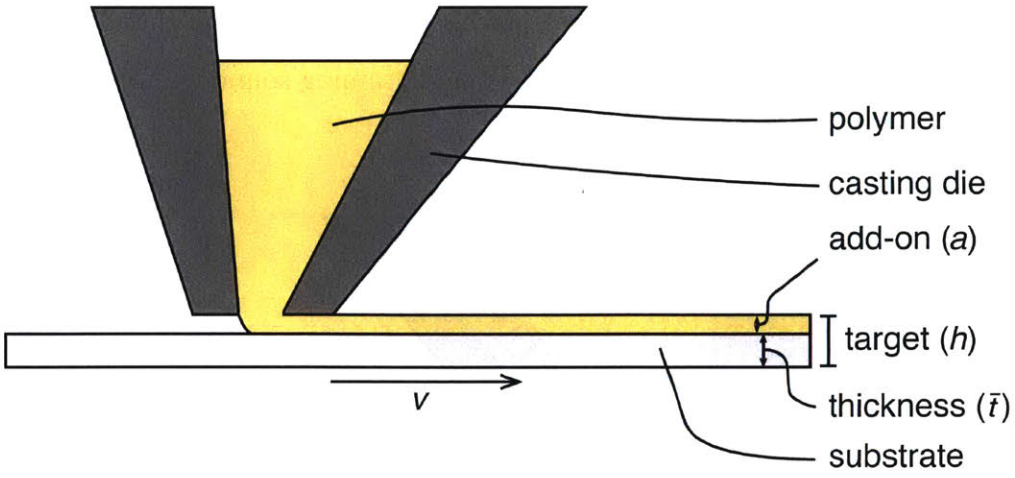

Figure 4-18: General layout of flat sheet membrane manufacturing, adapted from Ren et.al.[22].

media performance, and consists of the average substrate thickness ($\bar{t}$) and the target add-on thickness (a). Each media grade is assigned a specific polymer add-on thickness (a) that ensures conformance to Test A and B specifications as well as conformance to the mold design when the media sheets are stacked in the filter assembly process. Overall thickness ($\bar{t} + a$) is monitored throughout the manufacturing process and adjustments are made by moving the casting die vertically, relative to the surface of the substrate.

As per FilterCo's SOP, a substrate lot (or roll) is sampled prior to media manufacturing. Within each sample, numerous thickness measurements are obtained that quantify both CW and DW thickness. A global substrate average thickness ($\bar{t}$) is obtained by aggregating all measurements and is used to determine the target thickness (h) for the specific media grade to be manufactured. The gap between the casting die and substrate surface is set as in Figure 4-18 to initiate process step #2, but may be adjusted during the manufacturing run based on the updated thickness information received.

Once the Quality Control department is satisfied that the media has passed the applicable performance criteria, the entire roll of media is delivered to the Assembly department. Owing to the sampling strategy employed, each sheet is visually inspected for mechanical defects and passed/scrapped prior to use. During periods of high demand, scrapping media sheets

disrupts the scheduling of the Assembly department and results in unnecessary delays and/or poor OTD performance. For a company that places significant value on customer satisfaction, visual defects do not contribute towards FilterCo maintaining sound customer relationships.

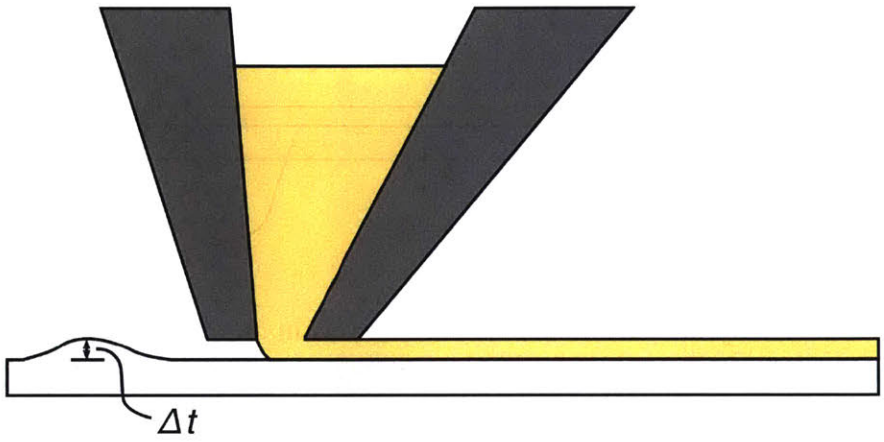

Figure 4-19: Impact of substrate thickness variability in flat sheet manufacturing using a fixed position casting die, adapted from Ren et.al.[22].

Owing to the importance of the polymeric layer, all of the processing steps have been designed such that contact with the media surface is minimized. Process step #2, however, is concerned with the application of the polymeric solution, and by design plays a critical role in the establishing the structural integrity of the polymeric layer. More specifically, the casting die controls the thickness of the media and its design "scrapes" away any excess solution. Since the casting die does not move dynamically, substrate thickness variability as defined in Figure 4-19 was identified as the root cause of the bald spot problem. It is determined that if the thickness variability of the substrate (Δt) exceeds that of the add-on target (a), the polymeric solution will be scraped away from the surface of the substrate because the design of the system assumes excess polymer has been deposited on a substrate of constant thickness.

Analyzing the historical substrate thickness results, it is confirmed that significant variability exists within roll as well as between substrate lots as seen in Figure 4-20. Comparing the add-on target to the variability in the moving range (DW thickness) and sample range

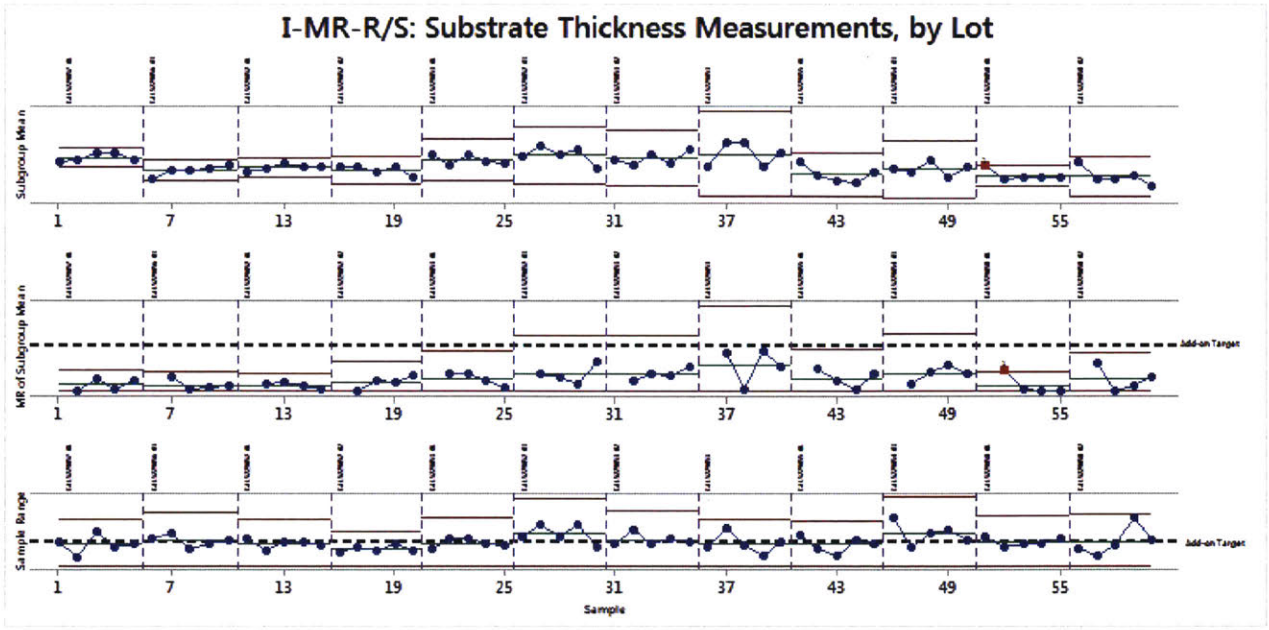

Figure 4-20: CW and DW substrate thickness variability greater than the minimum add-on polymer target thickness

(CW thickness) control limits, the prevalence of bald spots is understood.

The current design of the casting die assumes thickness uniformity and is not capable of responding dynamically to varying substrate thickness. A previously suggested solution included the design of an improved casting die that would be able to respond dynamically to thickness variability through the use of sophisticated feedback control. Although plausible, the solution represented significant capital expenditure and, due to the complexity in the design, could not be proven with rapid trialing methods.

Comparing and contrasting polymer application technologies within FilterCo, an alternative solution is identified that enables finer resolution of the gap setting, and that is also less sensitive to thickness variability of the substrate. Furthermore, the identified equipment is currently unused and is well suited to a rapid trialling event: as part of investing in new technology, FilterCo previously designed and manufactured an applicator technology in order to have improved the control over media thickness, and that could, to some degree, cater to variability in substrate thickness. Owing to the differences in mounting dimensions, significant mechanical design was required that accommodated the working mechanism of the equipment while catering to the physical constraints that the process step #2 platform

offered. Given the contrasting method of applying polymeric solution onto the substrate, the media manufactured in the trial would not be made available for assembly. Furthermore, owing to the time required to install the new piece of equipment, only three rolls of media are to be produced, and intentionally utilize a substrate roll with high thickness variability.

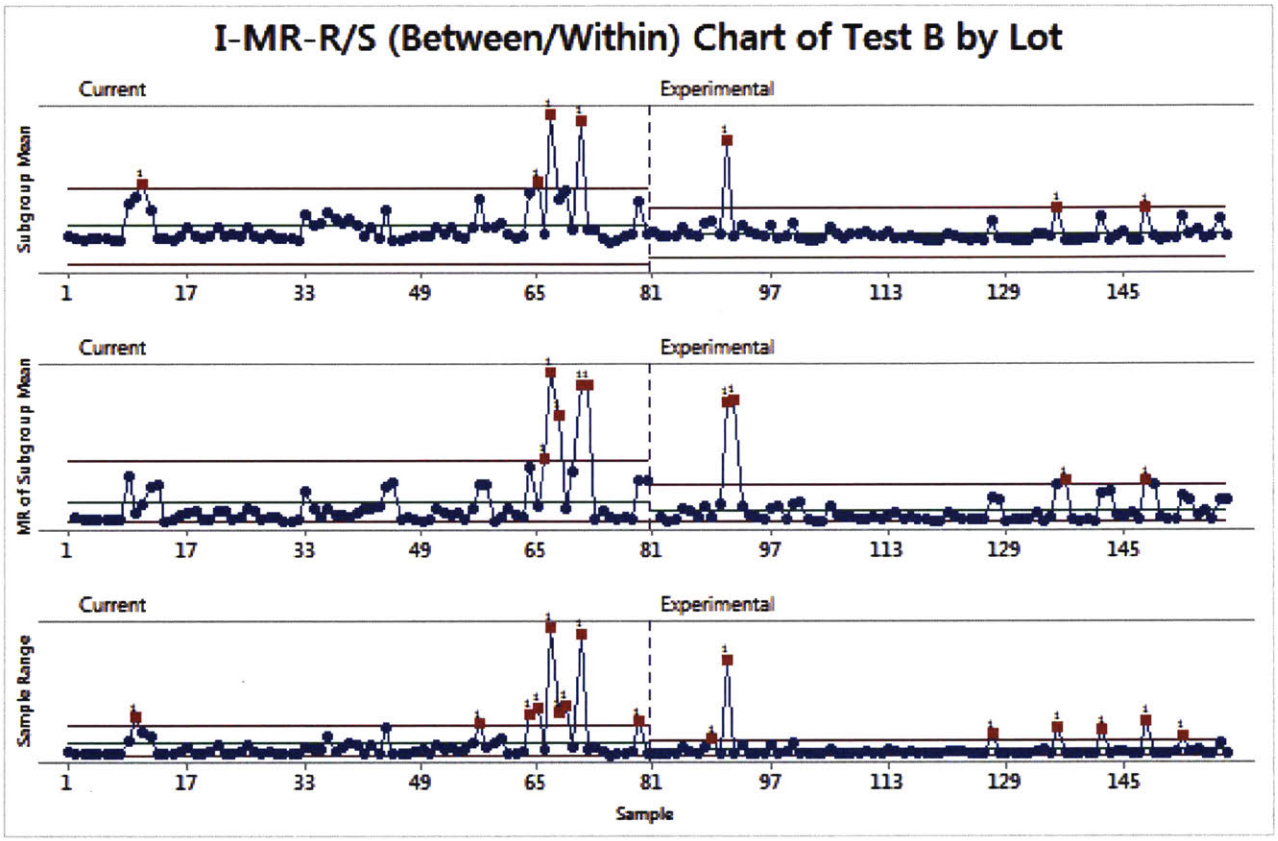

Figure 4-21: No statistical difference in Test B results of current casting die technology and experimental application technology.

The Test B results of the rapid trialing event are depicted in Figure 4-21, and show no statistically significant differences when compared to the current application technology. It is noted, however, that the mechanical defects of process step #3 had been highlighted at the time of this experiment and considerable effort was now being made to align material M#1 with the center of the web. In addition, the frequency of bald spots decreased significantly; whereas a previous roll of media manufactured conventionally yielded only 60% owing to bald spots, a roll manufactured using the experimental application technology and the same substrate lot yielded 90%, after factoring for bald spots. The success of this rapid trialing event has led to the formation of a new project to design and manufacture a mounting

bracket that is more user friendly and capable of accommodating the various equipment interactions.

4.6 Summary of Work and Results

In its continued pursuit for operational excellence, FilterCo had implemented a number of downstream initiatives that reduced WIP inventory while maintaining its OTD promises to customers. Production yield variability is not a recent occurrence, but had been hidden from both the Manufacturing and Assembly department owing to sufficiently large WIP inventory levels, and was finally exposed on account of inventory rationalization combined with increasing demand. In order for FilterCo to ensure continued future success, this project was conceived with the objective of reducing production yield variability.

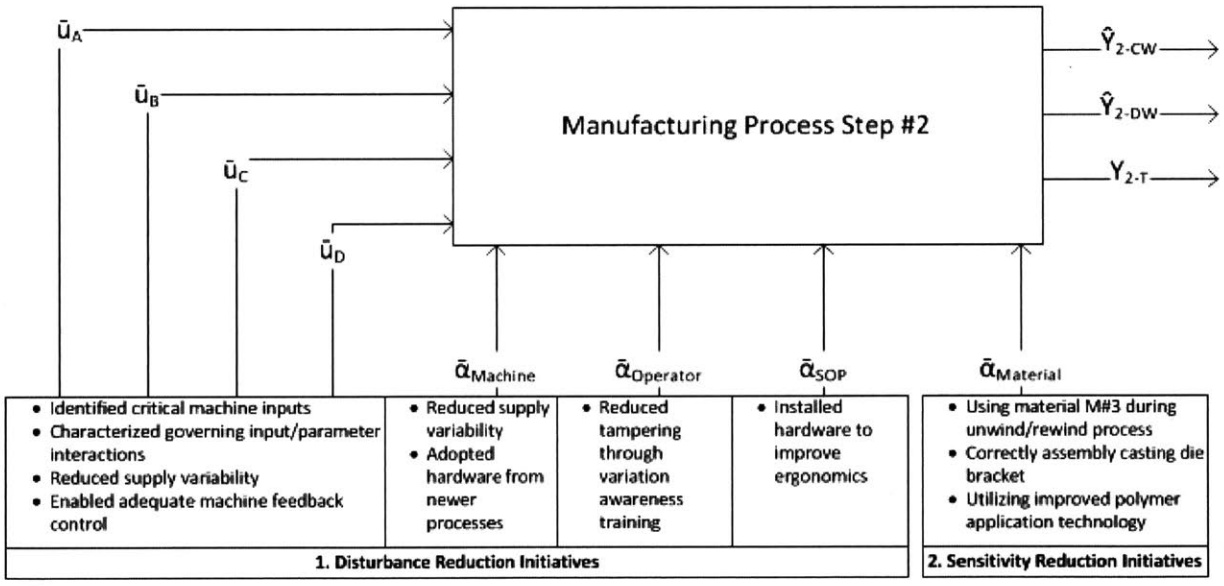

Figure 4-22: Summarized process control initiatives implemented during the project and categorized as per the control hierarchy.

The goal of the project was achieved by developing a robust process model, and implementing process control initiatives through an iterative cycle of learning that consisted of hypothesis formulation and rapid experimentation. Furthermore, the implementation of the interventions were prioritized according to how they pertained to disturbance reduction,

sensitivity reduction and disturbance counteraction. Figure 4-22 summarizes the process control initiatives implemented throughout step #2 of the media X manufacturing process, and details the machine inputs and process parameters that benefited from the specific interventions.

The impact of the process disturbance and sensitivity reduction initiatives are reflected in Figure 4-23 detailing the rolled throughput yield (RTY) as verified by the Financial department, and includes the experimental rolls manufactured during the project that are regarded as scrap. Increased yield performance with respect to variability is observed in the tightening of the control bounds across the board, as well as an average yield improvement seen in media grades fX and gX.

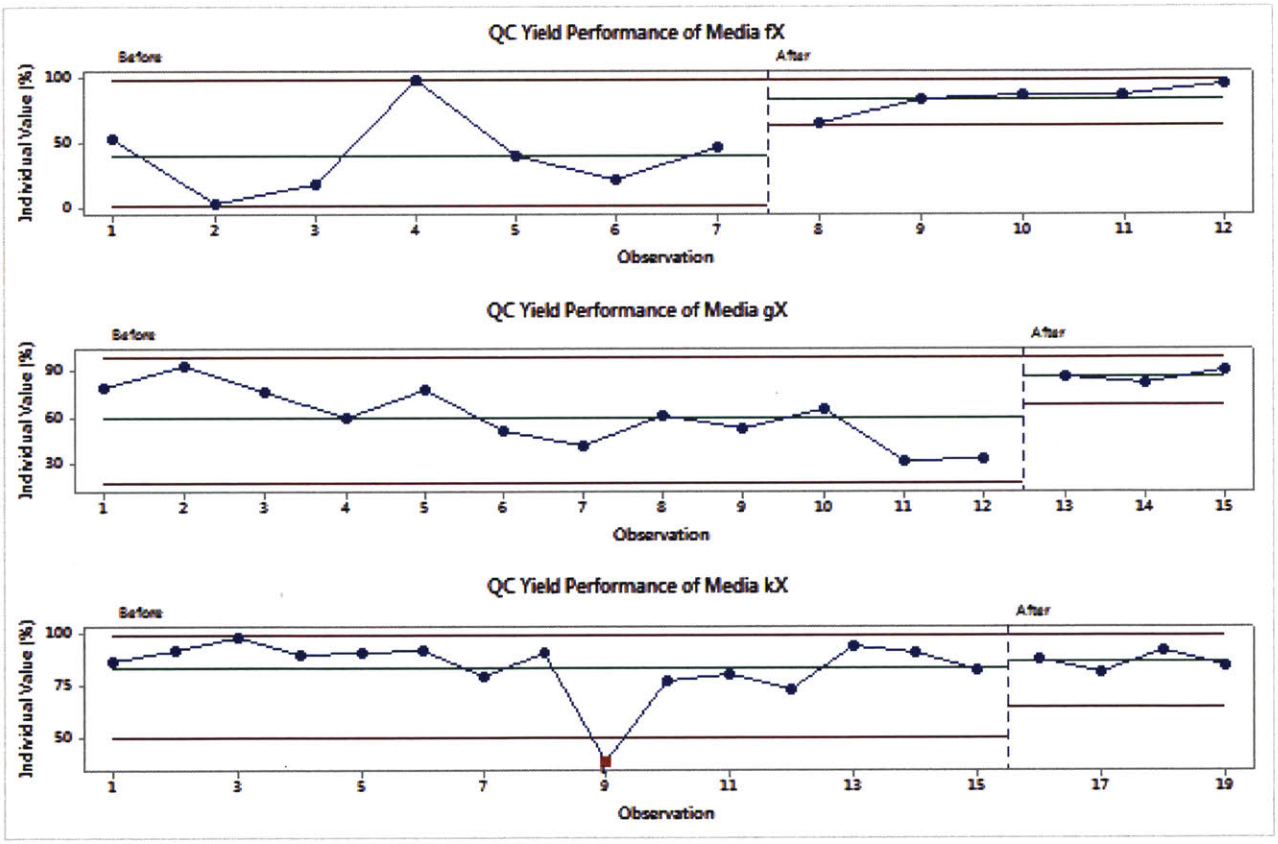

Figure 4-23: Improved rolled throughput yield in three high volume media grades.

Although media kX formed part of the initial scope of the project, FilterCo had experienced a surge in demand for media fX during the course of the project, while demand for media kX slowed. Owing to all media grades sharing the same manufacturing process, the

results of the project are more evident in media fX performance. Average RTY for media fX increased from 40% to 83% while yield variation decreased from 30% to 11%. Similarly, media gX and kX RTY increased from 60% to 87%, and from 83% to 88%, respectively. Most importantly, yield variability in these two grades also decreased by 60% and 40%, respectively. The financial impact of the project is found to equate to 60% of the total 2015 scrapped membrane value. The significance of this business impact highlights the benefits of employing the *80-20 rule* in project scoping, but also emphasizes the importance of a structured problem solving approach to deliver on the goals of the project.

Chapter 5

Conclusions and Future Work

This thesis demonstrates the power of formulating a block model of a manufacturing process, understanding the interaction of process parameters, and quantifying their impact on the properties and geometry of the process output. Further complimenting this is the rapid development and trialing of solutions which fosters superior learning rates amongst associates, and results in an efficient and proven concept through iteration. By addressing problems immediately through rapid experimentation, work-arounds are decreased and the propagation of errors within the manufacturing system ceases. The application of a scientific approach to problem solving ensures that the right questions are posed, hypotheses validated, and learning is incorporated into the next PDCA cycle. Key elements of this methodical quality process control approach as detailed in this thesis are summarized below and suggestions for future work are offered.

5.1 Understanding the System

Manufacturing is a system of interconnected processes that complement one another such that an output with the correct geometry and properties is created. Each of the processes need to be clearly defined and thoroughly understood with respect to the interaction of process parameters and machine inputs, and the extent of their impact on the transfer of energy must be quantified.

In this filter media manufacturing case, the development of a model for step #2 allowed for Test B results to be traced back to specific machine inputs and process parameters. Furthermore, thorough understanding of the system allowed for thoughtful observation and led to the development of refined hypotheses that ultimately resulted in valuable learning cycles.

5.2 Understanding Variation

Variation is and always will be a part of any manufacturing process. Variation represents fluctuations in the health of the process, and it is only through careful study that the root causes may be identified. SPC is a powerful tool, but must be applied to the specific process in a manner that reflects insight and in such a way that the right measurements are being monitored. A successful statistical process control campaign hinges upon adequately training associates to make the distinction between common cause and special cause variation, and instructing associates to only act on indicators of special cause variation. Associates are and will continue to remain a supervisor's most valuable data collection terminal, fault-finding guide and feedback tool, but they must be adequately trained, empowered and engaged.

As is highlighted in this thesis, many of the machine disturbances were as a result of operator tampering. Upon further inspection, tampering is directly correlated to the lack of knowledge as it pertains to statistical process control. Fault for continuously attempting to *maintain control* by altering machine set-points could not be assigned to the associate since they were not made aware of the distinction between common cause and special cause variation. Machine tampering ceased once the key principles of statistical process control were conveyed to the associate. More importantly, the training allowed for additional special cause variation to be highlighted by the associate that would have otherwise gone unnoticed or ignored.

5.3 Rapid Experimentation

Decisions regarding equipment and process design should only be made on the basis of good information in conjunction with process model. The sources of variation can only be correctly identified by *going to Gemba* and formulating hypotheses or causal mechanisms based on observation and subject matter knowledge. Insightful hypotheses, however, do not solve the problems alone and will remain conjecture unless tested experimentally. A process of rapid experimentation enables superior learning rates to be achieved, hypotheses to be validated and the process model to be refined. Quality can only be improved by instituting a formalized team-based problem solving approach that ensures the correct sources of variation are identified, prioritized and worked-on.

For this work, the process of rapid experimentation proved particularly valuable in the case of trialing the alternative polymer application technology. In the past, numerous solutions had been proposed to reduce bald spots, but never acted upon by FilterCo management owing to potential cost and the uncertainty of success. By rapidly experimenting with the previously purchased technology and manufacturing media rolls, we learned that the frequency of bald spots could be greatly reduced and no longer needed to speculate over the success of the technology. Furthermore, incorporating the lessons learned from the experimentation allowed for the development of a mechanical design that proved to be more refined and more cost effective than solutions previously proposed.

5.4 Team Work

A manufacturing system can be managed effectively by having a team that gathers at regular cadence and ensures operational discipline, and that is able to drive process improvements that lead to gains in critical business metrics, together. When it is clear that the process has shifted statistically, the team applies problem solving tools and takes urgency to identify the root cause and eliminate it. In many instances, the solutions to the problems exist within the larger organization and can only be accessed by breaking down the barriers between departments, and emphasizing knowledge sharing amongst team members. Creating

a team-based working environment presents a significant competitive advantage and will only be achieved by encouraging transparency, continuous learning and ownership at the lowest levels.

The importance of team work rang true in this project, specifically in the interventions implemented to reduce the cross-web variability of parameters as well as reduce supply variability to process equipment. Cross-web variability was reduced on account of a conversation with a long standing FilterCo engineer who had worked on the development of a newer manufacturing line, and had solved the cross-web variability problem. Similarly, many solutions had previously been proposed by the manufacturing associates to reduce the impact of variability observed in α_{C3}; the mechanical buffer solution discussed in the thesis was developed as a result of brainstorming and idea refinement alongside the associates.

5.5 Future Work

Based on the results of the variability reduction initiatives implemented in step#2 of the manufacturing process, it is recommended that FilterCo consider further work in the following areas:

1. Manufacture and install the final mechanical buffer solution as approved by the Advanced Engineering department. This solution incorporates the learnings from the implemented experimental setup and promises to deliver an improved level of control over parameter α_{C3} which may further reduce Test B variation.

2. Engage FilterCo's Research and Development department to identify a suitable substrate replacement whose manufacturer is able to show a significantly improved level of thickness control over the current supplier.

3. Actively pursue the development of a design to retrofit the advanced polymer application technology. This technology will greatly reduce the frequency of bald spots (as has been shown), and, assuming a substrate replacement is found, will also provide an unprecedented level of control over the media thickness leading to greater consistency

in Test A and B performance.

In addition, it is recommended that FilterCo apply the process control method presented to the remainder of the manufacturing process. A team based problem solving approach should be encouraged and viewed as an opportunity to cultivate and build a learning organization. Viewing the manufacturing activities as a series of ongoing experiments will allow for problems to be highlighted, and solved immediately through a process of collaborative rapid experimentation. By viewing the future work as an opportunity to foster team work amongst the associates within the department, FilterCo will ensure associates succeed in their daily tasks and ultimately assure the company's future success in meeting customer demand.

Bibliography

[1] C. Christy and S. Vermant. The state-of-the-art of filtration in recovery processes for biopharmaceutical production. *Desalination*, 147(1):1 – 4, 2002.

[2] R. Ghosh. *Biopharmaceutical Separations by Ultrafiltration*, pages 435–450. John Wiley & Sons, Inc., 2008.

[3] T. M. Przybycien, N. S. Pujar, and L. M. Steele. Alternative bioseparation operations: life beyond packed-bed chromatography. *Current Opinion in Biotechnology*, 15(5):469 – 478, 2004.

[4] C. Charcosset. Membrane processes in biotechnology: An overview. *Biotechnology Advances*, 24(5):482 – 492, 2006.

[5] A. Idris, I. Ahmed, and N. Noor. *Asymmetric Polyethersulfone Membranes*, pages 17–37. CRC Press, 2011.

[6] S. Ramamurthy. *Ultrafiltration Membranes: Technologies and Global Markets.* Wellesley, Mass. : BCC Research, 2015.

[7] W. E. Deming. *Out of the Crisis.* Cambridge, Mass.: Massachusetts Institute of Technology, Center for Advanced Engineering Study, 1986.

[8] R. Westbrook. Action research: A new paradigm for research in production and operations management. *International Journal of Operations and Production Management*, 15(12):6–20, 1995.

[9] C. A. Challener. Filtration technologies advance to meet bioprocessing needs. *Biopharm International*, 28(5):26 – 28, 2015.

[10] A. Saxena, B. P. Tripathi, M. K., and V. K. Shahi. Membrane-based techniques for the separation and purification of proteins: An overview. *Advances in Colloid and Interface Science*, 145(1–2):1 – 22, 2009.

[11] M. Ulbricht. Advanced functional polymer membranes. *Polymer*, 47:2217 – 2262, 2006.

[12] R. W. Baker. *Overview of Membrane Science and Technology*, pages 1–14. John Wiley & Sons, Ltd, 2012.

[13] M. Mulder. *Basic Principles of Membrane Technology.* Dordrecht: Springer Netherlands, 1996.

[14] Y. Wan, S. Vasan, R. Ghosh, G. Hale, and Z. Cui. Separation of monoclonal antibody alemtuzumab monomer and dimers using ultrafiltration. *Biotechnology and Bioengineering*, 90(4):422 – 432, 2005.

[15] S. Guo, H. Kiefer, D. Zhou, Y. H. Guan, S. Wang, H. Wang, Y. Lu, and Y. Zhuang. A scale-down cross-flow filtration technology for biopharmaceuticals and the associated theory. *Journal of Biotechnology*, 221:25 – 31, 2016.

[16] D. Low, R. O'Leary, and N. S. Pujar. Review: Future of antibody purification. *Journal of Chromatography B*, 848:48 – 63, 2007.

[17] S. M. Cramer and M. A. Holstein. Downstream bioprocessing: recent advances and future promise. *Current Opinion in Chemical Engineering*, 1:27 – 37, 2011.

[18] K.H. Kroner. *Cross-Flow Filtration of Biological Suspensions*, pages 59–83. Springer Netherlands, 1994.

[19] R. R. Bhave. Cross-flow filtration. In *Fermentation and Biochemical Engineering Handbook*, pages 149 – 180. William Andrew Publishing, Boston, 2014.

[20] General Electric Life Sciences. *Cross Flow Filtration Method Handbook.* General Electric Life Sciences, 2009.

[21] R. W. Baker. *Membranes and Modules*, pages 97–178. John Wiley & Sons, Ltd, 2012.

[22] J. Ren and R. Wang. *Preparation of Polymeric Membranes*, pages 47–100. Humana Press, Totowa, NJ, 2011.

[23] G. S. Prihandana, I. Sanada, H. Ito, and N. Miki. Antithrombogenicity of fluorinated diamond-like carbon films coated nano porous polyethersulfone (pes) membrane. *Materials*, 28(6):4309 – 4323.

[24] D. Linders. Development of a Risk Management System for Consumables Used in Biopharmaceutical Manufacturing. Master's thesis, Massachusetts Institute of Technology, Cambridge, MA, 2013.

[25] Center for Biologics Evaluation and FDA Research. Guidance for industry: Quality systems approach to pharmaceutical cgmp regulations. Standard, United States Food and Drug Administration, Rockville, MD, 2006.

[26] M. E. Pena-Rodriguez. *Statistical Process Control for the FDA-regulated Industry.* Milwaukee, Wisconsin: ASQ Quality Press, 2013.

[27] D. E. Hardt. Manufacturing processes and process control. *MIT Course 2.830 Lecture 1*, 2016.

[28] D. E. Hardt. Modeling and control of manufacturing processes: getting more involved. *Transactions of the ASME. Journal of Dynamic Systems, Measurement and Control*, 115(2B):291 – 300, 1993.

[29] W. A. Shewhart and W. E. Deming. *Statistical method from the viewpoint of quality control.* Washington, The Graduate School, The Department of Agriculture, 1939.

[30] American Society for Quality. Statistical process control. 2016.

[31] P. J. Frost and E. B. Gutoff. *The Application of Statistical Process Control to Roll Products.* North Quincy, MA : PJ Associates, 1991.

[32] D. J. Wheeler and D. S. Chambers. *Understanding Statistical Process Control.* Knoxville, Tenn.: SPC Press, 1992.

[33] S. J. Spear. Fixing health care from the inside, today. *Harvard Business Review*, 83(9):78 – 91, 2005.