

Achieving Business and Operational Excellence in the Pharmaceutical Industry

By

Shonna Coffey

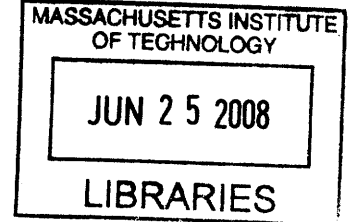
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ABSTRACT

Historically the pharmaceutical industry has been highly profitable. However, the increasing regulatory requirements, bargaining power of buyers, and drug failures together with the threat of biosimilars and decreasing R&D productivity are creating challenges for research driven pharmaceutical companies. With future revenue growth uncertain, pharmaceutical companies must focus on cost reduction to sustain the profit margins needed to support research and development of new medicines. The lean methodology first developed by Toyota is recommended as a way to achieve operational success. A deep analysis of the current state of the pharmaceutical industry and the operational inefficiencies inherent in regulated drug production is provided.

The renewed importance of operations within the pharmaceutical business model is explored through a case study of the biotechnology segment's leader, Amgen. Specifically, the design and initial rollout of the Amgen Process Excellence (APEX) initiative is studied. The APEX methodology is a six step process based on lean and six-sigma principles to guide operational improvement activities at Amgen. During the author's internship at the Rhode Island site the rollout of the APEX movement included a current state analysis of the site's financial and operational performance. As a result of this analysis, a prioritized list of improvement ideas was generated and incorporated into a future state vision for the site. Implementation of these improvement ideas is estimated to result in a reduction in cycle time by 55%, lower inventory levels, and the elimination of millions of dollars in waste.

The following major conclusions were developed as a result of this work. First, substantial improvement opportunities exist within current pharmaceutical manufacturing. Second, pharmaceutical companies must build operational efficiencies into manufacturing process design. Lastly, operational excellence cannot simply be attained through the implementation of an improvement toolkit.

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A Note on Proprietary Information

In order to protect proprietary Amgen information, the data presented throughout this thesis has been altered and does not represent the actual values used by Amgen, Inc. The dollar values have been disguised and names have been altered in order to protect competitive information where necessary.

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Table of Contents

ABSTRACT	3
Acknowledgments	5
A Note on Proprietary Information	7
Table of Contents	9
Table of Figures	13
1. Introduction	15
1.1. Overview of the Pharmaceutical Industry.....	15
1.1.1. The U.S. Pharmaceutical Industry	16
1.1.2. Pharmaceutical Industry Outlook	17
1.2. Thesis Motivation and Goal.....	18
1.3. Thesis Outline	19
2. Pharmaceutical Industry Analysis	21
2.1. Porter’s Five Force Analysis.....	21
2.1.1. Supplier Power.....	21
2.1.2. Buyer Power.....	22
2.1.3. Competition.....	24
2.1.4. Substitutes.....	25
2.1.5. Threat of Entry.....	27
2.1.6. Pharmaceutical Industry Analysis Summary	29
3. Overview of Operational Excellence	31
3.1. Lean as an Operational Excellence Methodology	31
3.2. The History of Lean	32
3.3. Key Elements of Lean Manufacturing.....	34
3.3.1. Waste Reduction	34
3.3.2. Standard Work	34
3.3.3. Jidoka	34
3.3.4. Visual Management/5S.....	35
3.3.5. Just-In-Time (JIT).....	35
3.3.6. Value Stream Mapping	35
3.3.7. Kaizen Event.....	36
4. The Pharmaceutical Industry Status on Achieving Operational Excellence	37
4.1.1. Small-Molecule Lean Transformations	39
4.2. What Makes Pharmaceuticals Different?.....	40
4.3. Overview of Regulatory Constraints	41
4.3.1. Overview of Pharmaceutical Manufacturing Processes	44
4.3.1.1. Pharmaceutical vs. Biopharmaceutical Operational Performance.....	45

4.4.	Overview of Biopharmaceutical Manufacturing	46
5.	The Status of Biopharmaceutical Operations	51
5.1.	Operational Inefficiencies in Biopharmaceutical Operations	51
5.1.1.	Receiving Inefficiencies.....	52
5.1.2.	Manufacturing Inefficiencies	53
5.1.2.1.	GMP Requirements Lead to Low Value-Added Time	53
5.1.2.2.	Media and Buffer Scrap	54
5.1.3.	Quality Testing Inefficiencies.....	55
5.1.4.	Disposition Inefficiencies	56
5.1.5.	Summary of Biopharmaceutical Operational Inefficiencies.....	57
5.2.	The Status of Operational Excellence in Biopharmaceutical Operations.....	58
5.3.	Regulatory Action: A Potential Aid in Operations Improvement	60
5.3.1.	PAT.....	60
5.3.2.	Implications of a Scientific Risk-Based Approach for Pharmaceutical Operational Excellence	61
6.	Road Map to Lean Transformation.....	63
6.1.	Lean is a Bumpy Road.....	63
6.2.	The Enterprise Level Transition to Lean Roadmap.....	64
6.2.1.	The Transition to Lean Roadmap Entry/Re-entry Cycle	66
6.2.1.1.	Step 1: Enterprise Strategic Planning	66
6.2.1.2.	Step 2: Adopt the Lean Paradigm	67
6.2.2.	The Transition to Lean Roadmap Long Term Cycle.....	67
6.2.2.1.	Step 3: Focus on the Value Stream	67
6.2.2.2.	Step 4: Develop Lean Structure and Behavior.....	70
6.2.3.	The Transition to Lean Roadmap Short Term Cycle.....	71
6.2.3.1.	Step 5: Create and Refine Transformation Plan	71
6.2.3.2.	Step 6: Implement Lean Initiatives	71
6.2.3.3.	Step 7: Focus on Continuous Improvement.....	72
6.2.3.4.	Step 8: Re-enter Long Term Cycle or Entry Cycle (when needed).....	72
6.2.4.	Enterprise Level Transition to Lean Roadmap Takeaways	72
7.	Case Study of Amgen Rhode Island.....	75
7.1.	Amgen Background	75
7.2.	Amgen's New Competitive Landscape	76
7.2.1.	Amgen Rhode Island.....	77
7.3.	Operational Excellence Initiative at Amgen	78
7.4.	Implementation of the APEX Methodology at Amgen Rhode Island	81
7.4.1.	ARI APEX Implementation Step 1: Initiate	81
7.4.2.	ARI APEX Implementation Step 2: Baseline the Current State.....	83

7.4.2.1.	The ARI Enbrel Manufacturing Current State Value Stream.....	83
7.4.3.	ARI APEX Implementation Step 3: Design Future State.....	88
7.4.4.	ARI APEX Implementation Step 4: Scope, Prioritize & Agree.....	90
7.4.4.1.	ARI Continuous Improvement Training Curriculum.....	90
7.4.5.	ARI APEX Implementation Step 5: Implement.....	93
7.4.6.	ARI APEX Implementation Step 6: Closeout.....	93
7.4.6.1.	ARI APEX Lessons Learned.....	93
7.5.	Recommendations for Future Work at ARI.....	95
7.5.1.	Further Cost Reduction.....	95
7.5.2.	Goal and Metric Re-engineering.....	96
7.5.3.	Recommendations for Continued Improvement.....	100
7.6.	Recommendations for the Amgen APEX Corporate Initiative.....	101
7.7.	A Reflection on APEX Implementation at ARI.....	103
8.	Achieving True Change.....	105
9.	Conclusions.....	109
	Bibliography.....	111

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Table of Figures

- Figure 1: Porter's Five Force Industry Analysis Framework..... 21
- Figure 2: New Drug Approvals on the Decline While Black-Box Labels and Safety Alerts Increase 24
- Figure 3: Expected Drug Revenue Loss Due to Patent Expiration Through 2012..... 26
- Figure 4: Increase in Pharmaceutical Research Expenditures and Approval Success Rate 28
- Figure 5: Pharmaceutical Industry Productivity 28
- Figure 6: Range of Pharmaceutical Operational Performance 38
- Figure 8: Example Process Improvement Regulatory Approval Value Stream Map..... 44
- Figure 9: Overview of a Biopharmaceutical Process..... 49
- Figure 10: High Level Example Biopharmaceutical Value Stream Map 51
- Figure 11: Example Biopharmaceutical Unit Operation 54
- Figure 12: Biopharmaceutical Sample Turnaround Times..... 56
- Figure 13: Key Measures of Quality Systems Performance..... 57
- Figure 14: Age of Operational Excellence Initiative (Based on Survey of 11 Companies) 59
- Figure 15: Key Drivers for Operational Excellence Initiative (Based on Survey of 11 Companies) 59
- Figure 16: Key Methodologies Used in Operational Excellence Initiative (Based on Survey of 11 Companies) 59
- Figure 17: Enterprise Level Transition to Lean Roadmap..... 66
- Figure 18: Balanced Scorecard Framework..... 69
- Figure 19: Overview of APEX Approach..... 80
- Figure 20: APEX Methodology 80
- Figure 21: Average and Top Performing Pharmaceutical Plant Cost Breakdown 82
- Figure 22: ARI Plant Cost Breakdown (pre-APEX)..... 82
- Figure 23: Current State High Level Enbrel Value Stream Map..... 84
- Figure 24: Enbrel Current State Cycle Time Breakdown..... 85
- Figure 25: Future State High Level Enbrel Value Stream Map..... 88
- Figure 26: Enbrel Current State Cycle Time Breakdown..... 89

Figure 27: Amgen's Bio-Kool Lean Simulation Example Current and Future State Value Stream Maps.....	92
Figure 28: Amgen Rhode Island Strategic Objectives and Metric Alignment- 2007'	94
Figure 29: Example Year-on-Year Variable Cost Productivity Metric	95
Figure 30: Suggested Amgen Strategic Map	98
Figure 31: Amgen Rhode Island Strategic Objectives and Metric Alignment Utilizing the Author's Suggestion	99
Figure 32: Levels of Operational Excellence (G.K. Raju 2003).....	100

1. Introduction

1.1. Overview of the Pharmaceutical Industry

The global pharmaceutical market is over \$700 Billion¹. The global industry is dominated by three major market segments: North America is the largest and comprises 50 percent, Europe is second with 28 percent, and Japan is third at 14 percent of 2007 sales². Although these combined markets account for a large percentage of global sales, the remaining emerging market segments—other Asian countries, Africa, and Australia and Latin America—are growing rapidly.

The pharmaceutical industry is dominated by a handful of super-large companies. However, the global industry is actually highly fragmented with over 2,000 pharmaceutical and biotech companies existing worldwide. In the top tier are the large, multinational companies that dominate the market, Big Pharma. In the middle tier are the specialty companies. Many large companies have tended to absorb second tier companies before they can pose a competitive threat. This trend has a contracting effect on the number of firms. The opposite happens on the third and lowest tier, which is composed of an ever increasing group of start-ups mostly focused on discovery research.

Most of the industry's revenue is based on mega-sales of blockbuster products, those that generate at least \$1 billion in sales. In 2006, the top 100 blockbuster drugs accounted for 36% of the total world pharmaceutical market³. However, a large number of the current blockbusters will be facing patent protection in the next few years, giving rise to the unbranded generics market, which has more than doubled in size since 2001⁴.

¹ IMS Health. "IMS Health Predicts 5 to 6 Percent Growth for the Global Pharmaceutical Market in 2008, According to Annual Forecast." 1 Nov. 2007.

² *ibid*

³ Seget, Stevens. *Pharmaceutical Market Trends 2007-2011: Key Market Forecasts and Growth Opportunities*. 2nd Edition. Urch Publishing, November 2007.

⁴ Nehru, Revati. "Future Growth Opportunities in Generics: The Impact of Consolidation on Market and Competitive Dynamics." *Business Insights Ltd*. November 2006.

1.1.1. The U.S. Pharmaceutical Industry

The U.S. pharmaceutical industry (tiers 1 and 2) is comprised of approximately 100 companies.⁵ The U.S. drug market is concentrated—the top 10 largest companies accounted for 60 percent of total retail sales in 2003, according to IMS Health, Inc⁶. The U.S. not only has the largest pharmaceutical market in the world but also the only one without government controls. That characteristic has major consequences on drug pricing, innovation and R&D investment.

Strictly speaking, the term “pharmaceuticals” refers to medicines composed of small, synthetically produced molecules, which are sold by large, fully integrated drug manufacturers. The largest of these players—companies like Pfizer, GlaxoSmithKline and Merck—as well as a handful of others are referred to as “Big Pharma” because they are huge research, development and manufacturing organizations with subsidiaries all over the globe. Indeed, Big Pharma is where over 50 percent of the industry’s sales are generated⁷.

Most biotechs are small, research-oriented companies dedicated to applying genetics to curing a multitude of serious diseases, ranging from Alzheimer’s to Multiple Sclerosis. A handful of companies—such as Amgen and Genentech—have broken through the rest of the pack to become “fully integrated” like Big Pharma. Biotech products are proteins, which need to be injected since they are very large molecules compared to the synthetic molecules Big Pharma sells. The largest biotechs are actually mid-sized pharmaceutical companies in the way they function and are sometimes called “Big Biotech.”

As for the largest Big Pharma players, most are either gobbling up small biotechs through outright acquisitions or, alternatively, entering into licensing agreements. This trend is likely to continue as it becoming increasingly difficult to find innovative new drugs through traditional science. Companies are using acquisitions and alliances to round out their product pipelines and meet investor expectations. Big drug manufacturers can now claim to research, manufacture and sell both synthetics and biologics. The biotech firms, tend to be organized around smaller market

⁵ www.phrma.org

⁶ IMS Health. “IMS Reports 11.5 Percent Dollar Growth in '03 U.S. Prescription Sales.” 17 Feb. 2004.

⁷ *ibid*

products as their products are targeted to small patient populations with rare genetic diseases. Biologics are much more expensive than small molecule therapeutics, costing over \$10,000 per patient per year⁸. So although these firms target much smaller patient populations, only a mere 100,000 patients are required to reach \$1 billion in revenue compared to the millions of patients for small molecule drugs like Prozac or Viagra.

1.1.2. Pharmaceutical Industry Outlook

The global pharmaceutical market is expected to grow at a 5 - 6 percent pace in 2008, compared with 6 - 7 percent in 2007, according to IMS Health's 2008 Global Pharmaceutical Market and Therapy Forecast⁹. The forecast predicts global pharmaceutical sales to expand to \$735 - 745 billion in 2008. In the U.S. and the five largest European markets, sales growth in 2008 is expected to range from 4 - 5 percent. This marks a historic low for the U.S. market. Japan market growth is forecast to grow 1 - 2 percent in 2008, down from the 4 - 5 percent pace expected in 2007. Key factors limiting growth in these markets include: a leveling off of growth from the introduction of the Medicare Part D prescription drug benefit in the U.S.; patent expiration of branded products, and an associated increase in the use of lower-cost generics; increased pressure from payers to control costs and limit access to certain treatments; and heightened safety scrutiny as well as healthcare legislation that is slowing, and in some cases halting, the introduction of new medicines¹⁰.

Drugs with approximately \$20 billion in annual sales will face patent expiry in 2008¹¹. Several products are expected to lose market exclusivity in one or more major markets around the world in 2008, driving the growth of generics to more than \$70 billion¹². Over two-thirds of all prescriptions written in the U.S. are expected to be for generics in 2008¹³. In addition, global

⁸ Pear, Robert. "Congress Seeks Compromise on Generic Drugs" The New York Times. 8 April 2007.

⁹ IMS Health. "IMS Health Predicts 5 to 6 Percent Growth for the Global Pharmaceutical Market in 2008, According to Annual Forecast." 1 Nov. 2007.

¹⁰ Ibid.

¹¹ Ibid.

¹² Ibid.

¹³ Ibid.

generics competition will continue to grow including competition within the biotech industry as biosimilars such as epoetin alfa have been approved in Europe.

1.2. Thesis Motivation and Goal

Operational Excellence (OE) is essential to the future commercial success of the pharmaceutical industry. In an industry that is facing bio-generics, pricing scrutiny, and decreasing new drug productivity with increasing R&D expenditure, OE is not just a competitive advantage, it is a competitive necessity. Biotech companies are starting to feel the performance pressure that other Big M manufacturing industries have previously faced. Biotech must learn to operate in a low-cost, high-quality world. They should learn from the automotive, aerospace, and electronic industries how to utilize lean methodology throughout an enterprise.

While many of these challenges are not new to the traditional Big Pharma players, biotech companies for the most part have been immune to these market forces. Reimbursement and generics issues are not new to Big Pharma because of the ease in which small molecule medications can be replicated. In the traditional pharmaceutical industry, once a drug is off patent the market is flooded with cheaper generic offerings. However, currently there is no way to exactly copy a protein based biopharmaceutical. The complexity of biopharmaceuticals has led to a lack of generics approval legislature in the U.S. to date. For the Biotech industry the lack of generics competition has been the equivalent of eternal patent protection. However, that may soon change. In the summer of 2007, the EU (the second largest drug market) approved several bio-generics including erythropoiesis stimulating agent (ESA), directly competing with Amgen's Epogen and Aranesp therapies. In addition, U.S. congress is under serious discussions on pathways to approve bio-generics or biosimilars.

The goal of this thesis is to examine the current competitive challenges facing the pharmaceutical industry and propose that achieving excellence within pharmaceutical operations is essential to future firm success. The author recommends that pharmaceutical companies follow other manufacturing industries in adopting lean principles to achieve operational excellence. Specifically, this thesis will focus on the biotechnology industry and the unique challenges it faces in adopting operational excellence. This work provides a thorough analysis of the current

state of biopharmaceutical operations and argues that a lean transformation results in operational efficiencies that will enable biopharmaceutical companies to compete within the world of bi-generics. The author includes a case study of the Amgen Process Excellence initiative to illustrate the improvement opportunities as well as implementation challenges the biotech sector faces in undertaking the transition to operational excellence.

1.3. Thesis Outline

This document is organized as described below:

Chapter 1 provides an overview of the pharmaceutical industry.

Chapter 2 utilizes Porter's Five Force Framework to perform an industry analysis. The analysis provides the evidence for why operational excellence is crucial to today's pharmaceutical manufacturing organizations.

Chapter 3 provides an overview of operational excellence (OE) and suggests lean as a methodology to achieving OE.

In **Chapter 4** the current status of the pharmaceutical industry on implementing lean is explored. This chapter provides an overview of the drug manufacturing process as well as the regulatory constraints on the industry. The specific challenges of biopharmaceutical manufacturing are discussed.

Chapter 5 explores the operating inefficiencies of typical biopharmaceutical drug substance manufacturing operations. Use of the FDA's cGMPs for the 21st Century and PAT guidance to achieve operational excellence is suggested.

In **Chapter 6** a framework is proposed to aid in the transition to lean.

A case study of Amgen's operational excellence initiative, APEX is presented in **Chapter 7**.

Chapter 8 explores the requirements for achieving true change.

Chapter 9 summarizes the findings of this research and also discusses how pharmaceutical companies can achieve a sustainable, true change in operations.

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2. Pharmaceutical Industry Analysis

The purpose of this section is to provide the reader with a deep understanding of the pharmaceutical industry through the use of Porter's Five Force analysis.

2.1. Porter's Five Force Analysis

Michael Porter provided a framework that models an industry as being influenced by five forces. Use of the Porter Five Forces allows an analysis of the industry and its competitive landscape.

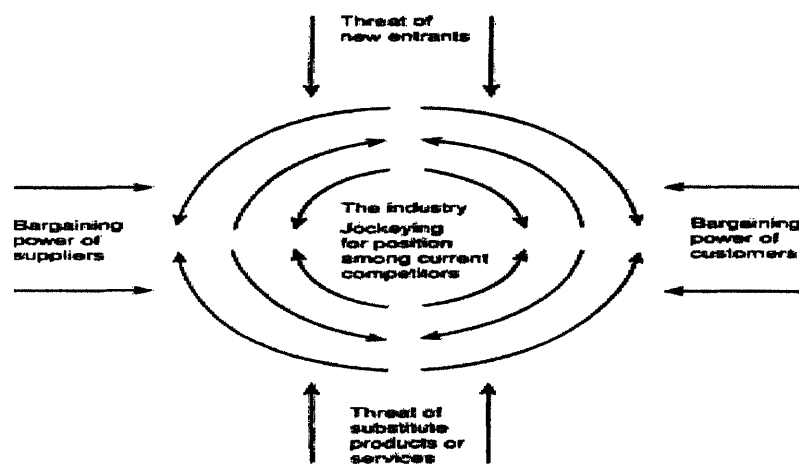


Figure 1: Porter's Five Force Industry Analysis Framework¹⁴

2.1.1. Supplier Power

In the pharmaceutical industry the sellers for the most part have very little power. Pharmaceutical suppliers provide mostly widely available chemical commodities. However in biopharmaceutical processing, there are some specialty materials such as resin and micro filtration assemblies needed for production, there are several suppliers for these raw materials. The caveat is that a pharmaceutical company must qualify any raw material and its vendor for commercial use. This gives a supplier power in that it is resource intensive and time consuming

¹⁴ Source: Porter, Michael. *Michael Porter on Competition*. Boston: Harvard Business School Publishing, 1998: 22.

to repeat this qualification after licensure is received. In response, most drug manufacturers will qualify several suppliers for any raw material prior to licensure.

2.1.2. Buyer Power

Unlike with most products, the users of drug products are not the primary payers. In the U.S. the majority of prescriptions are paid for by private insurance or the center of Medicare and Medicaid services (CMS) with a varying co-payment provided by the patient. Therefore, the primary buyer in the pharmaceutical industry is not the patient, but the patient's physician as well as insurer. In the case of the European Union, it is government agencies that are the primary buyer for pharmaceuticals. Due to the rising usage of prescription drugs, insurance companies and the CMS in the U.S. as well as government agencies in the EU have taken action to control prescription drug spending. In the EU, government agencies have the power to affect pricing and limit availability of newer, more expensive patented drugs. In many E.U. countries a drug must be deemed cost effective by a national committee before it can be available for prescription in that country.

As of June 2006, there are over 45 million Medicaid recipients and 44 million Medicare recipients in the U.S.¹⁵. The buying power of the CMS has resulted in a limit of reimbursement for some medications. In January 2006 the Medicare Part D prescription drug plan became active. This plan allows Medicare recipients to receive prescription drug coverage through insurers following a formulary classification system. Typically, each plan's formulary is organized into tiers, and each tier is associated with a set copay amount. Most formularies have between 3 and 5 tiers. The lower the tier, the lower the copay amount. Within each tier, the generic copay is considerably lower than the branded drug. Many independent insurers are also adopting this tiered coverage system. These systems pressure physicians to prescribe generics so that their patients will incur lower out of pocket expenses. In addition to reimbursement tightening, CMS and other independent insurers have also limited the patient population of some medicines in which it will offer coverage. For example, in 2007 the CMS limited coverage of

¹⁵ Centers of Medicare and Medicaid Services. *2006 Medicaid Managed Care Enrollment Report*. 30 June 2006

erythropoiesis stimulating agent (ESA) treatment for beneficiaries with certain cancers and related neoplastic conditions.

In addition to restricted reimbursement of commercial drugs, drug companies face many challenges in getting their product to market in the first place. Regulatory agencies such as the FDA and EMEA may be considered buyers of the pharmaceutical industry in that they must deem pharmaceutical medications safe and efficacious for human consumption. It is these regulatory bodies that must “buy” the clinical data supplied by the pharmaceutical company. For U.S. drugs are compared against placebos to gain approval. However, in the E.U. a drug is usually compared against what is currently available when deciding if the drug should be approved and added to the country’s formulary. In addition, these agencies continue to monitor and regulate the manufacture and distribution of approved medicines. It is the compliance with these agencies that dominates most drug operations. Recently the FDA has been criticized in exercising its power and raising the bar on both drug approvals and on-going compliance. In 2007 the FDA Center for Drug Evaluation and Research (CDER) approved 17 new drugs compared to 22 in 2006 and 20 in 2005¹⁶. The Dow Jones has reported that the FDA is under pressure from congress and consumer watchdogs to increase their scrutiny about drug safety¹⁷. In 2007 the FDA issued a number of non-approvable letters to drug giants including GSK and Wyeth, seemingly raising the bar on approvals for medications in which there is already an alternative drug on the market. Publicly Novartis and Wyeth CEOs have scrutinized the FDA’s increased requirements for drug approval¹⁸. It is believed that the FDA’s risk adverseness is a result of the 2004 Vioxx recall in which Merck withdrew its blockbuster painkiller over concerns of heart attacks. Following the Vioxx recall the FDA has dramatically increased its public drug safety warnings and drug label warnings (black box)¹⁹. See Figure 2 below for FDA trend data.

¹⁶ <<http://www.fda.gov/cder/rdmt/InternetNME07.htm>>

¹⁷ “FDA Approval Rate Slows: Who’s To Blame?” *Pharmatimes.com* 06 Nov. 2007.

¹⁸ Simons, John. “FDA Damned if it Does, Damned if it Doesn’t.” *CnnMoney.com*. 9 Nov 2007.

¹⁹ Ibid.

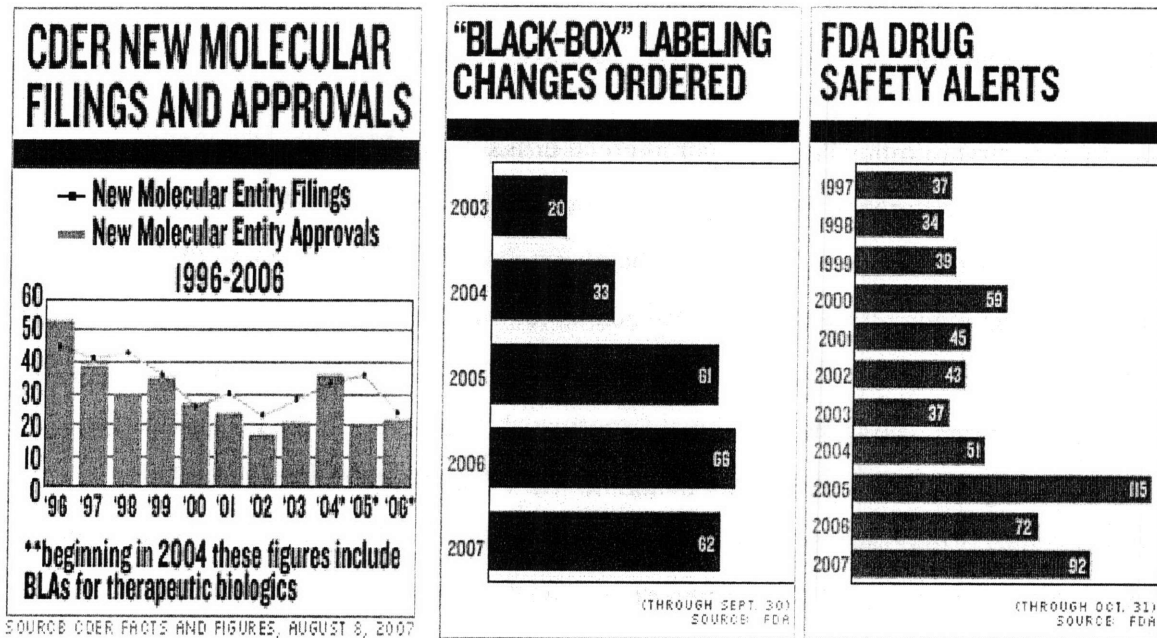


Figure 2: New Drug Approvals on the Decline While Black-Box Labels and Safety Alerts Increase²⁰

2.1.3. Competition

The pharmaceutical industry is highly competitive. The industry has undergone major market consolidation resulting in the top ten pharmaceutical companies accounting for over 60% of the total sales in the U.S. in 2003²¹. The branded industry is dependent upon intellectual property protection to maintain market exclusivity for their products. Once a product loses patent protection, generic manufacturers flood the market with cheap alternatives (unless the product is a biologic as previously discussed). Due to the long development times, the high profit earning period for a branded pharmaceutical is typically 11-12 years despite a 20 year patent life²². For many drugs the first to market captures the majority market share. However, this can change as the first mover actually develops patient awareness as well as physician diagnosis and prescribing practices. As a result of the intense pressure to capture market share, pharmaceutical

²⁰ Source: Ibid.

²¹ IMS Health. "IMS Reports 11.5 Percent Dollar Growth in '03 U.S. Prescription Sales." 17 Feb. 2004.

²² Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2007*.

companies aggressively sell and market their drugs, with most companies investing around 25% of revenues back into sales and marketing²³.

There is a high switching cost for most pharmaceuticals. Once a patient finds a medication that works, there needs to be a substantial potential benefit to trying a new medication. Most pharmaceutical companies try to capture patients through intensive commercial launches including expansive direct to consumer marketing campaigns. As any American consumer knows, pharmaceutical advertisements are rampant in TV commercials and magazine ads. Because of the blockbuster potential, certain disease areas such as cardiovascular or rheumatoid arthritis have seen increasing market concentration.

Not fully capitalizing on revenue during the IP protected commercial life of a drug is more costly now than ever. This is due to the fact that many branded pharmaceutical companies are facing a gap in their product pipeline. Historically pharmaceutical companies have relied on blockbuster drugs to achieve the double digit sales growth rates expected by analysts. However, the growth rate in the blockbuster market is expected to slow down in the upcoming years²⁴. As many as 19 blockbuster drugs may lose patent protection in 2008²⁵ but there is very little in the pipeline to replace lost revenue. IMS expects 29 new drugs to launch in 2009, but mostly in smaller disease markets²⁶. As a result, pharmaceutical companies are not only heavily investing in their pipelines through internal R&D and M&A but also competing heavily to elevate brand image as patent expiry looms.

2.1.4. Substitutes

The generics industry has exploded in the U.S. primarily due to pricing pressures and patent expirations. In 2008 the global generics industry is expected to grow to \$70 billion²⁷. IMS

²³ Friedli, Thomas et al. *Operational Excellence in the Pharmaceutical Industry*. Germany: Editio Cantor Verlag Aulendorf, 2006.

²⁴ Ibid.

²⁵ De Palma, Angelo. "Beating Patent Death." *PharmaManufacturing.com*. 2005.

²⁶ IMS Health. "IMS Health Predicts 5 to 6 Percent Growth for the Global Pharmaceutical Market in 2008, According to Annual Forecast." 1 Nov. 2007.

²⁷ Ibid.

health also projects that over 2/3 of the prescriptions written in the U.S. are for generics²⁸. In the EU, the generics market share varies by region. In Central and Eastern European countries generics make up over 70% of prescription volume, however generics make up less than 20% of prescription volume in Western European countries²⁹. In the U.S. the 1984 Hatch-Waxman act allowed generic companies to manufacture, test, and receive regulatory approval before a product went off patent. This act allows for immediate generic product distribution once a branded drug patents expires. Increasingly generic manufacturers are fighting patent protection and even launching drugs still with patent exclusivity. For instance, Bristol-Myers Squibb's blood-thinner, Plavix, patent doesn't expire until 2011. But in 2006, privately-held Canadian drug maker Apotex launched a generic version. Although Apotex was ruled not to have legal clearance to sell the generic, Plavix sales suffered until a legal injunction was granted³⁰.

Generic competition is expected to replace \$67 Billion from the top pharmaceutical companies annual U.S. sales from 2007 to 2012³¹. The generics sector in the EU is forecasted to grow from \$10.9 Billion in 2003 to \$21.2 Billion by 2010³². Included in the blockbuster drugs facing patent expiration are Lipitor, Plavix, and Zyprexa.



Figure 3: Expected Drug Revenue Loss Due to Patent Expiration Through 2012³³

²⁸ Ibid.

²⁹ "Generic Medicines in Europe." European Generic Medicines Association. < <http://www.egagenerics.com/gen-geneurope.htm>>.

³⁰ Smith, Aaron. "Federal Judge Whacks Generic Plavix." *CnnMoney.com*. 19 June 2007.

³¹ Martinez, Barbara and Goldstein, Jacob. "Big Pharma Faces Grim Prognosis." *The Wall Street Journal*. 6 Dec. 2007: A1.

³² "Europe's Generics Market Set to Double." 25 Oct. 2004. DrugResearcher.com. < <http://www.egagenerics.com/gen-geneurope.htm>>.

³³ Source: Ibid.

As previously discussed, currently there is no generic competition in the U.S. for the biotechnology drugs that have come off patent protection such as recombinant insulin or human growth hormone. Unlike small molecules, biopharmaceuticals do not fall under the Hatch-Waxman act. In 2007 U.S. legislature was proposed that would pave a regulatory path for biogenerics, The Biologics Price Competition and Innovation Act of 2007. However, this act was not adopted by congress in 2007. In contrast, biogenerics are a reality in the European Union. Novartis and Hospira have already received approval for biosimilars to epoetin alfa, equivalent to Amgen's ESA product line. Biosimilars for human growth hormone have also been approved in the EU.

Since biopharmaceuticals are the most costly drug therapies and represent the largest growth rate in the industry, there is a huge drive to push for legislation authorizing FDA approvals of biogenerics. The pharmacy benefit manager (PBM) Express Scripts unveiled a report in February 2007 projecting savings of some \$70 billion over 10 years from biogenerics³⁴. Another study put the savings for Medicare at \$14 billion³⁵. While the legislations is not yet there, the industry is preparing for the reality of generic competition for biopharmaceuticals.

2.1.5. Threat of Entry

There are a number of barriers to entering the pharmaceutical industry. First and foremost is the highly guarded intellectual property protection already discussed. Other barriers to entry are the large fixed costs to develop, manufacturer, and market drugs. In addition, a market entrant faces a very low success rate of bringing a product through clinical trials and reaching regulatory approval. There are also large switching costs involved in pharmaceutical manufacturing. For these reasons, the industry faces a low threat of entry by new entrants.

Development and commercialization of drugs requires a large upfront investment.

Pharmaceutical companies invest billions of dollars annually into research and development (see Figure 4). However only a fraction of the products that are discovered actually reach clinical

³⁴ Wechsler, Jill. "Manufacturing Issues Shape Follow-on Biologics Debate." *Pharmaceutical Technology*. 2 June 2007.

³⁵ Ibid.

phase and of those products less than 20% will be approved (see Figure 4 below). Not only is the probability of success low, but the financial investment is high. The Tufts Center for the Study of Drug Development estimates that the cost to bring to market a small molecule is over \$800 Million while the cost of a biopharmaceutical is over \$1.2 Billion³⁶. Only 3 out of 10 drugs that make it to market actually make back the development investment made³⁷.

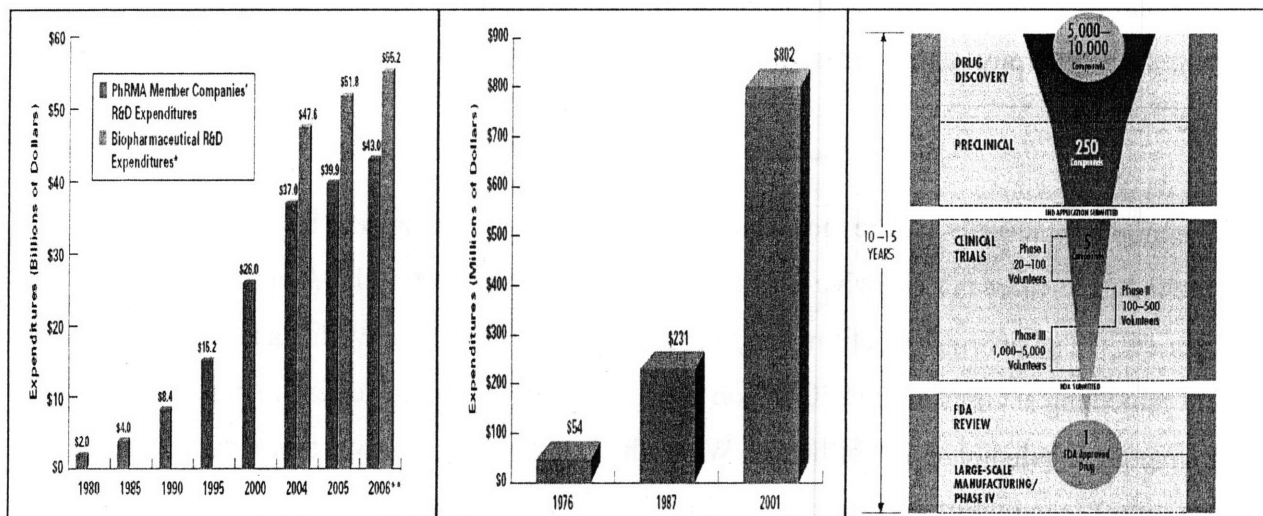


Figure 4: Increase in Pharmaceutical Research Expenditures and Approval Success Rate³⁸

Despite the major investment in research in development, the productivity of R&D has been decreasing as Figure 5 shows. Pharmaceutical companies are putting more and more into finding new treatments while the number of new drugs or New Molecular Entities (NMEs) approved has remained relatively constant.

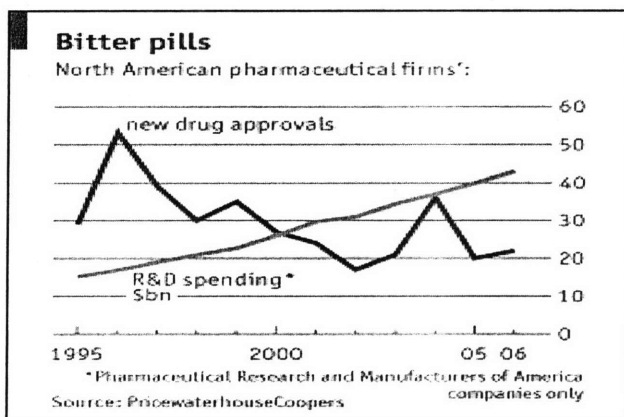


Figure 5: Pharmaceutical Industry Productivity³⁹

³⁶ Tufts Center for the Study of Drug Development. *Outlook 2007*. Boston, MA: Jan. 2007.

³⁷ Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2007*.

³⁸ Source: Ibid.

2.1.6. Pharmaceutical Industry Analysis Summary

The preceding sections described the dynamics of the pharmaceutical industry using Porter's Five Force Analysis. This industry analysis demonstrates that pharmaceutical companies are facing unprecedented pressure from buyers as well as an elevated threat of substitutes (in the form of generics). This section provides evidence that pharmaceutical companies must focus on improving operations in order to compete with generics, reinvest in research and development capabilities, as well as survive the pricing pressures of payers.

³⁹ Source: "Beyond the Blockbuster" *Economist.com*. June 28 2007.

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3. Overview of Operational Excellence

Operational Excellence is the routine delivery of exceptional performance through a systematic approach to continuous process improvement. An organization that is operationally excellent leads its competitors by providing the lowest cost, highest quality product to its customers. It does this by performing the *right tasks*, at the *right time*, in the *most efficient* manner. Those firms that are able to achieve operational excellence realize increased customer satisfaction through shorter lead times and increased quality while decreasing operating costs and increasing overall profitability. Operating in a state of excellence creates a positive reinforcing loop in which value is added to the customer, increasing overall demand, resulting in firm profitability, which allows the firm to reinvest into new product development to provide new medicines to patients. Producing these new medicines in a state of excellence continues the cycle.

3.1. *Lean as an Operational Excellence Methodology*

The principles of lean have become synonymous with operational excellence. Many of the top performing manufacturing and operations companies today have fully adopted this operating philosophy. Although there are other improvement methodologies widely used (six-sigma and Total Quality Management (TQM)), this author believes that the overarching lean principles provide a greater bandwidth for change. While there are many similarities between lean, six-sigma, and TQM, only lean looks at the entire enterprise and all of its processes. While quality is an important factor in value delivery, lean does not view quality as the sole factor in determining customer satisfaction as in six-sigma and TQM. Instead, lean tries to optimize quality, cost, and speed simultaneously for the customer. Another key difference in these improvement methodologies is that while six-sigma and TQM try to maximize value as viewed by the customer, lean attempts to optimize value as viewed by *ALL* stakeholders. Six-sigma and TQM techniques may be combined with lean principles, however they are not sufficient in isolation to realize true sustainable operational excellence.

3.2. The History of Lean

Lean was developed by the automobile industry, but has since been adopted by nearly all major manufacturing industries world-wide. Lean started exclusively as a manufacturing improvement technique, but its key principles are applicable to all business and operations processes. The remainder of this chapter explores these key principles and provides definitions for the major lean techniques. Subsequent sections of this thesis will analyze pharmaceutical operations and how lean techniques can be applied to achieve operational excellence.

The term lean was first coined in the 1990 James Womack book “The Machine that Changed the World”⁴⁰. In his book Womack describes how the Japanese auto manufacturers learned from the Ford system and adapted it to their specific needs. In the spring of 1950 a young Japanese engineer, Eiji Toyoda, traveled to Ford's Rouge plant in Detroit. After studying the Ford plant, he returned to Japan and with the help of, Taiichi Ohno, concluded that a different production model from mass production needed to be developed for economic success in Japan. Toyota devised a production system that worked on reducing waste inherent in mass production. Toyota developed flexible operations with very short changeover times, small batch sizes, low inventory levels and where decision-making was performed by front line workers. This new production system, the “Toyota Production System” was centered on not only detecting but also addressing the root causes of defects at their source. The cost and quality advantages that Toyota is able to achieve through its production system have allowed the corporation to thrive while its major competitors are facing record breaking losses.

The Toyota Production System (TPS) became the basis for what is now more widely referred to as lean manufacturing. The success of TPS has lead to adoption of lean manufacturing principles in the majority of manufacturing organizations as well as other non-manufacturing enterprises such as hospitals, banks, and retail enterprises. Lean manufacturing itself has developed into a mature business management methodology based on the principle of maximizing the value as viewed by the customer through waste elimination. Womack and Jones further refined the principles of lean manufacturing in their 1996 book “Lean Thinking: Banish Waste and Create

⁴⁰ Womack, James et al. *The Machine That Changed the World*. New York: Rawson Associates, 1990.

Wealth in Your Corporation”⁴¹. Womack and Jones were able to summarize the main elements of lean into five key principles: maximize value, identify the value stream, make the value flow, let the customer pull and pursue perfection.

Value is to be defined by the customer, what are they willing to pay for? The value stream is defined as all of the tasks required to bring the product or service to the customer. Once the value has been defined, effort must be made to eliminate any process that stalls the value from flowing to the customer. Through waste reduction in the value stream, operating systems should become more flexible, allowing the business to provide exactly what the customer wants. Manufacturing process like Just-In-Time have been established based on this principle. Although perfection is impossible, a key aspect of lean is the pursuit of perfection through continuous improvement. The process of value creation and flow, waste reduction, and servicing the customer is a reinforcing loop of improvement. The principle of continuous improvement is fundamental to Toyota’s TPS system, which has taken over fifty years to reach its current state and continues to evolve.

Lean is a complex web of mutually reinforcing and interlocking principles, practices and technical innovations. The principles and tools of the TPS have been copied and pasted into many organizations without realizing the same success as the originator. Spears and Bowen tried to explain this phenomenon in “Decoding the DNA of the Toyota Production System”. They argue that although hundreds of other companies have toured Toyota’s plants and tried to copy TPS, most have failed because they have only copied the “tools” and not the rigorous scientific problem-solving process underlying TPS⁴². Other companies have cherry picked some tools ignoring that it is the interlocking of the improvement tools along with the leadership strategy and people management practices that is critical to Toyota’s success.

⁴¹ Womack, James and Jones, Daniel. *Lean Thinking*. New York: Simon & Schuster, 1996.

⁴² Spears, Stephen and Bowen, Kent. “Decoding the DNA of the Toyota Production System.” *Harvard Business Review*. 1 Sept. 1999.

3.3. Key Elements of Lean Manufacturing

3.3.1. Waste Reduction

The Toyota Production System has identified 7 sources of non-value-adding waste (Muda) in both manufacturing and business processes that must be eliminated in order to make value flow to customers. These are:

1. Defects: Production of defective parts leads to rework, scrap, lost effort or wasteful inspections
2. Overproduction: producing more than the customer wants. Overproduction also means producing more, sooner or faster than is required by the next process
3. Transportation: unnecessary transportation of materials, parts or finished goods
4. Waiting: workers waiting to process due to downtime or paperwork waiting to be processed
5. Inventory: excess raw material, WIP, and finished good inventory leading to storage and expiration costs. Extra inventory in the system hides problems by allowing a buffer to supplier defects or internal quality problems
6. Motion: unnecessary motion employees perform including movement to search for tools or parts
7. Over-processing or incorrect processing: unnecessary steps or inspections in production. over-processing can also mean producing a higher quality item than the customer demands

3.3.2. Standard Work

Standard work defines the steps in a process and allows the work to be repeated without variation. Standard work reduces rework and scrap. It also should reflect the most efficient processes to perform a task.

3.3.3. Jidoka

Jidoka is the Japanese expression for automation, which means equipment that can stop itself when a problem occurs. Jidoka includes a number of methods that allow for detection of defects

at their source. Once a defect is detected, production is stopped to ensure that the defect is not passed downstream. Production is not resumed until the problem has been resolved. It is the responsibility of an employee to pull the Andon cords and stop production. In order to reduce defects, mistake-proofing or Poka Yoke is used.

3.3.4. Visual Management/5S

5S is a way to organize the workplace removing clutter, providing a safer work environment and reducing many of the 7 wastes including defects and excess motion. The name 5S comes from the five Japanese words Seiri, Seiton, Seiso, Seiketsu, and Shitsuke. These five words have been translated into the English Sort, Straighten, Shine, Standardize, and Sustain. These five principles are at the heart of most lean implementations and are described below:

- Sort: removing unnecessary items from the work area
- Straighten: set in order items and machines in order to minimize unnecessary motion or effort
- Shine: maintain a clear, organized work area
- Standardize: create guidelines for area organization and make it visually obvious when standard is not being met
- Sustain: ensuring 5S standards are maintained

3.3.5. Just-In-Time (JIT)

Just in time production focuses on creating a “pull” system originating with the customer. In a JIT system parts or services are supplied to a process as needed. To achieve JIT production the product must flow in the most direct, value adding path without interruption. Techniques such as one-piece flow, pull systems utilizing Kanban replenishments systems, and workload balancing (Heijunka) are essential to JIT.

3.3.6. Value Stream Mapping

One of the five key principles of lean is identifying the value stream. Womack and Jones recommend mapping the product value streams as an essential step in a lean transformation. However, many companies rush into waste elimination without understanding their product

value streams. This leads to isolated improvement without optimizing the whole. A product value stream map (VSM) is defined as the material and information path that must be followed to transform raw materials into the customer's final product. The primary purpose of developing product value stream maps is to identify and eliminate sources of waste while identifying opportunities for improving value creation, to increase overall value delivery to customers.

3.3.7. Kaizen Event

Kaizen is a Japanese term meaning continuous incremental improvement. Kaizen events focus on achieving small improvement in one area within a specified amount of time. A key to Kaizen success is to maintain the improvement achieved while continuing to find new opportunities for improvement. Once a current state value stream map is identified, kaizen events can be used to achieve the future state vision for the value stream.

4. The Pharmaceutical Industry Status on Achieving Operational Excellence

If one was to define operational excellence as ensuring the customer receives its product on time, at high quality while achieving a large gross margin, most of the pharmaceutical industry are top performers. However, pharmaceutical operations are far from efficient as was first widely communicated by the Wall Street Journal in September 2003 when it revealed that “the pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers”⁴³. For the most part pharmaceutical operations are characterized by long cycle times, high inventory levels, lots of rework, low yields, and inflexibility. Previously, manufacturing efficiency was never a priority. A pharmaceutical company’s ability to discover new breakthrough therapeutics and sell and market those medicines at premium prices enabled it to achieve very large profit margins. With high profit margins, companies focused on research and development as well as marketing and sales functions, ignoring operations. In addition, even if employees wanted to change operations to be more efficient, the manufacturing processes are highly regulated and would need revalidation and regulatory approval- usually a no win from a cost/benefit analysis.

Due to changes in the competitive environment pharmaceutical companies are increasingly focusing on reducing costs through improving operational efficiencies. According to a study of over 100 European pharmaceutical companies from August 2004 through June 2005, the average research driven pharmaceutical company cost of goods sold (COGS) is about 30%, second in expense only to SG&A⁴⁴. Indeed, the manufacturing process and its associated overhead cost are not negligible to a pharmaceutical organization.

Historically, manufacturing performance has been measured by a firm’s ability to provide drugs to patients while meeting regulatory compliance requirements. While most research based pharmaceutical companies have been very successful from a compliance standpoint, this success has come with a high cost of quality. The 2004-2005 international benchmarking study revealed

⁴³ Abbound, Leila and Hensley, Scott. “Factory Shift: New Prescription for Drug Makers: Update the Plants.” *The Wall Street Journal*. 3 Sept. 2003: A1.

⁴⁴ Friedli, Thomas et al. *Operational Excellence in the Pharmaceutical Industry*. Germany: Editio Cantor Verlag Aulendorf, 2006.

that even the lowest performers in the study group had a delivery rate of 98% and a reject rate of less than 4%, but that the cost of quality/total cost ranged from 16% for the lowest performer to 2% for the best in class. While the industry averages less than a 1% complaint level, quality is not built into the system but a result of testing, inspections, and verification. This benchmarking study also revealed that low performers in the pharmaceutical industry have nearly as many quality personnel as they do manufacturing operators⁴⁵.

According to the international benchmarking study nearly 57% of the 100 pharmaceutical companies (including research based, contract manufacturers and generic manufacturers) have implemented parts of a JIT production system including pull systems, setup time reduction, planning adherence and layout optimization⁴⁶. The following data are given for the bottom 10% (low performer) and top 10% (high performer) of the 100 companies surveyed. Even among these top performers few used lean pull system techniques.

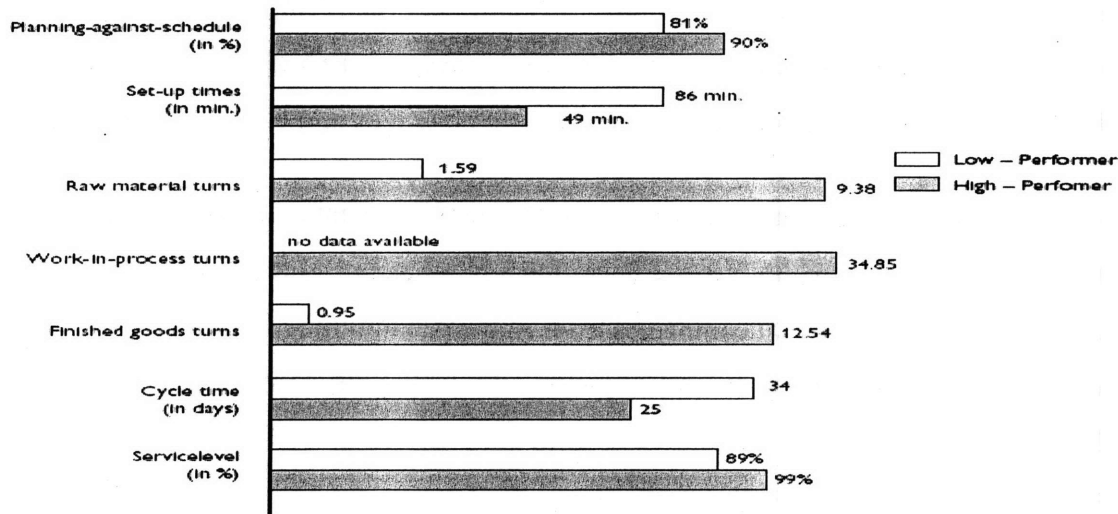


Figure 6: Range of Pharmaceutical Operational Performance⁴⁷

⁴⁵ Ibid.

⁴⁶ Ibid.

⁴⁷ Source: Friedli, Thomas et al. *Operational Excellence in the Pharmaceutical Industry*. Germany: Editio Cantor Verlag Aulendorf, 2006: 64.

4.1.1. Small-Molecule Lean Transformations

Unlike the biotechnology companies, traditional pharmaceutical companies are accustomed to generic competition and as a result are much further down the road to achieving operational excellence. Most of the top small-molecule pharmaceutical companies have well developed improvement programs institutionalized. The pharmaceutical industry has learned from Toyota and others that have implemented lean successfully. This section will provide some examples of operational excellence programs within the small molecule pharmaceutical industry.

Following the withdrawal of its blockbuster Vioxx, in late 2004, Merck launched the Merck Production System (MPS) as an operational excellence strategy it believes will allow it to become the “most competitive supplier of medicines and vaccines in the world”⁴⁸. MPS is based on the lean principles of maximizing customer value through waste elimination. Merck pilot tested its MPS program at its Arecibo, Puerto Rico manufacturing facility. Within 18 months of the program’s launch the site had achieved significant results:

- The number of days to perform quality testing was reduced 60%
- Investigation lead time was reduced 70%
- Manufacturing schedule was replaced with a system that reflects the variation in customer demand

These results were achieved through elimination of handoffs, redundant work, required approvals and by the co-location of employees. Merck has also started an incentive system to reward future improvements⁴⁹.

Wyeth and Novartis have also made strives in improving operational improvement. For example Wyeth’s Centrum manufacturing process was overhauled in 2006 with the following results⁵⁰:

- Production now paced to meet packaging requirements (the process’ customer)
- Pull Systems have been established leading to WIP inventory reduction
- Cycle time has been cut from 33 to 11 days

⁴⁸ Shanley, Agnes. “Merck’s Lean Mission.” *PharmaManufacturing.com*. 2006.

⁴⁹ Ibid.

⁵⁰ Thomas, Paul. “2006 TOTY Finalist Profiles: Wyeth Excellence in Operations Team, Pearl River, N.Y.” *PharmaManucaturing.com*. 2006.

Novartis piloted its operational excellence initiative at its Suffern, N.Y. manufacturing plant in November 2002. Through value stream mapping and waste elimination the site was able to reduce cycle time by 70% and spending by 40%⁵¹. The site also reduced the number of key performance indicators (KPI) it was tracking to only a few that allow for transparent performance management.

While pharmaceutical companies have begun to implement operational improvement programs, most programs are less than 5 years old. The companies that have taken the initiative have paved the way for how operational excellence can be achieved within the constraints of government regulations. The next chapter will explore in more depth the regulatory requirements of drug manufacturing as well as provide insight into the differences in small molecule versus protein manufacturing and hence operational performance.

4.2. *What Makes Pharmaceuticals Different?*

Pharmaceuticals are regulated by national agencies that ensure their safety and efficacy. It is the high requirement for quality assurance including extensive testing, documentation, and inspection readiness that are blamed for high pharmaceutical manufacturing costs. In addition, pharmaceutical production is conducted following a strict set of operating procedures and in-process testing requirements. Operating outside of approved ranges results in the rejection of an entire manufacturing batch. Although pharmaceuticals operate in this tightly regulated environment, other manufacturing industries have been able to adopt lean principles despite tight regulation (aerospace, electronics). However what sets pharmaceuticals apart is that pharmaceutical firms have a legal responsibility to produce and release product to the exact approved specifications. These regulations have lead to an industry that is resistant to change. Without change, operations can not improve.

The lack of improvement is especially striking in this industry because of the inefficient state of operations as originally filed. Since every day that drug approval is delayed is equivalent to

⁵¹ Shanley, Agnes. "Novartis Goes Lean." *PharmaManufacturing.com*. 2004.

millions in lost revenue, pharmaceutical companies are not able to file with process that has been fully optimized for large scale production. In fact, most pharmaceutical operations have only been performed a limited number of times in full-scale before licensure. Unlike other industries, changes to the drug manufacturing process must be approved by the governing regulatory agencies. Because the approval of process changes is both time and resource consuming many pharmaceutical companies choose to accept the inefficiencies in their process creating a barrier to process improvement.

4.3. *Overview of Regulatory Constraints*

In order to sell a drug in a country, it must be approved by the regulatory agency in that country for a specific clinical application. The approval process itself can vary country by country, but that of the FDA is considered to be the standard. There are several steps in the approval process, with the majority of drug candidates that enter the process not reaching approval. The approval process takes approximately 10 years, with the final approval coming approximately one year after the final stage of the application is filed, the New Drug Application (NDA) for small molecule products or Biologics Licensure Application (BLA) for biotech products in the U.S. and the Common Technical Document (CTD) in the EU. This is the formal step a drug sponsor takes to ask that the regulatory agencies to consider approving a new drug for marketing in that region.

A drug application includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured. Included in the approval process is an inspection and audit of the drugs manufacturing facilities. In the U.S. the manufacturing facilities must meet the regulatory requirements for Current Good Manufacturing Practices (cGMP).

Drug Review Steps

1. Preclinical (animal) testing. Pre-IND
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase 1 studies (typically involve 20 to 80 people).
4. Phase 2 studies (typically involve a few dozen to about 300 people).
5. Phase 3 studies (typically involve several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or find it either "approvable" or "not approvable."

Figure 7: The FDA Approval Process

Source: www.fda.org

Once a drug is approved by the regulatory body it has to be manufactured according to the process as described in its application. Drugs sold in the U.S must be in compliance with the GMP Regulations defined by the US Food and Drug Administration under the authority of the Federal Food, Drug, and Cosmetic Act. Section 21 of the Code of Federal Regulations contains the regulations pertaining to drugs. The European Medicines Agency (EMA) has a similar set of guidelines for drugs approved in the E.U. These regulations, which have the force of law, require that manufacturers, processors, and packagers of drugs take proactive steps to ensure that their products are safe, pure, and effective. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination or errors. This in turn, protects the consumer from purchasing a product which is not effective or even dangerous. Compliance with cGMPs is ensured through review of annual updates to the NDA and both announced and unannounced inspections and audits. Failure of firms to comply with GMP regulations can result in very serious consequences including recall, seizure, fines, and jail time.

Regulations address issues including recordkeeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling. The regulations state that there will be a quality control unit that has the responsibility and authority to approve or reject any drug material, drug WIP or raw material component. The quality control function must ensure appropriate procedures are in place to test the drug's identity, strength, quality and purity and that the requirements for these attributes are met for release. These regulations also require that all processes are well documented using standard operating procedures (SOPs) and

that documentation batch records are kept for each manufacturing batch. This leads to drug manufacturing producing two products: the drug and its associated paperwork.

Most requirements are very general and open-ended, allowing each drug manufacturer leeway for interpretation. However, changes to manufacturing operations, raw material components, expiration, or product containers require process validations, regulatory filings, sometimes new clinical trials and ultimately regulatory approval. The regulatory requirements for the change can range from a simple mention in the annual update to a new process validation, clinical trials and NDA supplement (taking nearly as long as the original NDA for approval). In addition, determining what the requirements are for a specific change can be unclear and take months to determine. Some companies work closely with regulatory agencies to determine the requirements to approve the change. This pre-work minimizes the time to approval as well as the risk that the change will not be approved. Due to the long lead time, drug product in hold-up that can not be sold, and the risk of non-approval, most pharmaceutical companies try to minimize changes to the original NDA approved process.

Figure 8 below provides an overview of the steps required for a process change. The regulatory approval process is a complicated one that has been established to protect the patient. Companies are required to perform formal validation of any improvement through the manufacture and testing of three drug lots. As part of these validations the company must follow an approved protocol. A formal validation report is also required. In addition, the regulatory body is allowed a time frame in which to respond to the regulatory submission. Within that time frame the agency must either respond with questions on the submission or an approval of the submission. With each round of questions the regulatory response time is reset. If the first round questions are not answered satisfactorily or if additional testing/analysis is required the approval clock stops until a formal company response is made. As the process change and approval value stream map indicates, a process change and approval can take 1-2 years and is filled with non-value added steps to the patient, including several rounds of internal approval. While some of these steps may be necessary, they are non-value adding. Actually, these internal quality constraints along with the regulatory review leads to a process with less than 20% of time considered value added (green block).

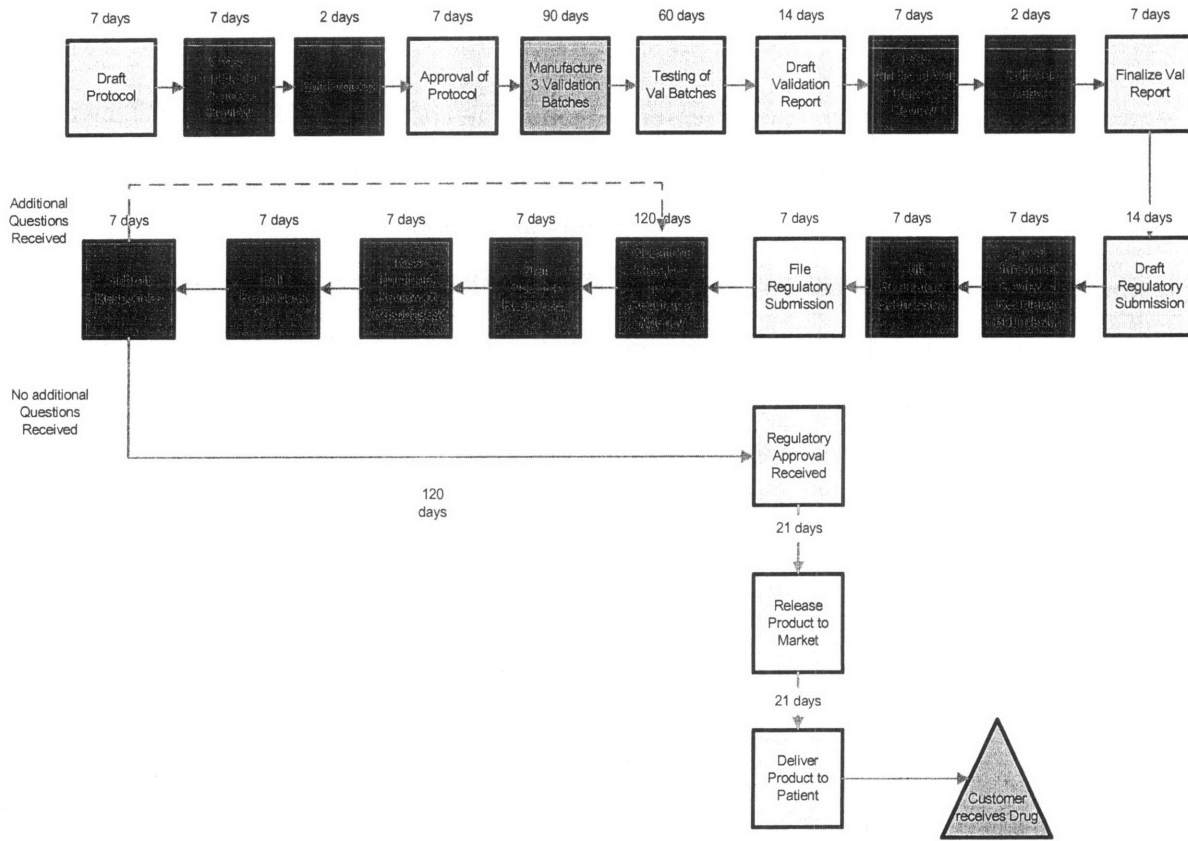


Figure 8: Example Process Improvement Regulatory Approval Value Stream Map

4.3.1. Overview of Pharmaceutical Manufacturing Processes

Pharmaceutical manufacturing processes are classified into two sections, drug substance and drug product. Drug substance processes are those that lead to the formation of the active pharmaceutical ingredient (API). Drug product processes then transform the API into a stable formulated product suitable for human delivery. Traditional drug manufacturing (small-molecule) has a series of chemical reactions to make the desired chemical entity. This entity must then be separated from its impurities through a series of separation processes (crystallization, precipitation, extraction). The purified chemical is then further processed into powder form and made into tablets.

Biopharmaceuticals differ from small-molecules in that they are protein compounds made from living cells instead of synthetic chemistry. These proteins must also be separated from

impurities through a series of separation processes, however these process differ from those used for small-molecules. The purified protein is then mixed with excipients for stabilization. The protein rich solution then undergoes freeze drying in order to produce a solid powder cake. This cake must then be re-suspended by the patient with a diluent solution. While most small-molecules are delivered through oral solid dosage form, protein drugs must then injected by the patient. Many biopharmaceutical drugs now come in pre-suspended in syringes for injection.

The differences in manufacturing process for small-molecule versus biological pharmaceuticals directly results in operational performance gaps. The next section will explore those differences as well as provide detail into a biopharmaceutical manufacturing process like that studied in the Amgen case study included in Section 7.

4.3.1.1. Pharmaceutical vs. Biopharmaceutical Operational Performance

While both small molecule pharmaceutical and biopharmaceutical companies produce drugs under the same regulatory controls, there is a striking difference in operational performance between these two segments of the industry. Traditional pharmaceutical companies take 10 to 14 days to release a batch, biopharmaceutical batches typically take 80 to 90 days⁵². The increase in time for release is a direct result of the difference in the level of complexity of the manufacturing processes and product testing requirements. Biopharmaceutical processes utilize living cells to produce protein drugs. This leads to a high level of uncertainty and variation within the manufacturing process and the finished good. In order to ensure product safety and efficacy biopharmaceutical products are tested extensively both in-process and at release. The analytical testing methods for proteins are much more complex and time consuming than the analytical characterization techniques for small molecules. Additionally, because biopharmaceutical products are derived from animal and/or human components they must undergo rigorous testing to verify a lack of infections agents in the product. Biopharmaceutical manufacturing processes are also much more complex than the chemical reactions of a small molecule, leading to more documentation (standard operating procedures). The variability and complexity of

⁵² Punich, Marc. "BioBenchmarkSM Biopharmaceutical Operations Benchmarking Study." *BioPharm International*. September 2003.

biopharmaceutical processes also tends to generate more deviations and investigations than in small molecule manufacturing, increasing the time and effort required for batch release.

4.4. Overview of Biopharmaceutical Manufacturing

In order to better understand the manufacturing processes involved in the Amgen Case study, an overview of biopharmaceutical drug substance operations similar to those used in Enbrel drug substance manufacturing at the Amgen Rhode Island site.

Pharmaceutical products are made from cells that have been genetically engineering through recombinant technology to produce the desired protein molecule. Popular cell lines in protein production are *E.coli*, yeast, and mammalian. *E. coli* is a popular cell line because of its rapid growth rate and high expression levels. However, *E.coli* is not able to glycosylate (add carbohydrates to the structure) the proteins it produces. Correct glycosylation is essential for proper protein function and avoidance of adverse effects. In addition, *E. coli* produces its proteins intracellularly which means that the cells will have to be disrupted in downstream purification. Cell disruption releases cell contents and increases the difficulty of separation as well as the problem of protease degradation. A number of recombinant proteins are expressed in yeast and fungi which are capable of glycosylation. However, the glycosylation from these organisms differs from those naturally found in the human body. The majority of current recombinant proteins are produced in mammalian cell lines with Chinese hamster ovary (CHO) cells being the most popular. These cells lines are well characterized, secrete the proteins extracellularly, and produce proteins with glycosylations patterns nearly identical to the native human protein⁵³.

In biopharmaceutical manufacturing the chosen cell line is extensively characterized for genetic stability. Once genetic stability is verified, the cell line is manufactured into a master cell bank and then a working cell bank derived from the master. The first step in any biopharmaceutical process is the thawing of one or two working cell bank (WCB) vials. Cells are initially grown in

⁵³ Walsh, Gary. *Biopharmaceuticals, an Industrial Perspective*. Norwell, MA: Kluwer Academic Publishers, 1999.

very small volumes (less than 25ml) in spinner flasks and then used to inoculate progressively larger volumes of media (cell nutrients) in bioreactors. Depending on the specific process, the production bioreactor (final stage) can be anywhere from 100L to 15,000L volume. Most pharmaceutical cell culture processes can be operated in batch, fed-batch or continuous mode⁵⁴.

In a batch process all of the nutrients needed for production are added to the reactor prior to inoculation. In this type of process, the cell growth is limited by the availability of substrate nutrient in the media. For a fed-batch process, nutrients are added either continuously or at set intervals to the reactor during culture. This allows cell growth to no longer be limited by nutrient substrate. Continuous perfusion processes are also popular. In a perfusion process, a smaller volume reactor is utilized because the protein product is constantly withdrawn from the tank. The tank is maintained at constant volume as fresh media is added at the same rate that spent media is removed. The spent media (containing protein and cells) is simultaneously processed through either filtration or centrifugation to separate the protein and cells. In a perfusion process, the cells are returned to the reactor to continue production and the protein is collected for further processing. Some perfusion processes can continue for months at a time while most batch processes run for one month or less per cycle. Continuous systems can allow for higher productivity over batch processes however most commercial fermentation systems are batch or fed-batch because of genetic instability that can occur in long continuous cultures⁵⁵. In addition, batch processes may be used for market reasons since the reactor can be campaigned for several products over the year.

Following the cell culture phase of processing, the desired protein must be separated from all of the other host cell's proteins and DNA as well as the cells themselves. Downstream processing is usually divided into three parts: recovery, low resolution purification, and high resolution purification. As the product stream moves through these phases of purification, the total mass of protein present decreases, but the solution becomes more concentrated with the relative amount of desired product. As the solution increases in purity, it becomes more difficult to separate out

⁵⁴ Vogel, Henry. *Fermentation and Biochemical Engineering Handbook: Principles, Process Design, and Equipment*. 2nd Edition. Westwood, New Jersey: Noyes Publications, 1997.

⁵⁵ Ibid.

remaining impurities because many are fragments of the desired protein. Since downstream processing exploits the chemical and structural properties of the desired protein for separation, this kind of product heterogeneity increases purification difficulty. A well designed downstream process exploits physical characteristics between product and impurities in successive steps with less expensive low resolution methods used initially when the volumes are large and impurity profile worse and then higher resolution steps are utilized as the purity profile improves and volume is reduced.

In the recovery phase a capture step is utilized in which the protein product is separated from the host cell and is concentrated. Typical unit operations for capture are ultra filtration, adsorption or ion exchange chromatography. Next, the protein solution is processed through a series of chromatographic steps. These usually include an affinity chromatography and one or two ion exchange steps. Affinity chromatography is a high resolution step based on a specific biological protein-ligand interaction that allows for several thousand fold purification. Ion exchange is the most commonly used chromatographic separation. Ion exchange separates proteins based on net charge at a given pH. Anion exchangers separate out negatively charged proteins while cation exchanges separate positively charged proteins. Variation is inherent in biological processes due to the formation of different products under varying conditions. As a result, purification processes must be robust enough to consistently produce pure product despite the varying input conditions. Affinity and Ion exchange chromatography are some of the most robust chromatography steps utilized in biopharmaceutical purification⁵⁶.

Gel filtration chromatography (sometimes referred to as size exclusion chromatography) is a polishing step that separates proteins based on size. The gel filtration beads are a cross linked three dimensional structure that allow smaller molecules to penetrate. Protein molecules then pass through the column while smaller molecules are held up. Since there is variability in the actual gel pore size, gel filtration does not provide a sharp separation. For this reason, gel filtration is mostly used in the later polishing phase of purification. Because of its ability to perform buffer exchange, gel filtration chromatography is frequently used as the last step of drug

⁵⁶ Ibid.

substance manufacturing to transfer the protein product into a stabilizing, excipient solution prior to further manufacturing ⁵⁷.

After protein purification most drug substances are frozen and then transferred to a fill/finish facility. At the fill/finish facility the protein is diluted to the necessary concentration, and then aseptically filtered. Lyophilization provides the most stable protein drug product, however liquid formulations are becoming much more popular due to the convenience provided to patients. An overview of biopharmaceutical manufacturing is provided in Figure 9 below.

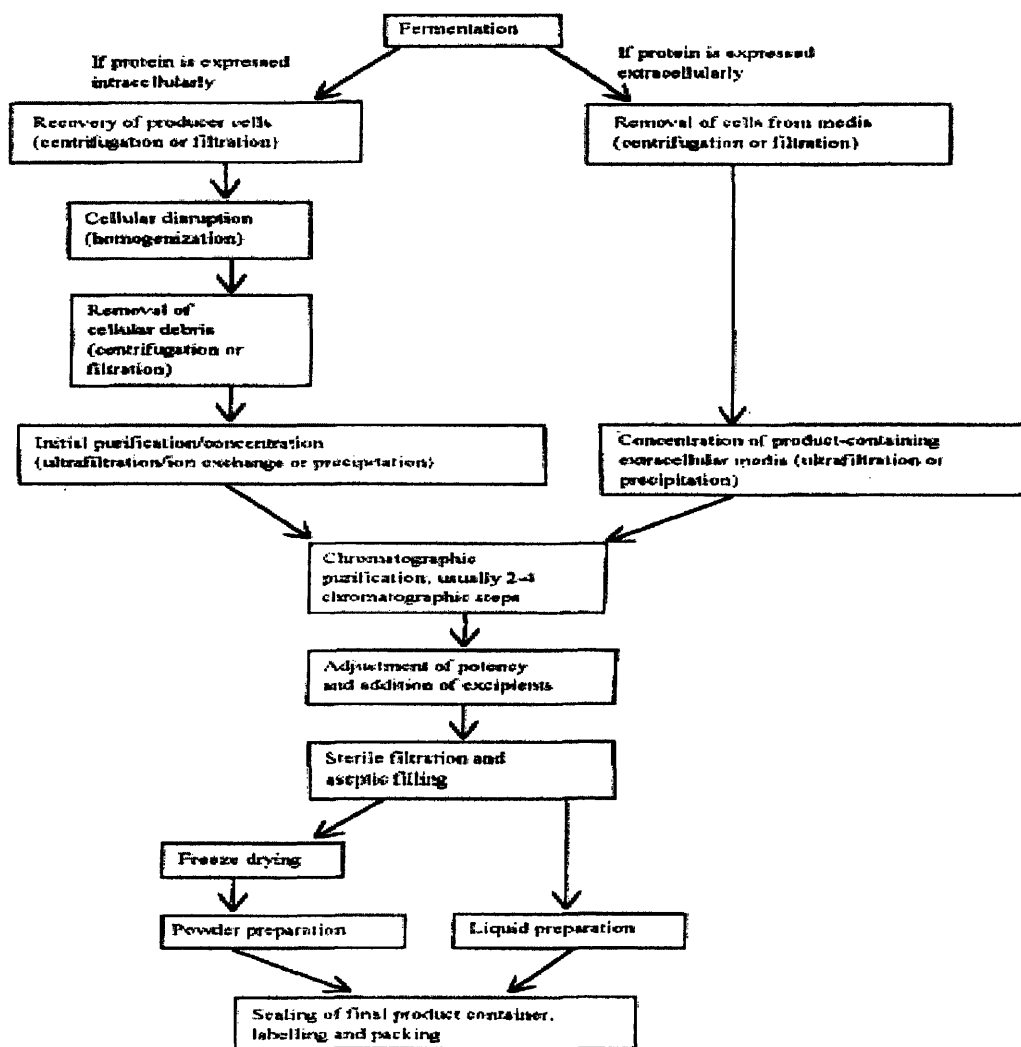


Figure 9: Overview of a Biopharmaceutical Process⁵⁸

⁵⁷ Scopes, Robert. *Protein Purification: Principles and Practice*. New York, NY: Springer, 1994.

⁵⁸ Source: Walsh, Gary. *Biopharmaceuticals, an Industrial Perspective*. Norwell, MA: Kluwer Academic Publishers, 1999: 9.

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5. The Status of Biopharmaceutical Operations

5.1. Operational Inefficiencies in Biopharmaceutical Operations

In this section the author will give examples of some of the operational inefficiencies she has witnessed during her professional career in biopharmaceutical operations. In addition to time spent at the Amgen Rhode Island facility, the author worked for 6 years in biopharmaceutical operations and was exposed to several different protein manufacturing processes. The author was intimately involved in process validations, technical transfers, facility startups, and product filings. This work has allowed the author to compare and contrast manufacturing processes, quality requirements, and inventory control philosophies.

While each product has its own specifics, Figure 10 below is a generalized overview of the processes performed at a biopharmaceutical drug substance manufacturing plant. As the figure indicates, it can take up to two years from raw material receipt to delivery of drug substance to the fill finish facility. While manufacturing is the heart of drug substance operations, it makes up less than 20% the total cycle time and an even smaller fraction of the operating cost. The inefficiencies within manufacturing, receiving, quality testing, and disposition are discussed below.

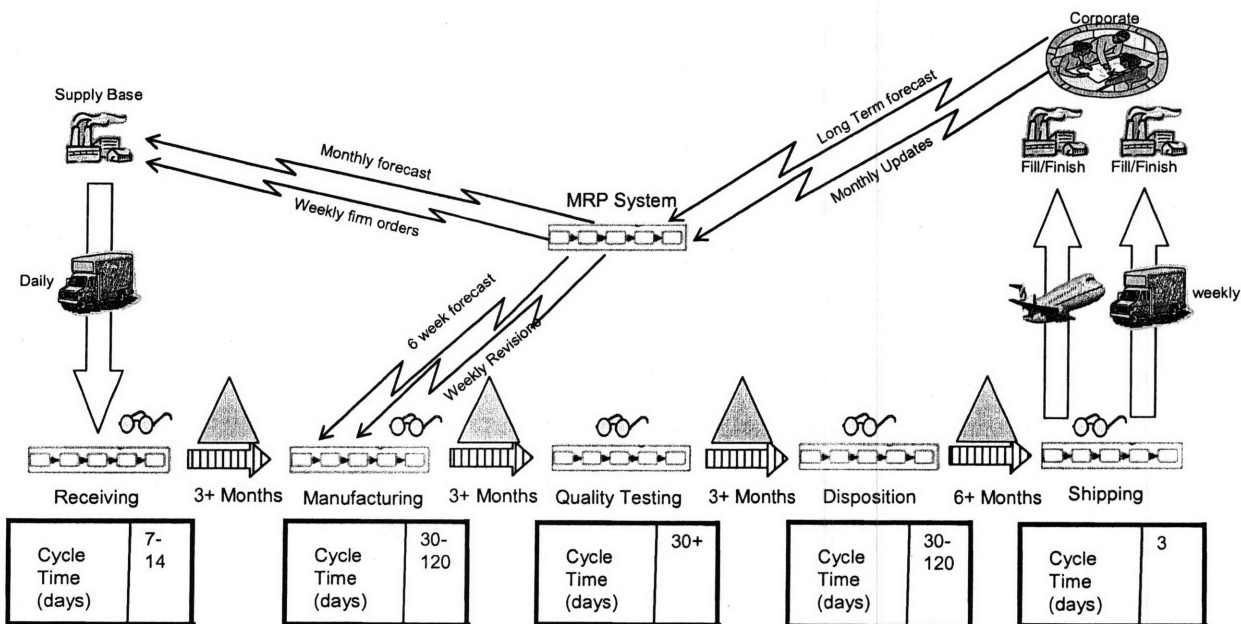


Figure 10: High Level Example Biopharmaceutical Value Stream Map

5.1.1. Receiving Inefficiencies

Biopharmaceutical production requires hundreds of raw materials from a variety of vendors. Some of these materials are chemical commodities, some are common reagents in the biopharmaceutical industry, while others are proprietary and specific to the drug's manufacturing. In order to meet GMP requirements, each raw material must meet strict quality guidelines. In most cases, the vendor is qualified through a rigorous audit and validation process. From an organizational point of view, there is usually an entire subgroup of the quality division dedicated to these activities.

For some "critical" raw materials, a vendor may need to go through the regulatory approval process including process validation to ensure that a change in raw material has no effect on the end drug substance and drug product produced. Once a vendor has been qualified, the site may receive material to be used in commercial production. The vendor provides a certificate of analysis (CofA) that guarantees that the material has been manufactured correctly and has passed the required release testing. Once the raw material arrives at the manufacturing site, a sample must be taken and tested by the quality control group. This sample is used to verify the identity of the raw material. In addition, some biopharmaceutical companies repeat the entire release testing performed by the vendor. Other companies have chosen to randomly test 1-2 lots per year from each vendor to maintain the vendor's qualification. Like the drug substance the site produces, the raw materials used must all be released prior to use. Quality professionals will review the vendor information including CofA and also the company's internal testing results. It can take up to several weeks for a raw material lot to be testing and released internally.

Due to the time to release raw material, as well as the long lead times for some specialty materials, many biopharmaceutical companies carry significant inventory. For the more common materials, inventory levels will usually be three or more months. However, it is not uncommon for pharmaceutical companies to carry a year or more of some materials. This is not only due to long lead times but also large vendor lots sizes. In addition, most manufacturing sites keep at least two lots from a given vendor at a time as a backup. Some companies even require lots from different vendors to be kept on site.

As indicated earlier, the pharmaceutical industry is risk averse. As a result, there is a tendency to buffer using large inventory holdings throughout the process. For raw materials, this leads not only to expansive warehouse requirements but also high raw material scrap rates due to expiration. While raw material worth is only a fraction of that of the finished product, some key raw materials, including chromatographic resins and media components, can cost up to several hundred thousand per lot. A slow down in production schedule due to contaminations or a reduction in demand can result in millions of dollars of raw material scrap.

5.1.2. Manufacturing Inefficiencies

A major driver for manufacturing, especially upstream, is the reduction in contamination risk. To avoid contamination, pharmaceutical processes utilize a large number of filters for material and product streams, run closed systems, and employ rigorous cleaning between batches. Raw material and product streams are also tested in-process to verify sterility. All of these practices ensure the integrity and quality of the drug substance, however they also lead to long processing time.

5.1.2.1. GMP Requirements Lead to Low Value-Added Time

In order to meet GMP requirements and ensure no product carryover most biopharmaceutical unit operations require significant cleaning and sanitation. Cleaning in place (CIP) is required before use of equipment for a new batch. CIP is an automated washing process consisting of several cycles of rinsing with detergent. Unit operation equipment must be steamed in place (SIP) to kill any biological remnants. These operations require significant setup times, cleaning times, and also hold times in the case of SIP. For a given unit operation cycle time, CIP and SIP time can be 5-10x the actual processing time, as Figure 11 below indicates.

Another precautionary element of biopharmaceutical processing that adds to process cycle time is filter integrity testing. Drug substance process can employ up to hundreds of filters per batch, however there are only a few critical filters in each process. These critical filters are usually a sterility filter for the media, a virus removal filter during downstream manufacturing, and a final filter before freezing. Filters can be integrity tested prior to use and also post use. Some companies have employed a risk based approach that limits the need for filter testing depending

on where the filter is used in production. However, other companies use a blanket integrity testing approach in which any filter used in production is subject to pre and post testing requirements. The actual time required to perform integrity testing time is dependent on the filter. However, it is not the actual processing time that creates the true inefficiencies, it is large number of deviations associated with filter integrity testing. While most deviations are able to be closed out (sometimes with vendor aid), the investigation process is time and resource consuming. It is this type of deviation and subsequent investigation that tends to limit the rate of product release and causes the variation around process cycle time. Since only a small fraction of these filters is considered critical and sterility can also be verified through in-process sterility testing results, most filter deviations will be closed without product impact independent of actual integrity testing results. Companies that have taken a risk based approach to filter integrity testing have seen a significant reduction in related deviations.

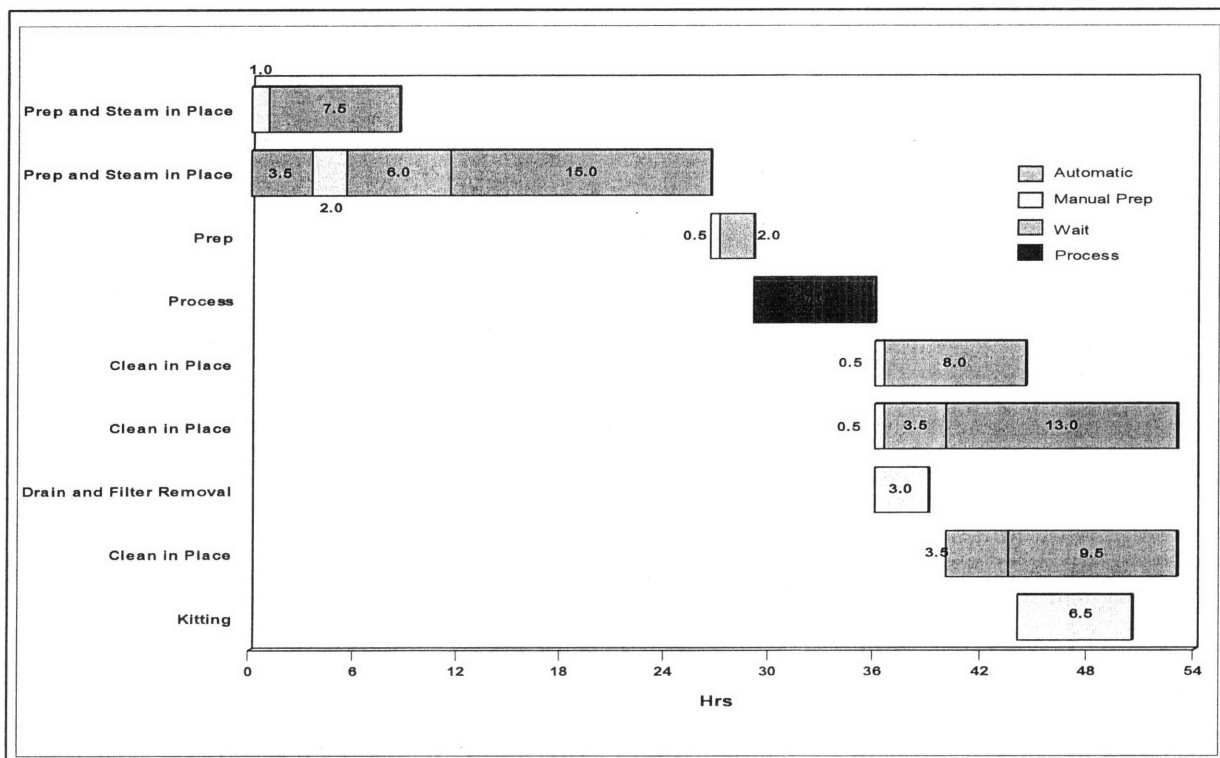


Figure 11: Example Biopharmaceutical Unit Operation

5.1.2.2. Media and Buffer Scrap

Additional inefficiencies are present in manufacturing due to the way production is scheduled. As Figure 10 indicates, the manufacturing schedule is pushed onto a site from a corporate planning function. As a result, the media and buffer needed for production are also pushed onto

the cell culture and purification processes, respectfully. Operating as a push system leads to scrap of media and buffer due to delays in the manufacturing schedule as these materials have finite life spans. Inefficiencies are also present in the handoff of media and buffers to production because most facilities lack a feedback loop. Pharmaceutical operations are inherently variable. As a result, manufacturing batch records provide a range for the media or buffer to be used in production. It is only until actual production has begun that the exact amount of media or buffer needed is known. As a result of the push system, media and buffer preparation prepare the maximum amount that may be needed. In the majority of batches, a fraction of the solution will not be needed and will be scrapped.

Media and Buffer preparation through a push system is not flexible. Process engineers have validated solution preparation for a certain volume, usually the capacity of the tank. Whether production needs to run 2 or 4 batches that week, an entire tank's worth of buffer will be prepared. However, some of this buffer lot may not be used due to expiration, again leading to scrap.

5.1.3. Quality Testing Inefficiencies

A biopharmaceutical manufacturing process is highly specified in regulatory documentation. Therefore every precaution is taken to ensure all requirements are met during processing as well as for the final product. A typical biopharmaceutical drug substance process has over 100 samples taken during production to provide quality evidence. These samples are used for protein chemistry, biochemistry, immunology and microbiology testing. The majority of these tests are performed in house by the quality control group (a subdivision of the quality group). Specialty testing may be outsourced. Inefficiencies exist in quality testing because of the large number of samples and tests that need to be performed. While most tests take less than a day to perform, there may be a long lead time for analysis because many laboratories operate in batch mode (see Figure 12 below). Quality testing and its associated deviations are commonly the bottleneck for product release since a manufacturing lot can not be released unless all in-process and final product specifications have been met. Performing over 100 analytical tests for each batch not only takes time but produces deviations. In pharmaceutical operations quality is tested in. For each test performed, a specified result must be obtained. For some drug processes the variability

inherent in the process results in out of specification analytical results. A survey of biopharmaceutical companies in 2004 indicated that over 10% of samples tested must be retested (see Figure 12 below).

Product Sample Turnaround Times				
	Average	Minimum	Maximum	(Standard Deviation Percent)
Sample cycle time (days)	29.2	17.5	45.0	(36%)
Percent retest rate (for all reasons – out of specifications, out of trend, laboratory error) (days)	11.6	2.0	20.0	(61%)

Figure 12: Biopharmaceutical Sample Turnaround Times⁵⁹

Pharmaceutical companies must take backup samples to test in case such a retest and investigation is required. Some companies also take backup samples during production to aid in any contamination investigation that may occur. While these samples will most likely never be tested (and if they are they only serve to identify what day the contamination occurred), they bog down the entire sample handling and storage process.

5.1.4. Disposition Inefficiencies

Most pharmaceutical companies track disposition time very closely. Although most drug substance plants keep several months of inventory onsite, shorter disposition times reduce overall cycle time and provide flexibility to meet demand changes. Disposition time is measured from the point of final processing to batch approval or rejection. Quality personnel review all batch documentation including: raw material release records, manufacturing batch records, testing results, and investigations. For a batch to be released, all documentation must be reviewed and approved as well as all test samples must meet specification, and all investigations must be closed out with appropriate corrective action taken.

⁵⁹ Sources: Punich, Marc. “BioBenchmarkSM Biopharmaceutical Operations Benchmarking Study.” *BioPharm International*. September 2003: S-31.

In a routine process, disposition is usually limited by quality testing. However, the disposition of many batches is delayed due to lengthy investigations. As Figure 13 shows, the average disposition time for a biopharmaceutical drug substance is close to 90 days, with a wide range around the mean. This wide range is driven by deviations. According to Figure 13 it takes over 40 days to close out a deviation whether major or minor. The range in disposition release cycle time represents the differences in biopharmaceutical companies' performance in disposition. For instance, while some companies will review batch records real time, others wait until all production has been completed (up to several weeks later) before initiating batch review. The survey data also indicates that some companies are better than others in closing out deviations. While all companies seem to track deviation close out, some seem to be more successful at timely closure than others.

Key Measures of Quality Systems Performance			
	Average	Minimum	Maximum
Bulk Release Cycle Time (days)	89	50	196
Average minor deviation closure time (days)	46	27	90
Average major deviation closure time (days)	56	29	93
Deviations in-process (weeks)	9	3	30

Figure 13: Key Measures of Quality Systems Performance⁶⁰

5.1.5. Summary of Biopharmaceutical Operational Inefficiencies

The proceeding section examined a typical biopharmaceutical drug substance operation. A review of the inefficiencies in these activities indicates that there are significant improvement opportunities within biopharmaceutical operations. Here is a list of some of the major improvement areas:

- Raw material, media, and buffer scrap reduction
- Raw material, work in process, and finished goods inventory reduction

⁶⁰ Punich, Marc. "BioBenchmarkSM Biopharmaceutical Operations Benchmarking Study." *BioPharm International*. September 2003: S-27.

- Increase in the % of cycle time that is value added
- Reduction in analytical testing requirements
- Reduction in the overall process cycle time including disposition

It is the hypothesis of this thesis that lean principles can reduce the level of inefficiencies within biopharmaceutical operations without jeopardizing the quality of the drug product.

5.2. The Status of Operational Excellence in Biopharmaceutical Operations

As previously stated, the biopharmaceuticals are beginning to face increased competition and for the first time in the industry's 25 year history, manufacturing is beginning to take center stage. However, most biopharmaceutical companies are immature with respect to the pursuit of operational excellence. As a response to the need for improvement, a consortium of biopharmaceutical companies, Biopharma Operations Excellence Consortium, was established in 2002 by the consulting firm, Tefen. During a June 2007 meeting Tefen surveyed 11 companies on the status of their operational excellence program. Data from this survey has been included below to provide insight into the status of operational excellence programs within the biotech industry. The survey indicated that nearly 20% of those companies surveyed did not have a formal operational excellence program as of June 2007. The survey also indicated that the majority of the programs are only in their infancy (less than 3 years) compared to the decades of improvement conducted by Toyota and others. According to the data, cycle time reduction is the key driver for improvement. Also, it seems that the industry has accepted lean manufacturing as the preferred methodology for achieving operational excellence.

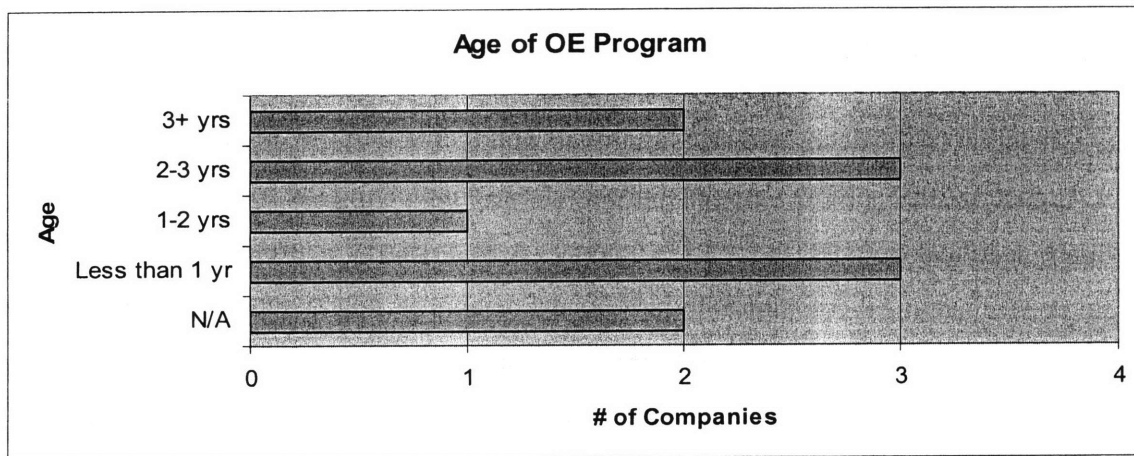


Figure 14: Age of Operational Excellence Initiative (Based on Survey of 11 Companies)⁶¹

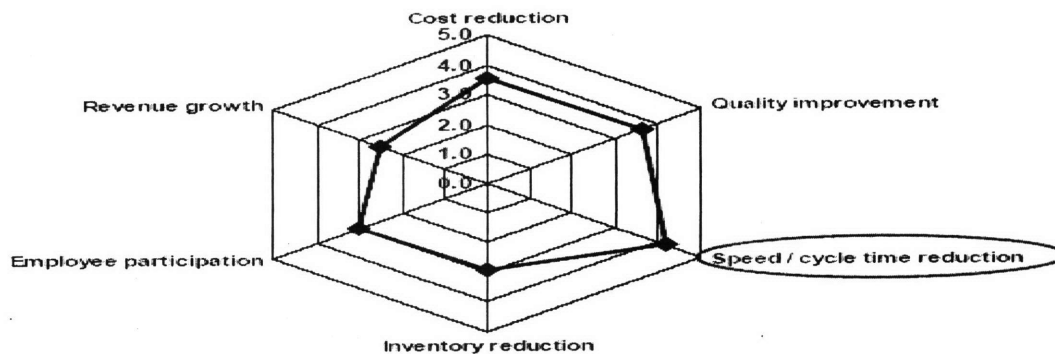


Figure 15: Key Drivers for Operational Excellence Initiative (Based on Survey of 11 Companies)⁶²

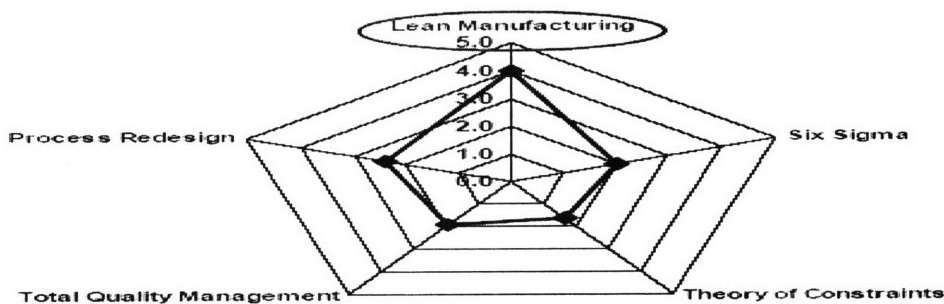


Figure 16: Key Methodologies Used in Operational Excellence Initiative (Based on Survey of 11 Companies)⁶³

⁶¹ Biopharmaceutical Operational Excellence Consortium Meeting Presentation June 2007.

⁶² Ibid.

⁶³ Ibid.

5.3. Regulatory Action: A Potential Aid in Operations Improvement

As a proactive reaction to the decline in drug approvals and increase in the number of drug safety concerns, in August of 2002 the FDA issued a press release announcing the rollout of its new initiative “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach”⁶⁴. The agency is encouraging pharmaceutical companies to introduce new approaches to quality management that they believe will not only result in higher product quality and safety but also reduce costs and cycle times throughout a product’s lifecycle. The guiding principle of the FDA’s initiative is the use of scientific methods to better understand and characterize product variability resulting in a more consistent and predictable process. Under the FDA’s risk-based approach, companies are urged to refocus their quality practices on high risk issues. It is the hope of the FDA that by overhauling its GMP regulations pharmaceutical companies will be encouraged to develop innovative technologies and processes that will make the entire drug development and delivery process more predictable and efficient.

5.3.1. PAT

According to the FDA, Process Analytical Technology, PAT, is a “scientific, risk-based framework intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance”⁶⁵. Under PAT the FDA is encouraging industry to develop more sophisticated tools to measure and predict product safety in real time processing.

According to the September 2004 FDA Guidance for Industry- PAT, the new initiative’s goal is to create a state of pharmaceutical manufacturing and regulation with the following characteristics⁶⁶:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance
- Continuous real time quality assurance

64 FDA. “Pharmaceutical cGMPs for the 21st Century: A Risk Based Approach.” 21 August 2002.

65 FDA. “PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.” September 2004.

66 Ibid

- Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge
- Risk-based regulatory approaches recognize
 - The level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance
 - The capability of process control strategies to prevent and mitigate the risk of producing a poor quality product

The agency is not only encouraging drug companies to innovate but is asking to partner with companies to ensure that the regulatory requirements are amended to reflect this innovation. The thought is that no longer should regulatory conformance be viewed as a barrier to change and improvement. In fact, the FDA seems willing to give pharmaceutical companies more leeway in making post approval changes as long as they are based on a vigorous scientific, risk-based approach that reflects true process understanding and control. The FDA has indicated that companies that have proven they understand their processes and their variability, based on a scientific risk-based methodology, will be allowed to make improvements without a prior approval supplement. The desired result is the overhaul of the drug development process in which drugs can be approved in a faster, less costly manner.

5.3.2. Implications of a Scientific Risk-Based Approach for Pharmaceutical Operational Excellence

The recommendation from the FDA to use a scientific risk-based approach to manufacturing should be considered an enabler to achieving operational excellence. As previously noted, the pharmaceutical industry as a whole tends to be risk averse and treat most manufacturing processes as fixed in order to avoid the regulatory scrutiny of a process change. However, with the “Pharmaceutical cGMPs for the 21st Century” initiative the FDA is setting a new standard for process improvements. While the FDA is not requiring that companies comply with this initiative, it is highly recommending that the industry adopts these changes.

This author believes the FDA initiative is a huge opportunity for biopharmaceutical manufacturers to stop testing quality into products, since a key concept of PAT is that quality should be built-in or by design. According to the FDA’s September 2004 guidance, quality is built into pharmaceutical products through a comprehensive understanding of “the design of

manufacturing processes using principles of engineering, material science and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product's shelf life"⁶⁷. The FDA believes that adoption of the PAT framework will not only improve product quality but also operating efficiency. In fact, the FDA claims in the September 2004 guidance that the following operational improvements can be achieved through the adoption of a risk-based approach⁶⁸:

- Reduction in cycle times
- Prevention of rejects, scrap and re-processing
- Real time release
- Decreasing material and energy consumption while increasing capacity
- Facilitating continuous processing to improve efficiency and manage variability

These principles should sound familiar as they are some of the key concepts of lean manufacturing. In fact, the FDA sites continuous improvement as one of the PAT tools. Through the adoption of PAT, a company should develop a greater understanding of its processes which in turn should result in a reduction in variability. Through PAT, non-value added activities such as excessive testing and quality review can be eliminated to reduce cycle times. A key principle of PAT is the detection of defects at the source; this is also a key concept of the Toyota Production System. Utilizing quality testing at point of production leads to the reduction of rejects, scrap and re-processing. The FDA is also recommending that pharmaceutical companies no longer rely on a series of post production testing to ensure product quality, leading to real time release, a current hurdle in the pharmaceutical disposition process as stated in Section 5.1. Also stated in Section 5.1, it is the product and process variability inherent in biological products that results in many of the operational inefficiencies. Utilization of PAT should enable pharmaceutical companies to reduce variation and increase performance. This author argues that PAT is very much aligned with the principles of lean and operational excellence and that pharmaceutical companies should adopt a risk-based approach such as PAT to realize these synergies.

⁶⁷ Ibid.

⁶⁸ Ibid.

6. Road Map to Lean Transformation

The preceding sections of this thesis have argued for the need for operational excellence in the pharmaceutical industry for competitive livelihood. The author has suggested that the implementation of lean production can deliver substantial improvements in cycle time, quality and cost. The next section of this thesis will introduce a suggested framework to enable adoption and implementation of lean in a manufacturing organization.

6.1. *Lean is a Bumpy Road*

The success of Toyota above its competitors, despite its openness with the inner workings of its production system with the world, indicates that lean is not a concept easily digested and transferred into the DNA of a corporation. In actuality, the largest stumbling block for companies to a lean transformation is not learning what the tools are and how to use them, but it is in the ability to truly adopt the operating methodology in every element of work that its employees perform, from running the equipment to developing corporate strategy. Robert Kaplan wrote that most companies do not fail at strategy, but at the implementation of that strategy⁶⁹. Wanting to adopt lean/operational excellence is not in itself enough. Achieving operational excellence is a journey of continuous improvement along the learning curve. Toyota has been working on TPS for over fifty years and still continues to learn and refine it. It may well be that these years of internal learning is exactly what contributes to the TPS imitation barrier. The good news is that most biopharmaceutical companies are just beginning their lean journey. Those that are behind can quickly catch up to their peers if they are willing to learn from those who have gone before them.

When describing the difficulties encountered in a lean transformation most companies cite ineffective change management as a leading cause. If any initiative is to be successful and sustainable it must be launched with strategic alignment, management commitment, stakeholder involvement, a sense of urgency, the organization structure to support the change, the right goals

⁶⁹ Kaplan, Robert S. and Norton, David. *The Strategy-Focused Organization*, Boston: Harvard Business School Press, 2000.

and objectives, a transformation plan, and some monitoring and nurturing⁷⁰. However, many companies decide to launch lean in a portion of the manufacturing process with a series of Kaizen events that are unsupported by many of these key principles of change management. Is it any surprise that these types of initiatives fail practically out of the gate? The workers don't know what the goal of the work is, how its success will be measured, how it has anything to do with the dozen other goals and metrics they are being measured on, or why they should really care. Even if the workers in a pocket of kaizen activity understand lean and are trying to reduce waste in their area, they will most likely become frustrated by the waste in the business systems or the hand-offs that surround their sphere of influence. To these workers, this lean attempt becomes a "flavor of the month" that is quickly abandoned. However, this failed result can be avoided through a thoughtful framework that incorporates the cultural, organizational, and change management considerations of a lean transformation.

6.2. The Enterprise Level Transition to Lean Roadmap

One such framework was developed by the MIT Lean Advancement Initiative (LAI) institute and is described in the 2002 paper "Development of a Lean Enterprise Transformation Maturity Model"⁷¹. The framework, Figure 17 below, is titled the enterprise level Transition to Lean (TTL) Roadmap and was developed based on extensive research by the LAI on lean transformations (both successes and failures) in the aerospace industry. The roadmap outlines suggested steps in the lean adoption process throughout an enterprise. The term enterprise here is important as it indicates that lean must not just be implemented in a division, function or single area of work but across an entire organization. Implementation of lean in a single business process results in sub-optimization and frequently to the "flavor of the month" mentality. However, a lean enterprise "*is an integrated entity which efficiently creates value for its multiple stakeholders by employing lean principles and practices*"⁷². The resulting lean enterprise is

⁷⁰ Nightingale, Deborah. "Enterprise Transition to Lean Roadmap". Integrating the Lean Enterprise Lecture. MIT, Cambridge, MA. 27 Sept. 2006.

⁷¹ Nightingale, Deborah and Mize, Joe. "Development of a Lean Enterprise Transformation Maturity Model." Information Knowledge Systems Management. 3 (2002): 15-30.

⁷² Nightingale, Deborah. "Enterprise Principles". Integrating the Lean Enterprise Lecture. MIT, Cambridge, MA. 13 Sept. 2006. (original source: LAI, MIT, 2001).

achieved through a much more aggressive initiative that has undergone a sustainable change in operations.

The enterprise level transition to lean roadmap provides a step by step process, based on lean principles, to initiate, sustain, and improve a lean transformation. The roadmap consists of three cycles of processes that are interlinked. The first cycle is the entry/re-entry cycle in which organizations make the strategic decision to implement a lean transformation. The second phase of lean transition is the long term cycle. In this phase the organization provides the necessary organizational changes and creates support structure for the transformation. In the last phase of the roadmap, the short term cycle, the detailed transition is planned, executed, and monitored. The results from the short term cycle are then feed back into the long term cycle in order to continuously improve the enabling processes, update goals and metrics, ensure improvement activities are aligned with the corporate strategy, and provide guidance for further improvement. As the organization realizes improved operating efficiency and freed up resources, it may then pursue a growth strategy and may reenter the roadmap's first cycle⁷³. The entry cycle should also be revisited as the organization transitions to ensure that the initiative stays aligned with enterprise strategic planning.

⁷³ Nightingale, Deborah and Mize, Joe. "Development of a Lean Enterprise Transformation Maturity Model." *Information Knowledge Systems Management*. 3 (2002): 15-30.

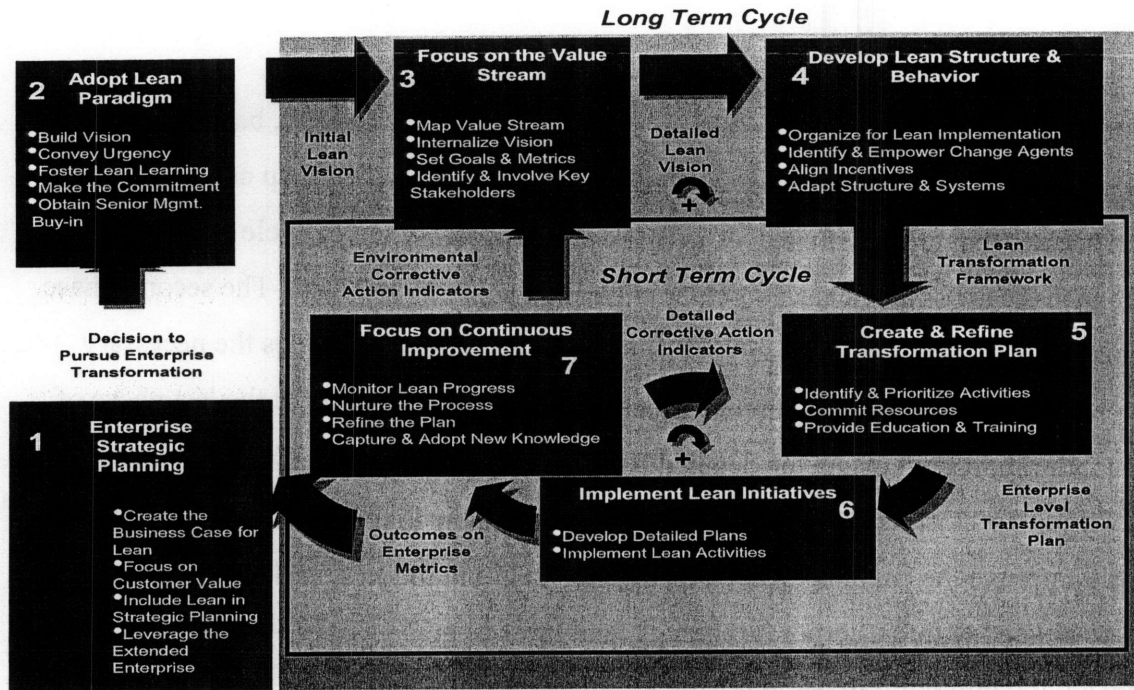


Figure 17: Enterprise Level Transition to Lean Roadmap⁷⁴

6.2.1. The Transition to Lean Roadmap Entry/Re-entry Cycle

6.2.1.1. Step 1: Enterprise Strategic Planning

The decision to adopt lean is not one that is made lightly. Usually an organization has examined its current capabilities with that of its competition and realized a need for change. However, a common mistake made is starting the lean journey without anchoring the initiative in the organization's strategic planning processes. The TTL roadmap suggests that the first steps in a lean transition are: creating the business case for lean, focusing on the customer value, including lean in strategic planning, and leveraging the extended enterprise. Following these steps ensures that lean is the right solution for the problem, that there is a strong link between the initiative and the business's current state and future aspirations, and that the initiative is being launched across the enterprise with the end goal of providing value to the customer.

⁷⁴ Source: Nightingale, Deborah and Mize, Joe. "Development of a Lean Enterprise Transformation Maturity Model." *Information Knowledge Systems Management*. 3 (2002): 16.

6.2.1.2. Step 2: Adopt the Lean Paradigm

In this phase of the roadmap, the organization must do the pre-work in order to ensure that the initiative is not seen as a “flavor of the month”. It is important that leadership build the vision for the change importance as well as provide the necessary lean learning support structure. Most importantly, it is essential that leadership make a vocal commitment to the lean transformation and ensure that the managers at the highest levels of the organization also buy-in to the vision. One of the most cited reasons for a lean initiative’s failure has been the lack of clear leadership support in driving the lean transformation. If a lean initiative is to have any chance for success, the message must come from the top and be reinforced with the overarching corporate goals and strategy. If employees aren’t convinced that lean is the future of the organization, they will not buy-in to the change and the initiative won’t achieve its full potential.

Some may argue that a lean transformation can start as a grassroots initiative. The author would argue that a lean initiative can ultimately be effective without initial grassroots support, but not the other way around. Lean can start at the lower levels of an organization but without the full support of senior leadership to drive change, only isolated areas of improvement will be achieved. However, if senior leadership initiates the change it can build the grassroots support during the entry phase of the transition and through the long term cycle activities. The author would argue that pull for change from a top down and bottom’s up direction simultaneously yields the best result- the full embracement of the lean transformation throughout the enterprise.

6.2.2. The Transition to Lean Roadmap Long Term Cycle

6.2.2.1. Step 3: Focus on the Value Stream

After the senior leadership of the organization have set the vision and motivated the troops, the first step in a lean transformation is “learning to see” through value stream mapping. As previously mentioned in Section 3.3, value stream mapping is a great tool to understand the business and its non-value added activities. Conducting a current-state value stream map helps get further buy-in for the need for change by pointing out the improvement opportunities. In addition, it provides opportunity for workers to realize how lean techniques can improve their everyday work. At the same time the senior management should be working to develop and set

new goals and metrics that are aligned with the value stream. What is the value delivered to the customer and other stakeholders? How can the organization accurately measure if it is doing a good job delivering that value? Are the right goals in place to motivate a lean transformation? Are the right metrics being measured to indicate when the goals have been achieved? To truly be an operational excellent corporation, operational performance must be aligned with corporate strategy and reinforced through incentive systems.

6.2.2.1.1. The Balanced Scorecard

A useful tool to use during this phase of lean transformation is that of the balanced score card. The balanced score card was developed by Robert Kaplan and David Norton. In the 1992 Harvard Business Review article “The Balanced Scorecard: Measures That Drive Performance” Kaplan and Norton laid out the idea of a scorecard that links strategy to metrics and utilizes four perspectives: financial, customer, business processes, and learning and growth⁷⁵. Kaplan and Norton argue that utilizing a scorecard based on these four perspectives allows a company to see if it is sacrificing performance in one area to better another. They urge that the following four questions must be answered when developing a firm’s strategy:

- How do customers see us?
- What must our company excel at?
- Can we continue to improve and create value?
- How well have we delivered value to our shareholders?

The answers to these questions should guide what metrics a firm needs to measure at the highest level to achieve balanced performance. Kaplan and Norton argue that what a company measures is the results it gets. The goals and metrics of a firm are usually widely available and linked to an incentive system. If you have a goal, your employees will make it; but at what expense? A balanced scorecard eliminates the “gaming” of performance management. In addition, the balanced scorecard reduces the number of metrics measured to a handful of those that most

⁷⁵ Kaplan, Robert and Norton, David. “The Balanced Scorecard: Measures that Drive Performance.” *Harvard Business Review*. 1992.

accurately measure the status of the business. Firms tend to measure a large number of metrics. However, very few firms can directly link a measurement to a strategic goal. Instead, like darts, companies throw a bunch of metrics at the dartboard hoping that at least some will come close to hitting the bull's-eye (the goal).

An enterprise level balanced scorecard should be developed. Balanced scorecards can also be utilized at lower levels of the organization, however there needs to be a clear link between department goals and metrics and those on the enterprise balanced scorecard. Optimally, no goals/metrics are measured at lower levels that do not directly result in observable performance at the enterprise level. A key benefit of the balanced scorecard is that it provides a clear line of sight at lower levels of the organization to how their metrics contribute to the overall objectives and goals of the enterprise. The balanced scorecard provides a vehicle for managers at all levels within the organization to understand the drivers and results of their actions.

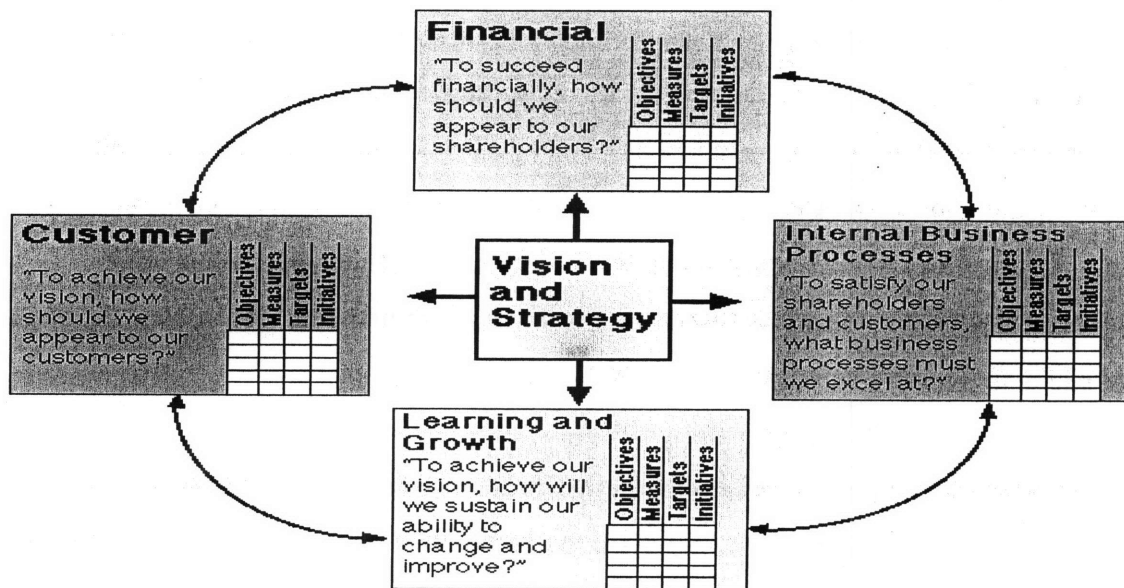


Figure 18: Balanced Scorecard Framework⁷⁶

The balanced scorecard is an important concept to incorporate into a lean transformation because it allows a company to ensure that improvement in one area is not being made at the expense of another. It also ensures that the organization is delivering value to all of its stakeholders

⁷⁶Source: < http://www.valuebasedmanagement.net/methods_balancedscorecard.html>

(customers, shareholders, employees, the community). As a company transitions to lean, it should see significant improvement in these key performance indicators listed on the enterprise's balanced scorecard.

6.2.2.2. Step 4: Develop Lean Structure and Behavior

Following the focus on the value stream and realignment of the organizations goals and metrics, the next phase of lean adoption is to develop the appropriate organizational structure and behavior to reinforce lean implementation. Depending on the needs of the firm, reorganization may be in order. Lean transformation requires that information flows freely and that people work across functional barriers. A company that is functionally organized and suffering from silos will find it difficult to have efficient information flow. Such firms may consider a matrix or hybrid organization structure that includes organizing according to a value stream. For most companies neither value streams nor enterprises have been explicitly recognized. As a result, employees are not use to considering what is best for the value stream or enterprise but usually just within their immediate function. Organizing by the value stream enables companies to create goals and metrics that run across functions. Such goals and metrics are far better aligned with corporate strategy because work has been focused on the important objectives of the overall organization. Companies can shift to a product focused organization to create value stream definition. As an alternative to a direct reorganization, companies should consider co-location of key functional teams to improve information flow.

In addition to a possible reorganization, a firm that wants to achieve lean excellence must also decide how it wants to handle the lean transformation process internally. An organization must be ready to deal with a lean transformation before improvement activities take hold. Will there be a separate team responsible for lean/operational excellence? How will the organization identify change agents? How should the incentive structure be changed to reward improvements and motivate a team or value stream approach? Are the data, financial, and IT systems capable of providing the required information? Are the businesses processes equipped to enable change?

6.2.3. The Transition to Lean Roadmap Short Term Cycle

6.2.3.1. Step 5: Create and Refine Transformation Plan

While setting the vision and ensuring that the support processes are enabled and the goals and metrics adjusted is critical to overall transition success, it is the short term cycle of the TTL roadmap in which the actual operations improvements are made. Lean improvement activities should begin with the opportunities identified through the value stream mapping process. As part of that process, a future state map should be prepared in addition to the map of the current state. The firm must then undertake activities to merge the gap between the current and the desired state. These activities should be prioritized and a firm may develop its own prioritization criteria. Where to start is an interesting question faced by the firm because of the importance of showing results and getting buy-in. For this reason, a company may pick to start out with “quick wins” that will enable the initiative to gain momentum with small improvements. In addition to identifying the improvement projects themselves, the organization must identify those who will take part in the efforts and provide the required education and training (mostly just-in-time in accordance with lean philosophy).

6.2.3.2. Step 6: Implement Lean Initiatives

In the next phase of lean implementation the improvement ideas are transformed into detailed plans that are acted upon. In this stage improvement results are captured and reflected in the metrics tracking. Once initial lean activities have been conducted, it is important that the team evaluate the progress of its efforts by looking at return on investment and measuring against the targets set in the transformation plan. Goals and metrics should be adjusted so that the improvements constitute the new current state. As all of the improvement projects are executed, new improvement opportunities will be discovered and added to the list. Once all of the original gaps identified are closed, a new future state map should be developed to push the value stream further towards perfection. It is this strive for perfection that encourages continuous improvement.

6.2.3.3. Step 7: Focus on Continuous Improvement

Continuous improvement is fundamental to lean. Too many improvement initiatives are undertaken, achieve some success, and then the processes slip back to their old inefficient state. In a lean transformation, not only is the success maintained, but it is expected that the processes will be further refined. To achieve this, process status must be continuously monitored. Also, employees must be inspired to make incremental improvements through the incentive structure.

6.2.3.4. Step 8: Re-enter Long Term Cycle or Entry Cycle (when needed)

The short term cycle provides the execution piece of the lean transformation. The organization must learn from these activities and transfer this knowledge into its value stream, vision, goals and metrics, and organizational structure through the long term cycle processes. The organization must ensure that it is providing the best business environment to support the detailed lean transformation work being undertaken at the all levels of the firm. In addition, the firm must recognize when there is a need to reenter the roadmap to either reinvent lean activities or modify the initiative's scope as the business changes.

6.2.4. Enterprise Level Transition to Lean Roadmap Takeaways

The TTL roadmap provides a step by step process for enterprise-wide transformation. Utilizing such a framework allows the organization to clearly see improvements as well as failures. The framework also highlights the people and leadership issues essential to success, but that might be easily forgotten about if one was to solely look at adopting lean techniques. The framework also highlights the need for the lean initiative to be integrated in the firm's strategy, goals, metrics, and incentives. Finally, the framework provides a systematic way to ensure that the transition is managed at a holistic systems viewpoint, reducing sub-optimization or isolated pockets of success.

However, achieving business and operational excellence is not as easy of simply following a roadmap. The roadmap is a business tool to aid transition and ensure the necessary management support structures are in place, however it alone will not realize operational efficiencies. The operations improvements are made by a firm's workers at every level who are able to utilize lean

tools to take on a new perspective of their work. With this new lean lens, employees are able to see the waste in their work and are motivated to eliminate it.

In the next section, one organization's journey to operational excellence and true change is explored.

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7. Case Study of Amgen Rhode Island

The preceding sections of this thesis have demonstrated that the current pharmaceutical industry dynamics are bringing new light on the importance of operations within the industry's business model. The author provided a background to the changes in the industry's landscape as well as described the current state of biopharmaceutical operations. The adoption of lean principles through a structured framework was suggested as a method for achieving operational excellence. In this section, the current competitive issues that the biotech leader Amgen is facing as well as the operational improvement program the firm has adopted to meet these challenges will be presented.

As the leading human therapeutics company, Amgen has defined the biotechnology industry. In 2007 Amgen experienced first-hand the emerging challenges in the competitive landscape of the industry. Amgen has been one of the first biotech companies to feel the new reimbursements pressures from payers as well as face biosimilar competition in the E.U. As a result, Amgen has recently launched the Amgen Process Excellence (APEX) program. This case study will provide a background to the challenges facing the firm as well as provide insight into the corporation's response, APEX. The information provided is based in part to a LFM internship by the author at the Amgen Rhode Island manufacturing (ARI) facility in 2007.

7.1. Amgen Background

Based in Thousand Oaks, California Amgen is currently the world's largest biotech company in terms of revenue⁷⁷. The company rose to industry dominance primarily with three blockbuster drugs: the anti-anemia medications Epogen (epoetin alfa) and Aranesp, which together account for half of the company's sales, and rheumatoid arthritis drug Enbrel.

Amgen got its start as Applied Molecular Genetics in 1980, formed by a mix of scientists and venture capitalists looking to create health care products based on molecular biology. Company scientist Fu-Kuen Lin cloned the human protein erythropoietin (EPO) in 1983. Armed with the

⁷⁷ Amgen information available at <www.amgen.com>

breakthrough, which stimulates red blood cell production, Amgen went public and formed a partnership with Japanese beer masters Kirin Brewery to develop and market EPO (brand name Epogen) in 1984. The two firms also teamed up to create recombinant human granulocyte colony stimulating factor (Neupogen), a protein that stimulates the immune system. Amgen joined Ortho Pharmaceutical, a subsidiary of Johnson & Johnson, in a marketing alliance in 1985 and forged a tie with Roche in 1988. Amgen's success skyrocketed with Epogen's FDA approval in 1989. In the industry's biggest deal in history, Amgen acquired Seattle-based Immunex Corporation, the industry's third-largest company in 2002. The \$17.8 billion deal gave Amgen significant research abilities, new pipeline drugs, and, most importantly, added Enbrel to Amgen's drug roster, a breakthrough new anti-inflammation agent.

7.2. Amgen's New Competitive Landscape

In 2006 Amgen continued its history of strong performance with 15% growth achieved and revenues, based mostly on the sales of its four major products Aranesp, Epogen, Neupogen, and Enbrel, of over \$14.2 Billion⁷⁸. However, Amgen's history of success suffered in 2007. In the spring of 2007 regulators placed a "black box" warning on Amgen's ESA (erythropoiesis-stimulating agents) drugs Aranesp and Epogen (together accounting for nearly half of 2006 sales). These labels warn that the treatments increase risk of death in some cancer patients. Since the black box labels, the FDA advisory board has limited its approval for prescribing ESAs. In addition, Medicare and Medicaid have also begun to limit the types of patients who receive reimbursement for ESA treatments. Congress is also debating further limits on ESAs as it looks to reign in healthcare expenditures.

As a result of the FDA's warnings and restrictions in 2007, Aranesp sales fell 12% in 2007 world-wide. 2007 Aranesp sales declined 23% in U.S. but were offset by a 10% increase in sales in the rest of the world. Aranesp sales have decreased over 38% in the latter half of 2007⁷⁹. Total Amgen revenues grew only slightly in 2007 to \$14.7 Billion. In addition, biosimilar erythropoietin products to Amgen's Aranesp were approved in the E.U. in the fall of 2007.

⁷⁸ Amgen 2006 Annual Report

⁷⁹ Amgen 2007 Annual Report

Through December 2007, there has been little affect on sales to date from the Aransep biosimilar competition, as overall international sales of Aranesp increased 10%⁸⁰. However, with over 40% of Aranesp sale's coming from international markets⁸¹, one could assume that increased competition within the E.U. market will lead to an overall sales decline in this market.

In 2007, Amgen felt first hand the increased scrutiny of regulatory agencies, increased buying power of payors such as the CMS, and also the international political movement towards lower cost biosimilar medications. Despite the firm's attempts to minimize the effect of the ESA situation and biosimilar competition in the E.U., Amgen's shares fell 26% in 2007, compared to the S&P's rise of 5%. In order to sustain projected earnings per share, Amgen announced a restructuring initiative in August of 2007. Included in the restructuring was a reduction in workforce by 14% (2,600) and the closure of some manufacturing plants.

7.2.1. Amgen Rhode Island

The Amgen Rhode Island (ARI) site manufactures Enbrel bulk drug substance, an intermediate in the drug manufacturing process. The site was acquired through the 2002 Immunex acquisition. Through the oversight of Amgen employees, the site gained FDA approval to manufacture Enbrel in 2002. Enbrel manufacturing capacity was expanded within recent years as an additional plant, one of the largest mammalian protein manufacturing sites in the world, was added. Amgen co-markets Enbrel with Wyeth and relies on both Wyeth and a contract manufacturer for additional drug substance supply.

Even prior to Amgen's 2007 sales issues, the ARI site was preparing to address operational inefficiencies. When the site was first approved for Enbrel production in 2002, there was a waiting list of patients needing drug. However, since 2002 the Rhode Island site has expanded and Wyeth's Grange Castle site has come online for Enbrel production. The ARI site had been highly successful in meeting Enbrel demand and in developing productivity improvements; however, the increase in productivity combined with the plant expansions has lead to overcapacity. At the end of 2006, the ARI site set forth a new goal it hoped would aid it in

⁸⁰ Ibid.

⁸¹ Amgen 2007 Annual Report does not breakout E.U. sales from other non-U.S. market sales.

becoming a flexible, multi-product facility that could compete with contract manufacturers. The following 2007 site goal was introduced: “improve operational efficiency and productivity, as measured by Cost of Goods Manufactured (COGM), while making sound investment decisions- Establish a systematic Business Process Excellence program that drives productivity improvements through a reduction of waste and non-value-added activities”. The objective of the author’s internship was to assist in accomplishing this site goal.

By the end of the first quarter 2007, only marginal progress had been made in accomplishing this goal. At the time, there was no immediately visible business driver, no burning platform. However, with the ESA safety and reimbursement issue as well as the new biosimilar competition the entire Amgen organization needed to look for cost reduction opportunities. One cost reduction solution for the firm included closure of one of the two Enbrel manufacturing plants at the ARI site. As a result, the need for operations improvement has taken on new meaning for the Rhode Island site. It is no longer an initiative for improvement but rather one for site survival. As a single product facility with biosimilars on the horizon, ARI must reinvent itself into a competitive, flexible, manufacturing facility before Enbrel faces patent expiration in 2012. The site must become best-in-class in terms of cost, quality, and speed.

7.3. Operational Excellence Initiative at Amgen

As previously stated, the competitive environment of the pharmaceutical industry is becoming much more cost sensitive and as a result more attention is being paid to operational inefficiencies. Amgen is a member of the Biopharma Operations Excellence Consortium run by the Tefen management consulting firm. A survey of the consortium member companies, including Amgen, revealed that these top biopharmaceutical companies agree that COGS reduction, cycle time reduction, and flexible, multi-product manufacturing facilities are essential for future competitive success⁸². In fact, this author’s internship is a prime example of manufacturing’s new importance in the pharmaceutical business model.

⁸² Punich, Marc. “Biopharmaceutical Operations Roadmap 2007.” *BioPharm International*. April 2007.

The operating pressure on the Amgen Rhode Island site as well as the rest of the corporation's operations intensified in mid 2007 due to the ESA warnings and looming biosimilar competition. In the short term, the announced staff reduction and plant closure were part of the solution for immediate cost reduction. However, in addition to staff reductions, the company was also developing a clear path to achieving long term cost savings and operations efficiencies. There began a strong pull throughout the organization to pursue operational excellence.

While the Amgen Rhode Island site was organizing its own business process excellence program, Amgen corporate manufacturing was also creating a corporate wide operational excellence initiative. These groups combined efforts and developed the Amgen Process Excellence (APEX) initiative. The APEX initiative is founded on a set of core operating processes to guide thinking as employees set out to make change. A six step process (see Figure 19 and Figure 20) was developed by the corporate manufacturing group with input from several manufacturing sites. The six step process incorporates the key principles behind the highly successfully six-sigma DMAIC (Define, Measure, Analyze, Improve, Control) model as well as those of lean manufacturing. In essence, this stepwise process is a defined approach to the execution of the short term cycle of the transition to lean roadmap discussed in Chapter 6. This new operating methodology was launched by the corporate operations team and distributed to all of the Amgen sites. The hope is that having a common language and process for achieving operational excellence will provide consistency in approach.

In addition to creating the equivalent of a lean transformation plan, the APEX program has also begun to be incorporated into the company's strategic planning process. The company has started value stream mapping activities, performed a goals and metrics reform, engaged key stakeholders throughout the enterprise, and developed a lean training program. By the end of the author's internship the larger corporate APEX rollout was just commencing.⁸³ However, the ARI site, with a highly vested interest in change, had begun APEX related activities starting in mid-2007. In the next section, the author will describe the improvement work undertaken during her internship at the ARI facility.

⁸³ For a detailed discussion of the Amgen corporate APEX development and rollout please see LFM Thesis "Lean Transformation Methodology and Implementation in Biopharmaceutical Operations" by Adam Villa 2008.

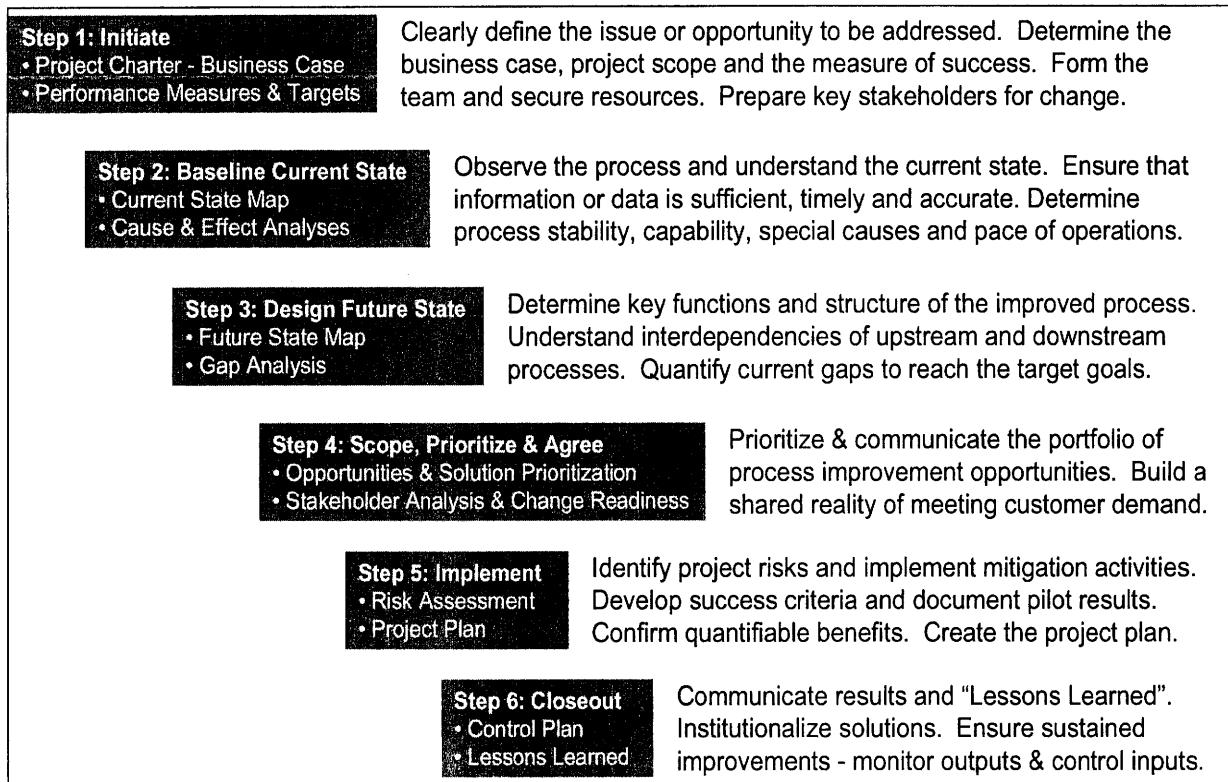


Figure 19: Overview of APEX Approach

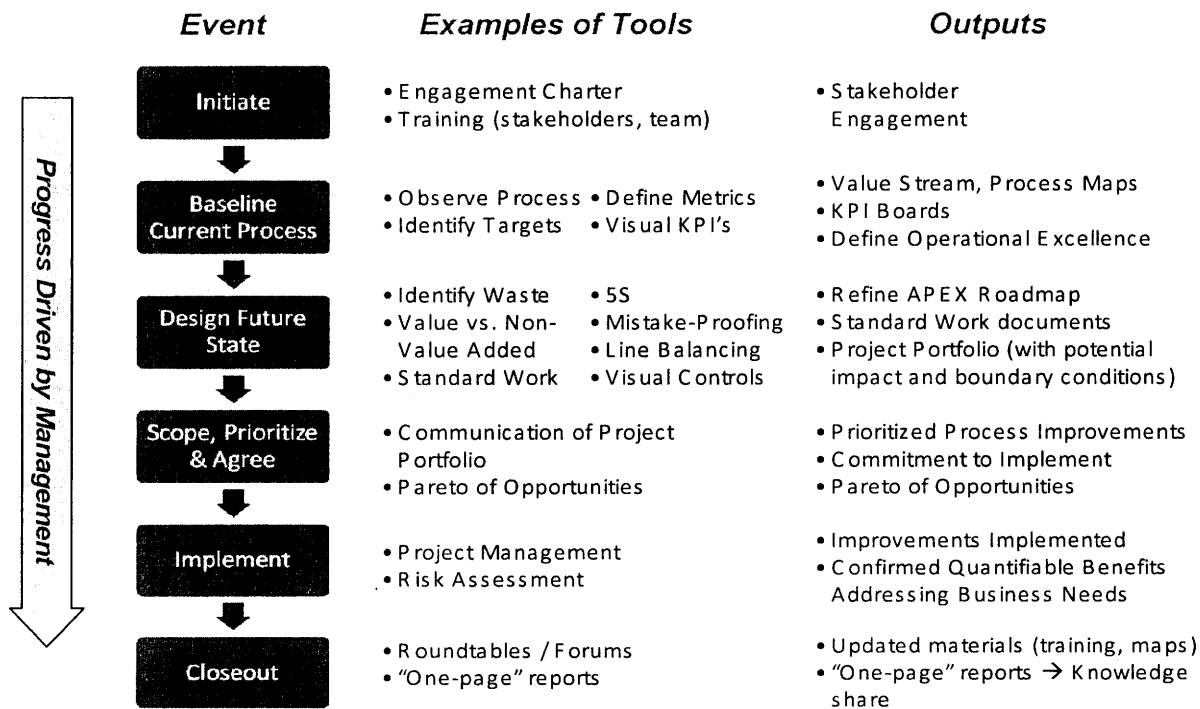


Figure 20: APEX Methodology

7.4. Implementation of the APEX Methodology at Amgen Rhode Island

The Amgen Rhode Island site took on the challenge of achieving operational excellence by establishing an APEX core team. This team set out to aid the site in achieving best in class performance. However, before it officially commenced activities, the team thought it imperative to define what the site meant by operational excellence. To the ARI APEX team, operational excellence meant being cost competitive with contract manufacturing while maintaining the high product quality the site had previously attained. The team developed a working definition of what achieving operational excellence meant to ARI: “Ensuring continuous supply of safe and efficacious medicines while maximizing profitability”. The team used this definition as a guiding principle as it launched the APEX methodology at the Rhode Island site.

The following subsections will discuss the launch of APEX at the Amgen Rhode Island Site. ARI APEX implementation is being presented within the APEX methodology framework to demonstrate that this framework is not only suitable for specific improvement project execution but also initial site evaluation and initiative launch.

7.4.1. ARI APEX Implementation Step 1: Initiate

The APEX team at ARI was developed as a cross-functional collaboration. The team engaged personnel from finance, development, engineering, manufacturing, project management, industrial engineering, supply chain, and quality. This multi-disciplinary representation provided a vehicle to gain site-wide consensus and prioritization of APEX activities. The team also provided a forum to pull together the functional information across the site into a holistic view of the site’s performance. In addition to serving on the APEX team, each member was responsible for information exchange between their functional area and the APEX change movement. This structure allowed the APEX lean transformation initiative to gain support from key stakeholders across as well as up and down the organization.

The APEX team also looked at the site’s cost structure during this initiation phase to provide a baseline and the financial information component for improvement project prioritization. The Rhode Island cost profile was benchmarked against that of the industry. The cost breakdown for

an average and top plant based on data from the 2006 pharmaceutical industry study previously mentioned in Section 4 was used. The ARI site's cost breakdown was determined following the cost category definitions used in the case study. Comparison against the average case study plant indicated that the Rhode Island site's operational cost was more labor intensive than that of the average plant of the benchmarking study. In addition, the comparison also indicated that the site's Plant, Property and Equipment (PP&E) costs were higher than average. The higher PP&E costs of the ARI site could be explained by the site's recent facility expansion and its associated depreciation. From a labor perspective, the site seemed to be spending a higher portion on labor than the average plant in the study. However, it should be noted that the benchmarking study included both small molecule and biopharmaceutical manufacturing plants. Some of the discrepancy in labor costs may be explained by the higher quality requirements of biopharmaceutical operations like Enbrel. In addition, future labor distribution would be altered after the staff reductions already planned for the site through the corporate restructuring plan.

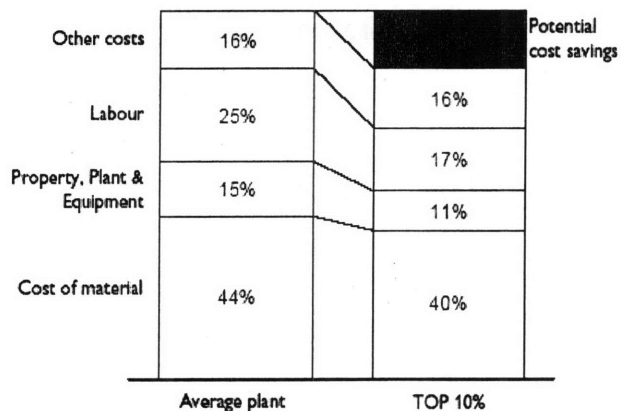


Figure 21: Average and Top Performing Pharmaceutical Plant Cost Breakdown⁸⁴

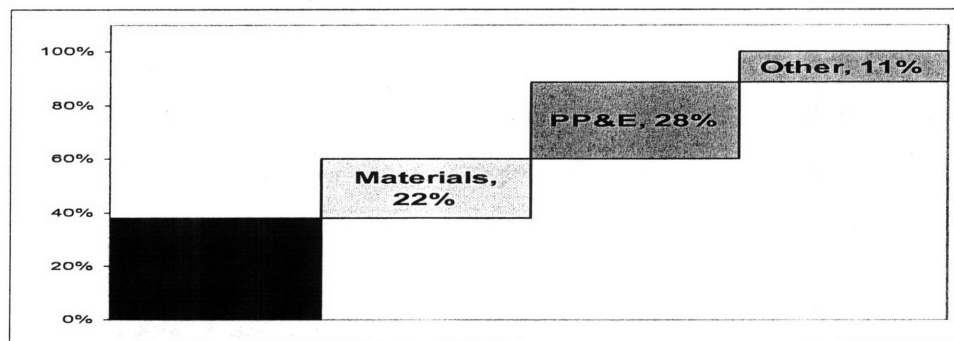


Figure 22: ARI Plant Cost Breakdown (pre-APEX)

⁸⁴ Source: Friedli, Thomas et al. *Operational Excellence in the Pharmaceutical Industry*. Germany: Editio Cantor Verlag Aulendorf, 2006: 57.

In addition to the comparison of costs with the international benchmarking study, the Enbrel drug substance manufacturing costs at Rhode Island were also compared against those of its contract manufacturing partner. This comparison indicated that there was room for improvement not only on the cost breakdown but also the total cost spent. Following this analysis, the APEX team agreed that an in depth cost analysis of the site's operations should be performed as part of the APEX implementation. Since a fundamental goal of the ARI APEX movement was to make the site competitive with contract and biosimilar manufacturers, the team thought it imperative to understand the components of the site's costs and understand which costs could be affected by operational improvement activities.

7.4.2. ARI APEX Implementation Step 2: Baseline the Current State

Following step 2 of the APEX approach the ARI team performed a current state analysis to clearly define the performance improvement opportunity at the site. An analysis of the site's current financial and operational state was performed to create a baseline for future comparison and also to help the APEX team prioritize improvement activities. The team first performed a financial analysis of the site's major activities in order to prioritize which area (manufacturing, quality, engineering, or development) would first be analyzed. Not surprisingly, the Enbrel manufacturing operations was revealed to be the site's most costly activity. Manufacturing was also chosen as the first area of APEX implementation because of its central role in the site's goal of becoming a flexible, multi-product facility.

7.4.2.1. *The ARI Enbrel Manufacturing Current State Value Stream*

A group of change agents were identified internally and began with value stream mapping the site's current manufacturing operations. The high level manufacturing current state value stream map is shown in Figure 23. The value stream map activity provided a benchmark for the site's current inventory levels, cycle times and value-added vs. non-value added activities. As Figure 24 indicates, manufacturing processing only makes up 14% of the current state Enbrel lead time. This time is not considered fully value-added time as it includes changeover and cleaning times within manufacturing.

Using the lean 7 wastes framework, the APEX team analyzed the Enbrel current state VSM to identify opportunities to increase value-added activities and time within the manufacturing process. Some of the key areas for improvement identified were:

- Reduction in media and buffer scrap
- Reduction in raw materials and finished goods inventory
- Reduction in the quantity of analytical testing
- Cycle time improvements in manufacturing, testing, and disposition

Not surprisingly, the improvement areas identified at the ARI site were very similar to those typical of biopharmaceutical operations as described in Section 6. In the next section, the use of the lean 7 waste framework was by the APEX team to identify operational improvement opportunities in the current Enbrel value stream is described.

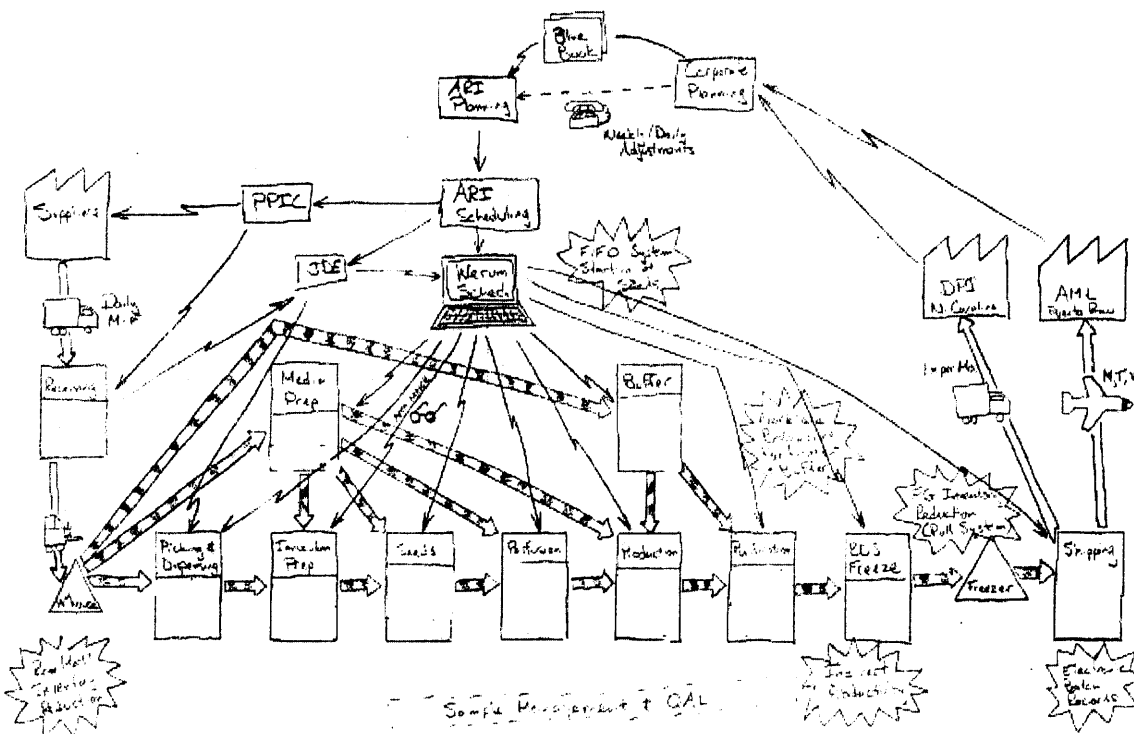


Figure 23: Current State High Level Enbrel Value Stream Map⁸⁵

⁸⁵ Cycle time data has been removed for proprietary reasons

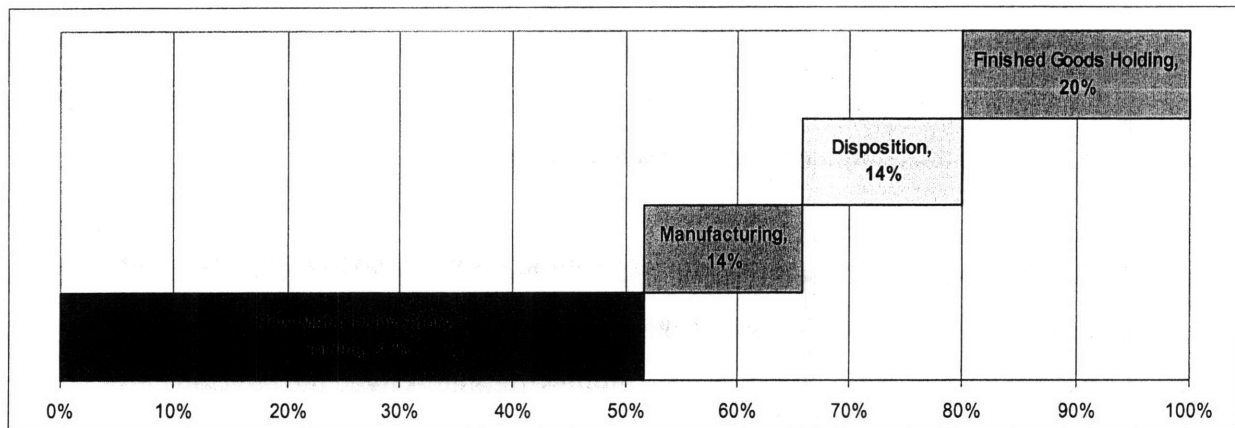


Figure 24: Enbrel Current State Cycle Time Breakdown

7.4.2.1.1. ARI Manufacturing Overproduction Waste

At ARI separate groups prepare (in advance) media and buffers that are then utilized in cell culture and in purification production respectively. The many inefficiencies in these activities have previously led to a large amount of media and buffer waste. This high level of scrap is a result of several sources, the majority of which can be linked to a disconnect between media and buffer preparation and production. In many cases the preparation departments make up more than can actually be held by the hold vessels. This discrepancy can be explained by the inflexibility of the batch records employed. The preparation batch records were designed so that every batch utilizes the full capacity of the preparation vessel. However, in many instances the hold vessel is smaller than the preparation vessel and therefore excess media is scrapped. Media and buffers are also scrapped because the hold volume is usually more than is actually required at the point of use. Due to the variable nature of the cell culture process, the production personnel do not know in advance exactly how much media or buffer will be required. Since both types of solutions are made in advance, the largest amount of solution that possibly could be needed is prepared. Often a smaller amount is actually used and the remainder is waste. In the current state there existed no feedback loop for production to communicate to preparation how much material is scrapped.

Another source of media and buffer scrap is that both preparation and production departments have a wide range around the target amount of solution required. For instance, if cell culture only needs 10L of media X, the batch record may list the quantity as 10L \pm 5L. To ensure that

cell culture has sufficient media, the media preparation batch record will then target 15L for makeup with its own range around the target. The wide ranges for these targets do not represent that actual accuracy of the equipment in use and lead to material waste.

In the current state of operations, a safety stock of solution is made up in every preparation. This safety stock is used in case a vessel leaks or production is delayed due to contamination.

However, media and buffer solutions only have a limited lifetime. Given the large quantities of solutions currently prepared, safety stock may expire before it is used. In addition, because the solutions are only currently prepared in one volume size a disruption in the production process may lead to loss because the solutions can not be used before they expire. This inflexibility in the preparation volume size means that media and buffer batch records need to be changed anytime production speed is altered. If the records are not altered either too much or too little solution will be prepared.

7.4.2.1.2. ARI Inventory Waste

Like many pharmaceutical sites, Amgen Rhode Island carries large amounts of inventory to reduce risk. In the current state, the site has millions of dollars worth of raw material, spare parts, and finished goods inventory. Because of the high level of inventory the site has experienced some write-offs due to material expiration or obsolescence. The data from the current state value stream map activity indicated that over 50% of the average Enbrel drug substance lead time is spent in raw material inventory. Drug substance held in inventory accounts for an additional 20% of the site's average lead time. The APEX team believes there is an opportunity to streamline inventory management to increase cash flow.

7.4.2.1.3. ARI Over-processing Waste

Enbrel drug substance manufacturing is a complex process with a large quantity of analytical testing of raw materials, in-process, and finished goods. The workload of the analytical team is complicated by the large number of retention and backup samples that are taken but not necessarily used. The APEX team's analysis revealed that over 40 % of samples taken are used for retention or backup. Because these samples are not necessary if operations were to run perfectly, they are considered over-processing waste. While these samples can not be totally

eliminated, reduction in the number of samples is possible. The large number of total analytical tests performed (over 100) for each Enbrel batch (including some stat samples) may also be considered an over-processing waste if they are not truly needed to guarantee the safety and efficacy of the Enbrel drug substance product.

Another example of over-processing discovered during the VSM mapping activity is that of long media hold times. At several steps in Enbrel production, media is held beyond the minimum time required. This extra time of the media hold prolongs cell culture inoculation and adds to overall cycle time.

7.4.2.1.4. ARI Waiting Waste

During the value stream mapping activity, the team noticed a large amount of time spent by manufacturing operators waiting. As indicated in Section 6, biopharmaceutical process cycle times are driven by changeover and cleaning activities. At the ARI site, equipment changeover and cleaning is limited by SIP capacity. For this reason, equipment often needs to wait to be turned over. The actual Enbrel product spends a lot of time waiting as well. For instance, routinely cell culture material is kept in a reactor after the minimum cell density to inoculate the next step has been reached (also an example of over-processing). Although the excess cells will be dumped (another example of over-production waste), the current manufacturing procedures allow for a ± 24 hour window on inoculation. At other steps in the Enbrel manufacturing process, the protein solution is held in a holding tank for a length of time beyond the minimum required. While these activities provide flexibility for the manufacturing staff, they lead to an increase in Enbrel production time. The VSM activity revealed that eliminating the excess hold times within manufacturing, essentially making Enbrel production Just-In-Time, could eliminate a minimum of 10% of the time spent within the manufacturing suite.

7.4.2.1.5. ARI Motion, Transportation and Defect Waste

The current state Enbrel manufacturing activities are filled with excess motion and transportation. For instance, the APEX team had the opportunity to witness a filter step changeover activity. The team was amazed by the amount of searching for parts and walking required to perform the task and dispose of the used filters. By implementing several of the

visual management tools of the 5S lean framework, including providing the operators with the appropriate tools in an organized fashion as well as a standardized work detail, the equivalent of several FTE hours were eliminated from this filter changeover step.

The ARI APEX team did not identify any significant defect waste opportunities in the Enbrel current state. The lack of defect waste is a clear indicator of the high level of quality already present in the current state of manufacturing.

7.4.3. ARI APEX Implementation Step 3: Design Future State

The APEX VSM team incorporated the identified improvement opportunities into a “theoretical” future state value stream map for manufacturing (see Figure 25). In this VSM pull systems have been added throughout production. The APEX team believes that implementation of pull systems will reduce Enbrel cycle times significantly. A pull system will not only reduce cycle time but also inventory levels as well as media and buffer scrap. With a pull system there is less over-production because nothing is made until a signal is received.

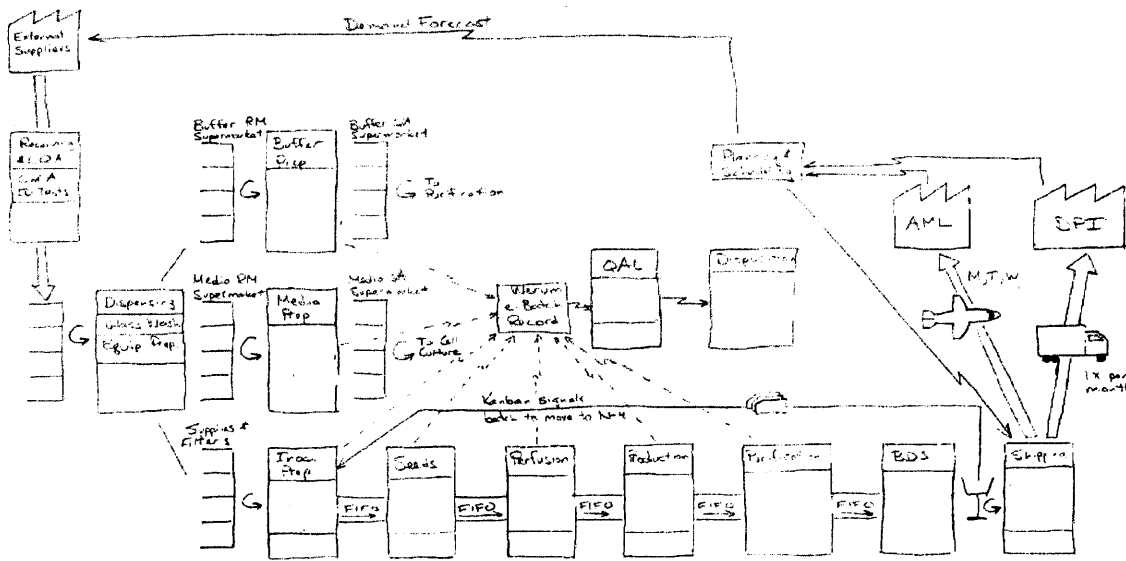


Figure 25: Future State High Level Enbrel Value Stream Map⁸⁶

In the future state map media and buffer scrap has been reduced utilizing the following suggestions:

⁸⁶ Cycle time data has been removed for proprietary reasons

1. Aligning preparation volume to hold volume
2. Creating flexible batch records so that preparation volumes can be adjusted to production needs
3. Reducing the width of the range given around a solution volume target to that of the actual accuracy of the equipment utilized
4. Implementing a pull system so that media and buffer are not prepared before required volumes are known. This will also reduce the need for the preparation of safety stock with each makeup
5. Reducing the volume of solution that is prepared at each makeup. While this may result in more makeup instances per production batch, it reduces the risk of excess and expiration

In addition, the raw material and finished goods inventory levels have been reduced based on the utilization of a vigorous inventory holding model based on usage, lead times, and their variability. The future state map also includes the reduction of any unnecessary wait time in the Enbrel process. Media hold times have been eliminated through retrospective validation. Bioreactors are inoculated when the minimum required cell density in the previous reactor is reached. Elimination of these unnecessary wait times has taken several days off the Enbrel processing time. The finished goods analytical testing and disposition processes have been streamlined to meet their theoretical minimum lead times. All in all, the implementation of the process improvements suggested by the APEX team could yield a lead time decrease of 55%. See Figure 26 for the new breakdown of this decreased Enbrel lead time. It should be noted that the portion of time spent within manufacturing has increased to over 25% in the future state map.

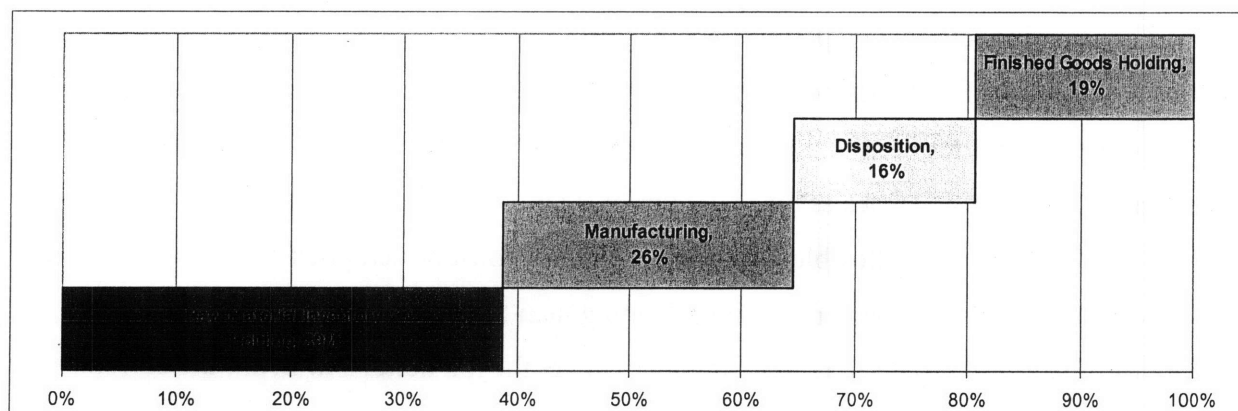


Figure 26: Enbrel Current State Cycle Time Breakdown

7.4.4. ARI APEX Implementation Step 4: Scope, Prioritize & Agree

After the ARI APEX team developed a future state map based on the list of improvement ideas the team needed to prioritize activities. In order to prioritize the list of improvement projects identified, a prioritization tool was developed. The projects were prioritized based on alignment with strategic objectives, urgency, compliance, and potential time, cost and quality improvements. The projects were also weighted based on risk. According to the prioritized list, improvements within the media preparation area of the Enbrel manufacturing operations were selected for the first ARI improvement events.

7.4.4.1. ARI Continuous Improvement Training Curriculum

In order to facilitate the first of the APEX improvement activities, the APEX team developed a continuous improvement training program. The training curriculum was co-developed with the corporate manufacturing function and utilizes the basic lean tools. In addition, a lean simulation specific to biopharmaceutical manufacturing was developed. The biotech simulation turned out to be imperative in the successful launch of the APEX program. As previously indicated, lean is new to biotech and there are many skeptics within the industry that believe lean can't be applied in this highly regulated environment. The Amgen lean simulation, Bio-Kool, not only provides a great vehicle to teach lean concepts in action, but also supplies the evidence to naysayers that lean concepts are applicable to biopharmaceutical operations.

7.4.4.1.1. The Amgen Bio-Kool Lean Simulation

In the Amgen Bio-Kool simulation participants make Kool-aid through a series of processes similar to those used in drug substance manufacturing (receiving, quality testing, mixing, filtering, inspection, and shipping). The current state of the Kool-aid value stream has many of the same operational inefficiencies as those of current state biotech manufacturing. The batch records are cumbersome and inflexible, solutions expire and must be scrapped before they can be used in production, operators spend more time cleaning than they do processing, and operators spend a lot of time searching for the right equipment to get the job done. All in all, the current state is a bit chaotic, but very representative of current operations. After the current state is executed, participants are given a basic overview of lean principles and asked to provide

suggestions for improvement which are then incorporated into a future state (see Figure 27 for an example Bio-Kool current and future state value stream maps). Most of the future state maps include the following improvements:

- Use of 5S and visual management
- Introduction of standard work sheets
- Revised batch records with less words and more pictures
- Pulls systems utilizing kanbans
- Elimination of unnecessary testing and inspections
- Reduced batch sizes
- Reduced rounds of approvals required

When the future state is executed participants witness a much calmer, higher throughput process with less waste and a reduced cycle time. Even the most lean averse production manager can not deny the realistic simulation Bio-Kool is able to provide.

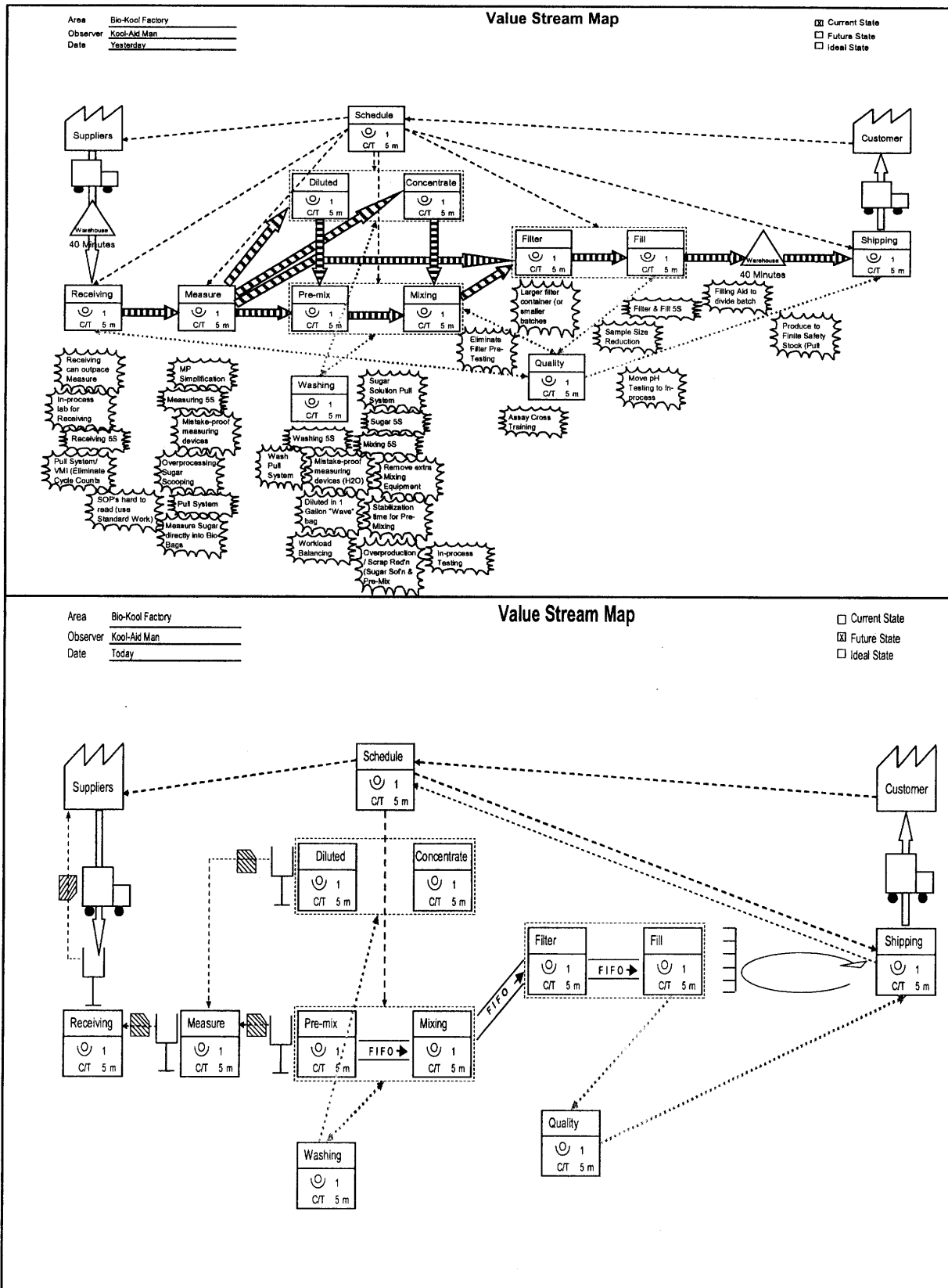


Figure 27: Amgen's Bio-Kool Lean Simulation Example Current and Future State Value Stream Maps

7.4.5. ARI APEX Implementation Step 5: Implement

Following the value stream mapping activities and training, the first of the ARI APEX improvement activities was launched at the end of this author's internship. The improvement team was first trained according to the newly developed training curriculum described in the previous section. Although the author was not on site to see the actual improvement activities take shape, based on the level of enthusiasm and engagement across the site, she is confident that these activities will successfully bring the site to the future state map developed.

7.4.6. ARI APEX Implementation Step 6: Closeout

In coordination with the first APEX improvement activities, the APEX team shared its value stream mapping results with the ARI site, including its senior leadership team. Providing a high level of visibility to the team's efforts allowed the improvement suggestions to gain support and commitment from personnel across as well as up and down the organization.

7.4.6.1. ARI APEX Lessons Learned

7.4.6.1.1. Need to Improve ARI Site Goals and Metrics

As part of the APEX methodology implementation the APEX team realized the site's goals and metrics needed to be adjusted to support the operational improvement activities. The APEX team felt that the current site goals did not explicitly state what the site was trying to accomplish through its operational excellence program and that the metrics being measured were not necessarily the right ones to use to judge the level of operational performance. In addition, there seemed to be some strategic objectives that were being measured by several metrics, while other objectives didn't have an associated metric. Figure 28 below is a visual representation of how well the current state objectives are being measured. Each cell represents the intersection of a goal and metric. A color system is used to indicate the level of this interaction: yellow =weak, blue=strong and white =none. Although this is a subjective measurement tool, it provides a visual manner to check how well metrics and objectives are aligned.

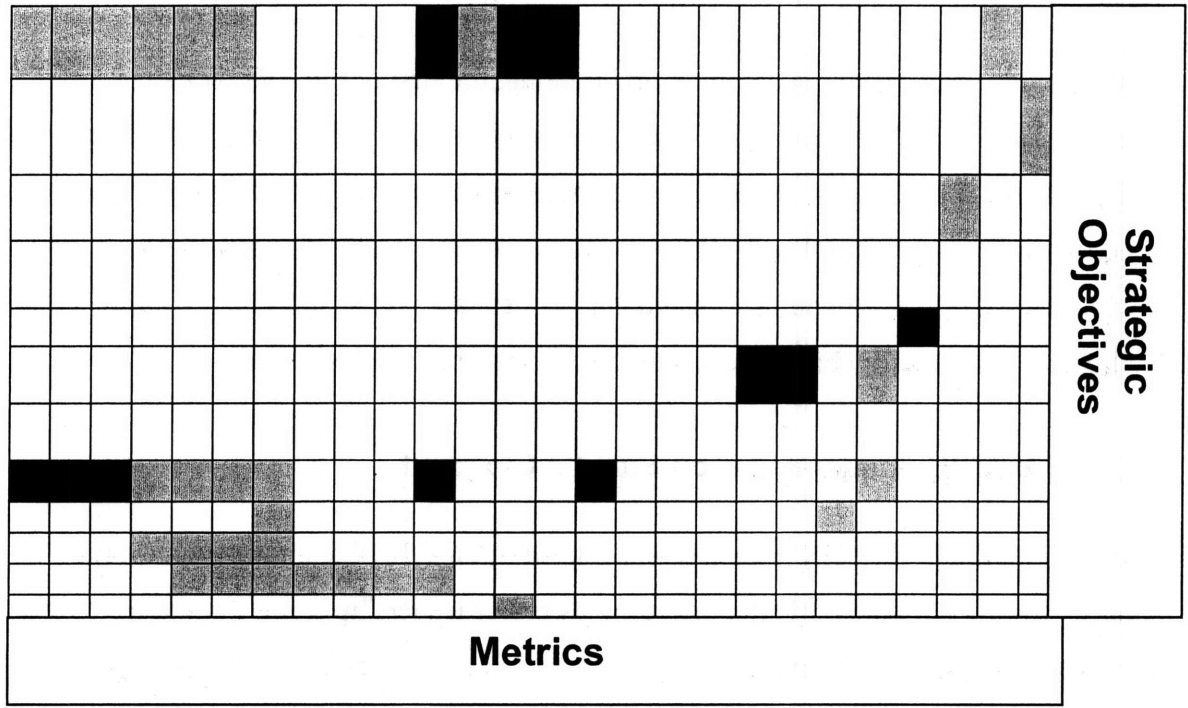


Figure 28: Amgen Rhode Island Strategic Objectives and Metric Alignment- 2007^{87,88}

As Figure 28 indicates, there is a need to improve metric and strategic objective alignment. Also noted by the APEX team was that some of the current metrics did not provide a clear link to the operational performance within the site’s control. For instance, the site’s financial performance was measured based on the cost of goods manufactured metric. However, a large portion of the costs that go into the measurement are fixed. This metric frustrated employees because it was hard to “move”. The APEX team saw a need to develop another financial metric that would allow employees to see the results of their improvements. The author, along with other Amgen LFM interns, developed the variable cost productivity metric as an alternative. The metric compares year on year variable cost change, accounting for product volume and mix changes. This metric is sensitive enough to capture incremental improvements. It is a simple, straightforward, and transparent way to measure cost improvement. Having simple and transparent metrics are a key when implementing lean. An example of the variable cost productivity metric for a site is given in Figure 29 below.

⁸⁷ ARI Goal/Metric alignment is not the opinion of Amgen but solely that of the author.
⁸⁸ Visual Tool has been adapted from the X-matrix tool developed by D. Nightingale, MIT, 2006.

	YEAR	2006	2007	Account for Mix	2007 (2006 equivalent)
Product X	Total Variable Cost	\$ 300	\$ 200	\$ 150	\$ 350
	Kg Produced (released)	100	50		100
	Variable Cost per KG	\$ 3.00	\$ 4.00		\$ 3.50
Product Y	Total Variable Cost	\$ 600.00	\$ 800.00	\$ (300.00)	\$ 500.00
	Kg Produced (released)	50	75		50
	Variable Cost per KG	\$ 12.00	\$ 10.67		\$ 10.00
Site	Variable Cost per KG	\$ 6.00	\$ 8.00		\$ 5.67
Y-O-Y Variable Cost Productivity(%)					5.6%

Figure 29: Example Year-on-Year Variable Cost Productivity Metric⁸⁹

7.5. Recommendations for Future Work at ARI

7.5.1. Further Cost Reduction

During the author’s internship at the Rhode Island site, she worked with a small team of individuals to dive more deeply into the cost structure of the manufacturing operations. The resulting effort produced a model of the current site’s direct labor and material requirement by process step. Not only was this information useful in deciding which manufacturing process steps to prioritize for improvement, but it also made evident some potential cost saving opportunities. An important outcome of this work was the identification and quantification of the media and buffer waste as previously mentioned. The author also identified other cost saving opportunities.

This analysis demonstrated that together three out of the sixteen Enbrel drug substance process steps makeup nearly 75% of the total raw material cost. Two of these process steps are in cell culture, where the major raw material cost is that of media. Due to the large volume of media required for extended cultures and unit price of media at \$2-5 per liter, it is not surprising that media costs play a major role in raw materials cost. The high cost of media reinforces the need for the site to minimize media over-production in the form of making more than is needed (in

⁸⁹ No actual figures were used in this calculation example

advance) and also eliminate continuation of a cell culture reactor beyond the necessary production time.

The second most costly step in the Enbrel production process is a chromatography step. This step is very costly because of the high priced resin that is used in the chromatography column. This work suggests that the site can reduce the total cost of resin in this step (as well as other chromatographic steps) by increasing the resin's lifetime. As part of a drug's process validation process its chromatographic steps are validated for a specified number of cycles. This cycle lifetime represents the number of cycles for which data has been provided that demonstrates that the step has maintained its integrity (able to achieve product yield while removing host cell protein, DNA and providing viral clearance). In many cases, the actual filed resin lifetime is much shorter than the resin's technical lifetime. Because pharmaceutical companies must demonstrate process validation data at the time of filing many resin lifetimes are limited by the amount of data available. It is recommended that Amgen Rhode Island consider establishing column lifetime protocols to extend the life of Enbrel chromatographic resins.

It is also worth noting that both the Enbrel media and resin costs were designed into the process before it was transferred to commercial operations. This points out how the decisions made by development scientists create a lasting effect on the commercial production costs of drugs. In this case, the raw material costs to manufacture Enbrel drug substance could have been reduced if lower cost media was chosen or if longer resin lifetimes had been validated.

7.5.2. Goal and Metric Re-engineering

The site needs to continue to re-evaluate its goals and metrics to support a lean transition. The site should adopt a balanced scorecard approach to goal setting and metrics. Utilization of the balanced scorecard will ensure that the site is delivering value to all of its stakeholders simultaneously. Taking this balanced approach is especially critical during this time of financial constraint. The site does need to reduce costs, but not by sacrificing quality.

It is also suggested that that site work on linking its strategic objectives to its metrics through the Kaplan and Norton balanced scorecard based strategy mapping technique⁹⁰. This approach allows the company to answer the four questions described in Section 6.2.2.1.1 and carefully select metrics that best measure performance on strategic goals. In doing this, the site should end up with a smaller set of higher quality metrics that are more closely linked to the site's strategy. The author has provided an example of what a strategic map might look like for the Rhode Island site in Figure 30. The suggested strategic objectives and metrics have also been mapped in Figure 31 using the same visual tool as Figure 28. Figure 31 below illustrates that using a balanced scorecard provides one or two good metrics for every strategic objective (as evident by the colored diagonal). Through utilization of a balanced scorecard approach, several metrics are no longer required to come close to the bull's eye. Instead, only one or two metrics are required to get a direct hit.

⁹⁰ Kaplan, Robert and Norton, David. "Having Trouble with Your Strategy? Then Map It." *Harvard Business Review*. 2000.

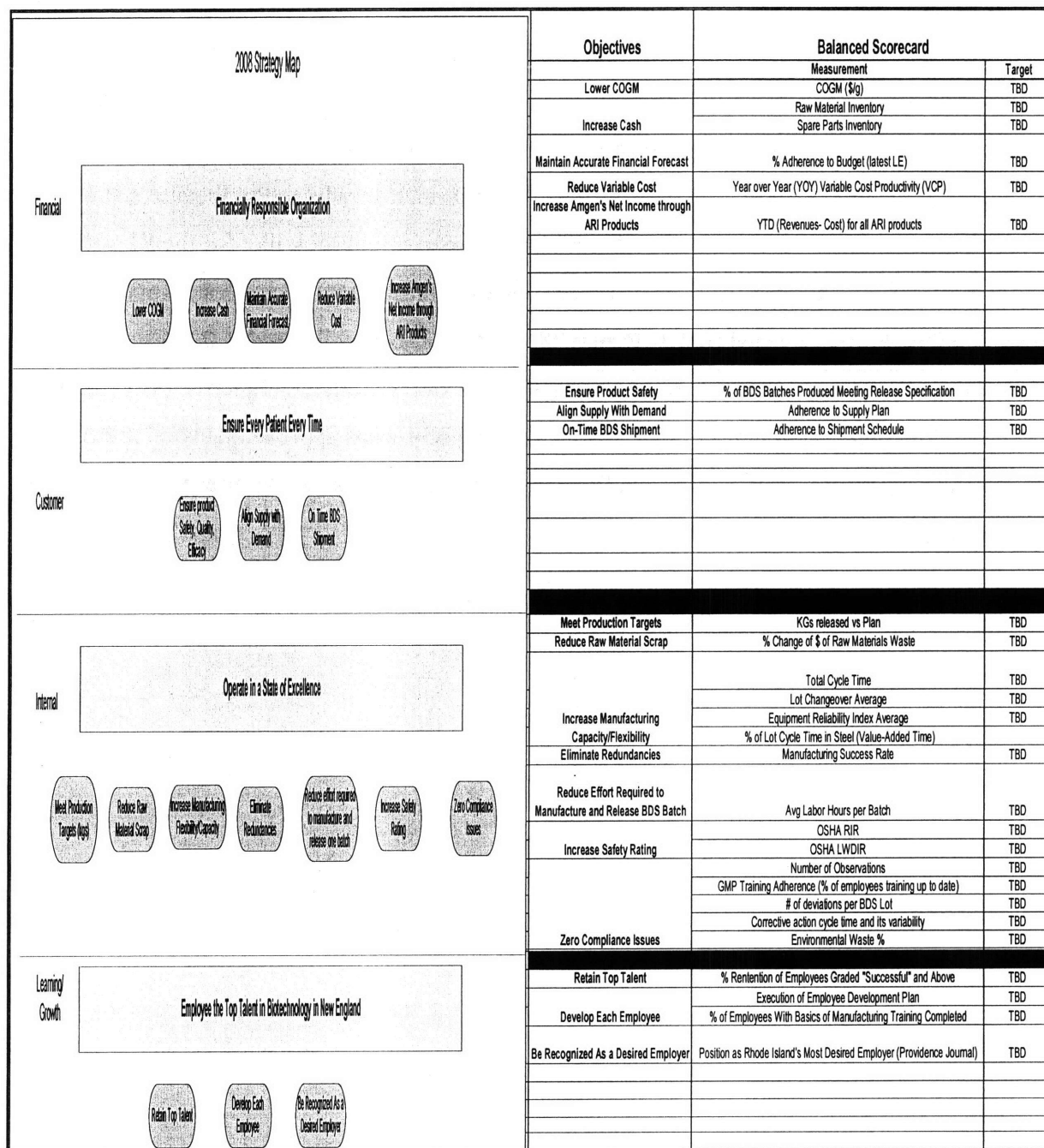


Figure 30: Suggested Amgen Strategic Map⁹¹

⁹¹ Strategy map is author's suggestion only and does not represent actual Amgen strategy

By clearly developing the strategy for the site, leadership is able to create a vision for what APEX is trying to accomplish. However, to reinforce the right behavior and motivate change, the site must also align the incentive structure to its new vision. The ARI site rewards its employees on an individual basis. There is no additional incentive structure dedicated to the overall plant success. It is recommended that a plant-wide incentive program be instituted that links the site's performance to an employee bonus program. This type of program signals to employees that it is everyone's job to ensure that the plant is successful. In addition, an incentive program where everyone is rewarded creates a sense of teamwork and unity, which is critical to morale at a site undergoing change and uncertainty.

7.5.3. Recommendations for Continued Improvement

As the APEX team celebrated its initial site analysis and improvement plan, the author reflected on where these activities placed the site on the transition to lean evolution. The author decided to use G.K. Raju's four levels of operational excellence to provide some definition to where the site was and where these improvement activities would bring it on an operational excellence scale. In the author's opinion, moving the ARI site operations from the current to future state is the equivalent of moving the site from a Level 1 on the G.K. Raju's four levels of operational excellence to a Level 3.

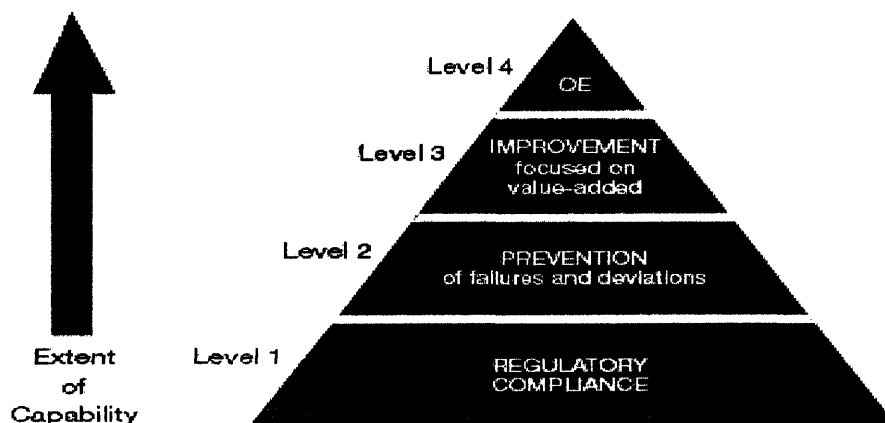


Figure 32: Levels of Operational Excellence (G.K. Raju 2003)⁹²

⁹² Source: Friedli, Thomas et al. *Operational Excellence in the Pharmaceutical Industry*. Germany: Editio Cantor Verlag Aulendorf, 2006: 85.

Level 1: The main objective is to meet regulatory requirements by performing excessive quality control.

Level 2: A company develops capabilities that help to get a scientific understanding about the process and root causes of deviations to move to a predictive performance rather than a reactive compliance.

Level 3: A company develops capabilities to understand value from the viewpoint of the customer and to eliminate waste- especially inventory, which reduces responsiveness and masks process problems.

Level 4: A company eliminated all significant root causes of deviations and has simultaneously managed to eliminate all sources of waste throughout its operations. At this stage a company has managed to tackle the two goals of “effectiveness” and “efficiency” simultaneously becoming a leader in operational excellence.

While the ARI transition from the current to the future state will provide a cycle time, inventory, and overall waste reduction, these initial events are not sufficient to bring the site to a Level 4 ranking on the above operational excellence scale. In order to reach Level 4 status, work needs to be done (potentially using PAT methods) to identify the root cause of deviations within operations. The identification and subsequent elimination of these root causes will result in much less variable manufacturing and quality processes, further reducing the required inventory levels, need for quality inspection, and overall the site cycle time. Bringing this new level of consistency to the site’s operations will enable the site to achieve business and process excellence.

7.6. Recommendations for the Amgen APEX Corporate Initiative

In addition to the recommendations given to the Rhode Island site, the author would also like to suggest improvements for the corporate Amgen APEX initiative. While the current APEX methodology is sound for executing lean improvement, it is insufficient to deliver a complete lean transition. The current methodology creates a structured lean improvement cycle similar to the short term cycle of the enterprise transition to lean roadmap described in Section 6.2.3 and illustrated in Figure 17. However, further emphasis in the other two major phases of lean transition, the entry and the long term cycles, is needed. The APEX initiative is still in the process of building a visible firm commitment, a clear company-wide vision, and sufficient senior management buy-in. She believes these activities require continued attention. In addition, it is recommended that the APEX program focus effort in some of the major long term cycle activities such as aligning incentives with the new initiative and re-engineering the goals and

metrics at the corporate level. The author has already indicated the benefits of these activities under her recommendations for the Rhode Island site. She believes consistency in the corporate APEX message should also include consistency in how the sites' performances are evaluated and rewarded.

It is also suggested that the corporation develop a lean assessment tool to monitor progress towards a state of operational excellence. An assessment tool allows the organization to monitor and nurture its lean progress as well as provides a check that the organization is actually where it believes it is on the transition journey. While the author has used the G.K. Raju operational excellence scale, a much more sophisticated and objective tool has been developed by the LAI and is described in the Nightingale and Mize 2002 paper "Development of a Lean Enterprise Transformation Maturity Model"⁹³.

Finally, it is recommended that Amgen look at applying lean to its non-manufacturing operations and business systems. Currently APEX has only been launched within manufacturing operations. However, the majority of the non-value added cost and time is found within quality and business systems. The APEX team members have already encountered the inefficiencies within the business systems that limited the rate of improvement and the accuracy of the data available to make evaluations. For instance, most changes within biopharmaceutical operations need to be approved through the change control system. However, this system can become bogged down and slow down improvement implementation. As APEX teams work to make rapid improvement they will become frustrated with the time required to go through the internal approval system. Redefining the change control approval system should be a priority for the APEX team.

The author also suggests that Amgen look into using an activity-based cost accounting system. Due to the allocation of overhead to production, it is difficult to identify the true cost of an operation. Since cost reduction is a fundamental part to an operational excellence program (in

⁹³ Nightingale, Deborah and Mize, Joe. "Development of a Lean Enterprise Transformation Maturity Model." *Information Knowledge Systems Management*. 3 (2002): 15-30.

addition to quality and speed), it is important to have accurate cost information. Activity-based costing is the only accounting method which allows for traceability of overhead costs to manufacturing operations.

7.7. A Reflection on APEX Implementation at ARI

Amgen launched the APEX initiative during a time of transition for the corporation. The business challenges the firm faced for the first time in its history very much affected the way in which the APEX initiative was viewed and received. As one would expect, after the corporate-wide layoff announcement was made in August of 2007, the motivation level of employees was low. As a result, management had to decide if this was the right time to be discussing lean. However, management also knew that at no other time in Amgen's history was making improvements as critical.

Leadership decided to continue to pursue a lean transition but refocused its efforts away from actual implementation and improvement projects to that of building the methodology and operating procedures of the program. In addition, it was during this time that the continuous improvement training and Bio-Kool simulation were developed. In retrospect, before the layoff announcement was made, the APEX team was utilizing a bottoms-up approach to improvement without leadership buy-in or visibility to what the team was trying to accomplish. The stall of improvement blitzes during the layoffs and refocus on establishing a strong organizational foundation to the APEX program allowed the initiative to gain the leadership vision and company-wide visibility to the change effort. While the bottoms up approach initially gained local support, the senior leadership buy-in accelerated penetration of the APEX initiative as well as provided the confidence in the program beyond that of a "flavor of the month". In addition, by waiting to officially launch APEX, Amgen was able to separate the concept of lean implementation from that of layoffs which was critical in getting buy-in across the organization.

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8. Achieving True Change

This work has provided the motivation for change, recommended lean as the improvement methodology, and provided a framework to aid in the transition, however one question remains: How can an organization ensure that it will achieve a true sustainable change? How can a firm like Amgen know that the accomplishments achieved through the APEX initiative will last?

Many improvement initiatives in fact do not last beyond the time of the effort's champion. The initiative's champion and selected change agents push the organization to adopt their new philosophies. However, the improvements achieved are only short lived because the fundamental way in which work is done did not change. Employees simply superficially bought into the "flavor of the month" improvement technique but did not truly change their perspective on how work should be performed.

Arguably, the most important factor in a lean transformation's success is its leadership. Driving a change management program like APEX does not just take managers but it takes transformational leaders. Transformational leaders are those that understand the business, have leadership skills, emotional intelligence, analytical intelligence and can execute⁹⁴. These leaders understand the cultural norms of the organization and how things are done. However, what sets these leaders apart is their ability to wear two hats. A transformational leader is able to be an "insider" while at the same time having an outside perspective on change. Transformational leaders are "outsiders on the inside" that are able to see through the company's culturally accepted norms to objectively evaluate the organization's current state and the root causes of operational deficiencies that need to be addressed in order to survive competitive pressures⁹⁵. Transformational leaders are able to question the basic assumptions on how work is done. They are able to see the invisible within an organization and they also have the potential to teach others how to see their organization through a new perspective. These are not the employees that say "we can't do this" or "we're different", but are the ones saying "why can't we?".

⁹⁴ Mohan, Pankaj et al. *Pharmaceutical Operations Management: Manufacturing for Competitive Advantage*. New York, NY: McGraw Hill, 2006.

⁹⁵ Klein, Janice A. *True Change: How Outsiders on the Inside Get Things Done in Organizations*. San Francisco, CA: Jossey-Bass, 2004.

Below are “14 points for management” developed by W. Edwards Deming in his 2000 book *Out of Crisis* on how to lead a transformation⁹⁶.

1. Create constancy of purpose toward improvement of product and service, with the aim to become competitive, stay in business, and provide jobs
2. Adopt the new philosophy (understand the need for change)
3. Cease dependence on inspection (build quality in design)
4. Minimize total cost
5. Improve constantly and forever the system of production and service, to improve quality and productivity, and thus decrease cost (improvement strategy to include both innovation and continuous improvement)
6. Institute training on the job
7. Institute leadership
8. Drive out fear
9. Break down barriers between departments
10. Eliminate slogans
11. Eliminate work standard and management by objective on the factory floor by substituting it with leadership
12. Remove barriers
13. Training education and self improvement
14. Participative transformation program

Deming’s 14 points should be adopted by those trying to make true change. However, they should not be limited to just management personnel, for management is not the equivalent of leadership and leadership is not strictly limited to those in a position of power. Instead, the author would argue that transformational leadership can be found at any level of the organization. A transformational leader is any employee that is able to wear two hats (insider-outsider) to drive change and motivate and inspire others to do the same. A good manager is one that is able to identify these transformational leaders within his or her organization and provide them with the empowerment to lead change. A sustainable true change initiative is one that is supported by transformational leaders at all levels, throughout the organization. This network of leadership creates a change initiative that is much bigger than one person, one division, or one site’s agenda.

In summary, the transition to lean is not as simple as implementing improvement tools and frameworks. Achieving operational excellence through a lean transformation “requires a

⁹⁶ Mohan, Pankaj et al. *Pharmaceutical Operations Management: Manufacturing for Competitive Advantage*. New York, NY: McGraw Hill, 2006: 327.

technical solution, a cultural change, and a behavior modification”⁹⁷. Arguably the easiest part of a lean transformation is building the toolset and training employees, but this alone will only achieve short term change. Transitioning to lean requires that companies change the way they communicate, what they measure, and how they are organized. In essence, lean requires that organizations rethink the fundamental ways in which they do business. A sustainable lean transformation also requires that the organization has the discipline to make changes and stick with them. Organizations must be disciplined to stop producing when a defect is found, to always find the root cause and to give up fire-fighting practices.

⁹⁷ Klein, Janice A. *True Change: How Outsiders on the Inside Get Things Done in Organizations*. San Francisco, CA: Jossey-Bass, 2004: 41.

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9. Conclusions

- **Substantial opportunity exists to improve the current state of biopharmaceutical operations**

Current pharmaceutical operations are highly inefficient. Biopharmaceutical processes, like that studied at the Amgen Rhode Island site, are even further behind small-molecules because of the variability and increased safety concerns associated with biological processing. However, the previous underestimate of the importance of manufacturing performance has created a substantial opportunity for pharmaceutical companies to achieve competitiveness within the industry through cost and cycle time reduction. Through the implementation of simple frameworks like value stream mapping and waste elimination biopharmaceutical companies can realize gains through inventory reduction, scrap and over-processing elimination, diminished people, equipment, and product waiting, as well as reduced quality testing and inspection.

- **Operational efficiencies must be designed into the manufacturing process**

Many of the ineffectiveness present in today's commercial processes could have been avoided during development phase. By the time a product reaches commercial approval many of the operational inefficiencies have already been built into the process. It is recommended that pharmaceutical companies front end load building operational efficiencies into processes by performing cost analysis early in the product's lifecycle and by performing end-to-end process analysis. A total operational cost understanding that includes a sensitivity analysis that takes into account how simple decisions like media selection and column resin lifetime can affect the drug's commercial manufacturing costs is needed before a drug process is transferred into commercial operations. Because unit operation process design is performed by individual specialty engineering groups, analysis of the end-to-end process is key to eliminating waste and redundancies that occur once unit operations are combined into an overall manufacturing process.

More efficient processes can be brought to commercial operations if pharmaceutical companies adopt lean principles along with PAT techniques in the earlier phases of a product's lifecycle. By utilizing lean principles together with PAT techniques, product development could deliver manufacturing processes to commercial facilities that are less variable. In addition, if product development utilized process standardization, manufacturing plants could easily convert from one product to another, reducing process validation times and learning errors.

- **Operational excellence cannot simply be attained through implementation of an improvement toolkit**

Operational excellence initiatives, like the Amgen APEX program, need to include people, process, and performance management analysis as well as feedback methods. In order for an organization to achieve true change it must have the discipline to re-examine its culture, build in feedback processes for learning, and objectively measure performance. This type of learning organization can be achieved through the development of transformational leaders that rethink the fundamental way in which work is done and institutionalize this "outsider-insider" manner of thinking throughout the organization.

To aid change management, these transformational leaders should develop a transition to lean roadmap for the corporation. Not only does this roadmap need to include the long-term program strategy, execution, and feedback mechanisms but it must also include activities that will bring the organization an outside perspective like industry benchmarking as well as participation in knowledge sharing arenas like the Biopharma Operations Excellence Consortium run by Tefen. This type of industry forum for best practice sharing is essential for pharmaceutical companies to collectively gain the operational competitiveness to overcome regulatory, payer, and generics pressures as well as continue to collectively raise the bar on operational performance standards.

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