# Process Improvement in Biotech: Dealing with High Complexity Processes

By

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Bachelor of Science in Biotechnology Engineering, Ben-Gurion University, 2005

Submitted to the MIT Sloan School of Management and the Department of Biological Engineering
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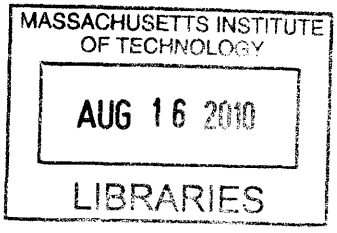


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# Abstract

Across numerous conventional manufacturing sites, process improvement initiatives have been shown to increase production capabilities while decreasing costs – all without a required system-wide overhaul of the manufacturing site. For the biotech industry, this presents an interesting challenge. Through its upbringings as a highly interdisciplinary field, manufacturing unique biologics poses new and complex barriers to a process improvement initiative. However, though the challenge is daunting, process improvement in this field will in fact increase the reward two-fold. First, as with conventional manufacturing sites, costs and lead times will decrease while potentially increasing profits. Second, the ability to better produce more life improving drugs, and at a more affordable price to patients is in fact a reward unto itself – one that is at the forefront of Genzyme`s culture. The turnaround process, where the manufacturing of biologics is halted in order to maintain a key manufacturing process, is a critical point in the production of biologics. The ability to reduce the time and variability of this process will directly and significantly increase Genzyme's manufacturing capacity. Currently, this turnaround process takes approximately $8\pm1$ days, and it is hoped that it will be possible to attain a new turnaround time of $6\pm1$ days through a number of process improvement methodologies such as lean manufacturing. The effects of implementation of a number of lean tools such as standardized workflow, visual management and an automation of the pressure-hold test were studied here. Our observations reveal that by introducing lean methodology the communication and coordination around the complex turnaround process improved, which led to a more manageable and repeatable process. By automating the pressure-hold test it will be possible to significantly reduce the test time and free up resources to perform additional turnaround activities. Even with these preliminary results, it is clear that the path to process improvement at Genzyme is possible, though not without its inherent difficulties. This work provides a critical framework for a number of techniques used, and serves as a case study in understanding the underlying rewards and difficulties with process improvement in the biotech industry.

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# 1. Introduction

## 1.1. Problem Definition

Genzyme's Genetic Disease segment, which includes Cerezyme®, Fabrazyme®, and Myozyme®, grew 26 percent in the past year (2008), and peak revenues are expected to double (Genzyme press release, 2009). The launch of Myozyme® has been extremely strong, especially due to the fast adoption of this product by physicians and patients. Approval of $4m^3$ bioreactors for Myozyme® production is expected for mid-2009. This approval will be necessary to meet the predicted demand for this product, and supply is expected to be tight until then (Genzyme press release, 2008). With this fast increase in production requirement, Genzyme has begun looking at some opportunities to improve capacity capabilities. One option which was suggested, is reducing the turnaround process cycle time. This process is performed between production cycles, and is a production downtime. By reducing the turnaround process cycle time, Genzyme would gain additional production days, or additional production capacity, without a large capital investment.

## 1.2. Company Background

Genzyme is one of the world's leading biotechnology companies. Since its founding in 1981, Genzyme has grown from a small start-up to a diversified company with over 10,000 employees and revenues of over $3.8 billion (2007). The Genzyme business model comprises of a highly diversified portfolio centered on novel therapies with high efficacy, leveraged across a vertically integrated global infrastructure. The company is driven by its commitment to its patients, and is dedicated to addressing currently unmet medical needs. Genzyme is constantly working to develop new products and to ensure that patients have the required access to any and all possible treatments (Overview of Genzyme Corporation, 2008).

Over the years Genzyme has introduced a number of breakthrough treatments which are saving and improving the lives of patients with no other viable treatment options. Genzyme focuses on six broad areas of medicine:

- Lysosomal Storage Disorders (LSD)
- Renal Disease

- Orthopaedics / Biosurgical Specialties
- Transplant and Immune Diseases
- Oncology
- Genetics / Diagnostics

Table 1 - Genzyme's top products, based on FY 2007 revenue (Genzyme Fast Facts, 2008)

| Product Name | Disease/Condition | Revenue |
|---|---|---|
| Cerezyme® (imiglucerase for injection) | Gaucher disease | $1.13 billion |
| Fabrazyme® (agalsidase beta) | Fabry disease | $424 million |
| Renagel® (sevelamer hydrochloride) | end-stage renal disease | $603 million |
| Synvisc® (hylan G-F 20) | osteoarthritis of the knee | $242 million |

Genzyme constantly reinvests cash from operations in order to build a solid base for long-term growth, with a focus on expanding manufacturing capacity to meet its growing product demand. By the end of 2008, Genzyme expects FDA approval for alglucosidase alfa produced at the $2m^3$ bioreactor scale. European approval of Myozyme® manufactured at $4m^3$ scale is expected in the first half of 2009 (Genzyme press release, 2008).

The work presented in this thesis focuses on Genzyme's Allston Landing manufacturing site, which produces five life-saving medicines – Cerezyme®, Fabrazyme®, Myozyme®, Aldurazyme®, and Thyrogen® – which are delivered to patients in more than 90 countries across the world. Three of these products, Cerezyme®, Fabrazyme®, and Myozyme®, are produced using cells cultured in $2m^3$ bioreactors. These biologic drugs are used in enzyme replacement therapies which trigger a biochemical reaction in the body. These manufactured proteins can be administered to patients who lack these enzymes in order to replace the missing or compensate for an abnormal enzyme type (Genzyme, Allston Landing).

## 1.3. Biologic Drugs Manufacturing

The production of genetically engineered proteins tends to be longer, more complex, and more expensive than that of conventional pharmaceutical drugs. There are three main stages to the production of genetically engineered human enzymes for use in enzyme replacement therapies (Genzyme, Pompe Disease, Manufacturing):

1. Cell culture growth and harvest

In order to manufacture complex protein products, such as enzymes, mammalian cell cultures are most commonly used in fermentation manufacturing. The most frequently used cell line in genetic engineering is the Chinese Hamster Ovary (CHO) cell. In order to produce a certain enzyme, the human gene for that enzyme is inserted into the CHO cells, causing them to express it.

The CHO cells are then grown under a carefully controlled environment in a large, stainless steel, stirred tank called a bioreactor. The cell culture is grown in a perfusion mode. In a perfusion culture, a liquid growth medium, rich with nutrients, is constantly added to the bioreactor. At the same time the liquid inside the bioreactor, which contains the manufactured enzyme, is transferred into the harvest tank.

2. Enzyme purification

The liquid which is collected in the harvest tank is then transferred to the purification step, where the desired enzyme is separated and isolated from the mixture using chromatography based methods.

3. Filling and finishing

In the last stage of the production process the manufactured enzyme is filled into vials, which then undergo a freeze drying process. These vials are later sealed, labeled, and inspected.

The focus of the project was on the first production stage, cell culture growth and harvest. During this stage, mammalian cells are usually grown in suspension cultures, attached to microcarriers, in bioreactors. Microcarriers are small spherical particles, usually with a diameter of a few hundred micrometers, which act as a solid support for the cells. Since cells are shear-force sensitive, the stirring speeds are relatively low. This might result in poor oxygen transfer to the culture; hence oxygen is usually added by bubbling it into the liquid medium in a process called sparging. The bioreactor vessel is jacketed in order to achieve better temperature control.

Additionally, the bioreactor contains control probes for acidity, temperature and dissolved oxygen content. Additional features of bioreactors which operate in perfusion mode are cell retention mechanism, liquid level controls, and inflow/outflow growth media pumps (McGlinchey, 2007). Figure 1 displays schematic of perfusion bioreactor.

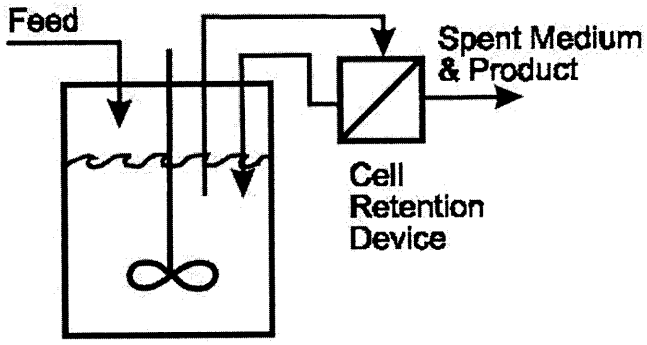


Figure 2 - Perfusion process.
Liquid media is continuously supplied, while the cells are retained in the bioreactor after separation from the outward stream which contains the product (Woodside, Bowen, & Piret, 1998)

Changes in the cell culture environment may harm the proliferation of the cells and also influence the enzyme production (Woodside, Bowen, & Piret, 1998). Another major concern, since the cells can be grown for up to several months at a time, is maintaining the culture sterile throughout the duration of the growth process. Microbial, fungal , and viral contaminaiton can result in significant costs, both in lost time and in material cost (McGlinchey, 2007).

Upon completion of a cell culture growth cycle, which can last between one and four months, the bioreactor, media tank, and harvest tank go through a turnaround process. This process includes repairing, cleaning, and sterilizing these vessels in preparation for the next production cycle.

## 1.4. Turnaround Process Overview

The turnaround process is a very complex process. First, the process consists of multiple discrete activities; most of them require specialized training. While some of those activities can be performed in parallel, most must be sequential, which significantly increases the cycle time and variability of the turnaround process. Second, the turnaround process is performed by a minimum

of four different departments. This requires a high level of coordination among the departments in order to successfully execute the process. Lastly, the turnaround process is time sensitive. Once the preparation of the cell culture begins, there is defined number of days by which the turnaround process must be completed; otherwise additional production days will be lost.

The bioreactor turnaround process, which consists of mostly sequential activities, is commonly referred to as the critical path of the turnaround process. Figure 2 illustrates the key activities of this critical path.

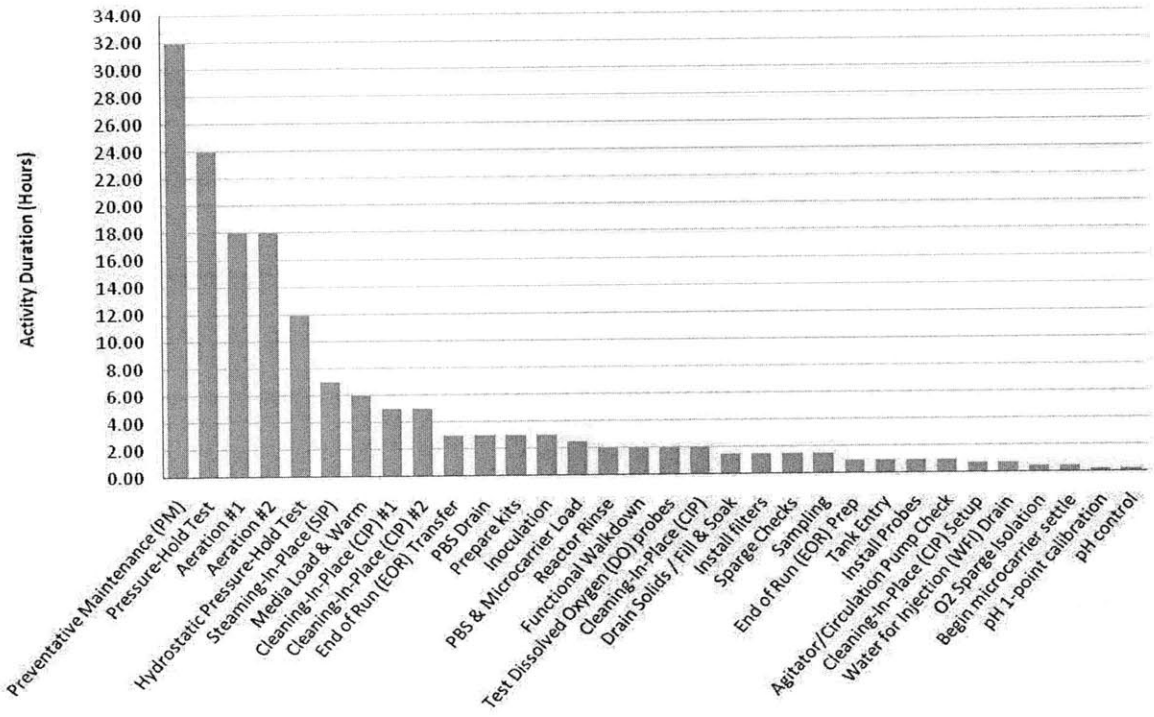


Figure 2 - Key activities of the bioreactor turnaround process

As can be seen from Figure 2, some of the activities are noticeably more time consuming than others. The project's primary focus was on the preventative maintenance (PM) work and on the pressure-hold test. During the PM work, all of the gaskets and diaphragms on the vessels are replaced; any removable stainless steel parts are stripped from the vessels and soaked in caustic solution. Then, the bioreactor is rebuilt, a process which requires skilled workers. The pressure-hold test is an equipment integrity test, in which the vessels are pressurized then monitored to detect any leaks.

Throughout the biotechnology industry, the turnaround process between different production cycles ranges from 35 to 408 hours (BioBenchmark, 2003). This process is a net production down time. Reducing the turnaround cycle time is an opportunity to significantly and directly increase capacity without a large capital investment.

### 1.4.1. The Turnaround Process Improvement Initiative

The first attempt to shorten the cycle time of the turnaround process was a part of a site-wide improvement program called the Manufacturing Systems Improvement (MSI). The MSI program addressed three barriers to achieving process improvement: subject matter barrier which relates to knowledge, skills, experience or training; business process barrier which is characterized by non value added activities; culture barrier which is usually the most difficult to remove.

The second attempt to improve the turnaround process was as part of the Business Process Improvement (BPI) program. The BPI team aimed to create common process improvement methodology throughout Genzyme's global operations, and to grow internal process improvement capabilities within the different sites. The approach that was taken included:

Value Stream Mapping: A diagram of all the process steps that are needed to bring a product from order to delivery; includes both material and information flows.

Kaizen: Continuous improvement of a value stream or a process in order to create more value and reduce wasteful activities.

Set-up Reductions: Techniques to help improve changeover times.

Visual Management: Placing all tools, parts, and production activities in plain sight, so the status of the system/process is visible and quickly understood by everyone involved.

5S: A method for organizing the work place. The 5S's are Sort, Straighten, Shine, Standardize, and Sustain.

Strategy Deployment: A management process that aligns an organization's functions and activities with its strategic objectives. (Marchwinski & Shook, 2008)

The turnaround improvement effort began with a value stream mapping. Currently the turnaround process takes place over a 12-day span, the desired future state of the turnaround process was set at a 7-day cycle time. Additional features of the future state included shorter PM cycle time through reduction of a number of PM activities, improved training in order to achieve around-the-clock turnaround activities, and a site-wide focus on the turnaround process. Other findings from the value stream mapping depicted a need for minimizing equipment handoffs between groups, creating an effective communication tool, scheduling non-routine turnaround activities, and streamlining the PM process.

The goal that was set for the turnaround cycle time reduction project (turnaround project) was to reduce the turnaround time of the bioreactor and associated assets down to seven days without compromising safety and sterility. The primary focus of the turnaround project included establishing a standardized work process in terms of sequence, duration, and timing of activities, achieving detailed planning and scheduling of the turnaround activities, and launching real-time management and communication of activities within and across departments. Furthermore, improving the training methods to ensure around-the-clock coverage, conducting risk assessments to streamline the PM procedures, and evaluating Lean and other process improvement tools were also defined as project goals.

## 1.5. Project Scope and Approach

The turnaround process improvement project was scoped within the overall turnaround project. This project's goals included introducing and prototyping Lean tools and other process improvement methodologies and assessing opportunities for process cycle time reduction. The scope of the turnaround improvement project included all of the associated assets – bioreactors, media tanks, and harvest tanks. The specific activities which were included in the project were the PM and the pressure-hold test activities. Lean methodology was introduced into the Facilities Engineering department.

The approach taken for this project was twofold; first to develop a framework for successful implementation of process improvement methodology and second to generate a numerical model for pressure-hold test time reduction based on theory and empirical data.

The first step was a robust analysis of the turnaround process in order to gain a comprehensive understanding the challenges and obstacles. This was achieved through direct observations and interviews with key personnel. A highly detailed process map was created which illustrated the activities performed by the different departments during a turnaround process, as well as the duration of these activities. Then, focus groups were held both to facilitate open communication between floor workers and managers, as well as to generate a decisive implementation plan which mapped out the process improvement approach. The next step included a time studies and analysis of the PM process, and generating a standard work flow for this process. The time studies were executed using direct observations, interviews, and questionnaires. Finally, visual management tools were introduced with the aim that they would improve communication, track the process progress, and enhance the transparency of the PM process. In conjunction, data on past pressure-hold test was collected and analyzed to asses opportunities for process cycle time reduction.

## 1.6. Thesis Overview

This thesis comprises of six chapters, which are described below:

Chapter 1 introduces the complex turnaround process and describes the turnaround cycle time reduction project.

Chapter 2 provides an overview of existing process improvement frameworks and introduces Lean methodology with an emphasis on the biotech industry.

Chapter 3 presents the hypotheses on which the project was based.

Chapter 4 gives an overview of the research methodology that was used throughout the project.

Chapter 5 describes the findings of the project, including case studies, models, and organizational issues.

Chapter 6 concludes the thesis with recommendations and explores opportunities for further research.

# 2. Literature Review

## 2.1. Lean and Process Improvement in the Biotech Industry

The idea of operational excellence is relatively new to the biotech industry. The competition in this industry is based mostly on the product pipeline rather than on product cost and ability to deliver with short lead times. As a result, until recently Lean and other process improvement methodologies were not a top priority for the biotech industry (BioBenchmark, 2003). However, this situation of limited focus on costs and efficiency is starting to change. The biotech industry is starting to face growing pressure on drug prices as well as rising sales, marketing, and material costs. Additionally, the industry might soon have to cope with bio-generics, which would risk the revenues of branded products and directly bring forth the need for more efficient operations. To meet these rising challenges, the biotech industry is beginning to embrace the concepts of Lean and operational excellence (Jagschies, 2008). Implementing these concepts would help companies across the industry achieve better yields and shorter lead times by creating better process flow, eliminating non-value added activities, and reducing changeover time between production campaigns.

Findings from surveying drug industry professionals (Swichtenberg, 2007) showed that companies in the biotech industry are indeed looking for ways to enhance their manufacturing efficiencies and reduce costs. To achieve this, many drug manufacturers are placing their focus on reducing cycle and setup times. Shortening changeover times, especially in short production cycles, leads to increasing manufacturing capacity. Additionally, more and more biopharmaceutical companies are acknowledging the importance of bridging the "islands of information" across their operations groups.

On the other hand, many in the biotech industry still remain dismissive to Lean concepts despite the fact that these concepts have worked for years in other industries. These drug companies do not recognize the waste within the industry, both in R&D and manufacturing. One should ask the question why an industry that has one of the highest wastes levels, mainly due to rework, multiple process steps, and extremely long cycle times, should ignore these Lean concepts (Shanley, 2006).

The benefits of using Lean manufacturing in the biotech industry are exemplified in Massai's case study of reducing set-up time in a biotechnology company (Massai, 2002). The first step towards improvement taken in this case was mapping the entire value chain of the drug manufacturing process and looking for opportunities to increase capacity. Extremely long cycle times were detected for the changeover process between production campaigns, and this process was chosen as an opportunity to increase capacity. The next step taken was performing a two-part process Kaizen. This led to eliminating redundancy, kitting tools and parts, defining the role of each operator, and most importantly formalizing standard operations for the changeover process. The greatest challenge to this process improvement effort was that in a biotech plant careful action is more important than fast action due to risk of contamination. After all the changes were implemented, the changeover time, which is the bioreactor downtime, was cut by 70 percent to only four days (Massai, 2002).

## 2.2. Process Improvement Frameworks

Many organizations are pursuing process improvement initiatives due to changes in customer needs, rising demand, or growing competition (Adesola & Baines, 2005). When successful, process improvements efforts can have significant benefits. However, many process improvement initiatives end in failure since the improvement team often lose its way among all the available tools and methods, and fail to come up with a clear and decisive plan course of action. In order to achieve the desired improvement, Rohleder and Silver suggested a framework for systematic yet flexible process improvement (Rohleder & Silver, 1997):

The starting point of any process improvement effort should be, according to Rohleder and Silver (1997), achieving a commitment from senior management to ensure sufficient organizational support. The next step is to select the appropriate process to improve. Once a process is chosen, a process improvement team needs to be formed. The team's first task is to define and understand the process in question, including identifying metrics for process performance. Here the team should avoid the dangerous shortcut of jumping straight to implementation of drastic changes. Instead, the next stage should be the removal of obvious wastes that add no apparent value to the process. After monitoring the process and collecting data that is relevant to the predefined

measurements, the improvement team can then determine if there are any identifiable problems with the process. These problems are to be resolved and changes to be implemented until all of the measures of the process are in line with the predetermined specifications. Once the process meets its expected measures, the team should continue on to improving additional processes.

According to the aforementioned framework, the key for process improvement success is empowerment, especially of the improvement team. The majority of the people in the organization should be actively eliminating waste and solving problems at all times. Additionally, management must provide adequate time and resources for the improvement teams to maintain a smooth flow through the improvement stages.

Adesola and Bines (2005) identified a number of different business process improvement (BPI) methodologies and created a structured and practical methodology for BPI implementation. Their framework was designed to be structured, generic, simple, flexible, and industry relevant. The seven steps of this framework are shown in Figure 3 (Adesola & Baines, 2005).

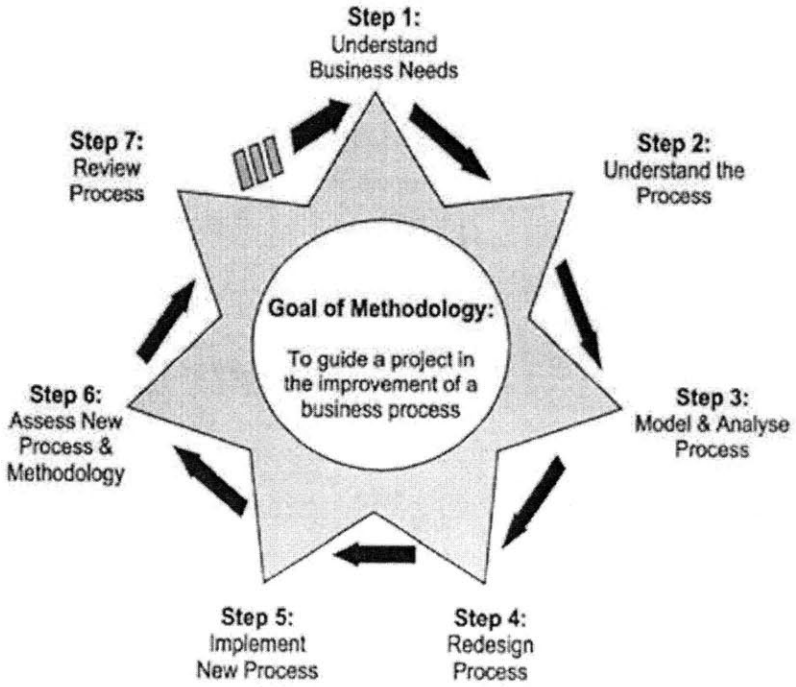


Figure 3 – A generic model for business process improvement
(Adesola & Baines, 2005)

The first step focuses on developing a vision and strategic objectives, evaluating current practices, scoping the needed changes, and establishing measurable and realistic targets. The techniques that should be used throughout this first step include, among others, stakeholder analysis, process prioritization matrix, and Pareto analysis. The second step includes defining the process and modeling its current state through, for example, process flowcharts. The third step consists of verifying and validating the current state model and measuring the current process performance. Then the forth step focuses on modeling the future state process and estimating the performance of the re-designed process. This step includes brainstorming with all of the people involved in the process in question. The fifth step of the framework involves communicating the desired change, planning the implementation, making the new process operational, and training the staff. The sixth step consists of reflecting on the measured data of the newly implemented process and construction of an action plan for further improvement of the process. The final step is setting process targets and performance, and then developing a plan to meet those targets.

Adesola and Bines' (2005) framework described above was tested for feasibility, usability, and usefulness. After applying their methodology in several different cases, which included companies in the public sector, IT service providers, and logistics firms, Adesola and Bines (2005) concluded that their methodology is easy to follow and all of its steps can and should be applied in the order mentioned above.

## 2.3. Overcoming Resistance to Change

In many change management initiatives, resistance to change remains largely an unmanaged process (Trader-Leigh, 2002). Major change often results in failure due to struggles between forces which support and those which resist the change. This may be followed by long and bitter implementation battles. Furthermore, many change initiatives fail since cultures do not easily accept change, and do not effectively anticipate the impact on human systems. It is critical to understand how the stakeholders are affected by this change, especially since programs that satisfy one group may dissatisfy another. Trader-Leigh (2002) describes some key resistance forces, which include self-interest, psychological impact, redistributive effects, culture compatibility, and political factors. Stakeholders must clearly realize how they will benefit from the change in order to buy-in and

support it. The effect which change has on an individual will dictate this person's actions toward one direction or another. Additionally, perception of threat in the form of job security or one's social status in the organization has great effect on whether one would support or oppose a change. Change redistributes resources, power and relationships, and that may upset the balance of power and control in the organization. This in turn may lead to a defensive behavioral pattern which increases the breadth and depth of the change obstructing activities which must be dealt with.

There are several levels of resistance to change (Trader-Leigh, 2002). Resistance is in its first level when people start to question or openly oppose the change idea. In the second level, the resistance is deeper indicating there are other forces at work such as distrust, cultural change, and loss of control. Third level resistance is a deeply imbedded, deeply entrenched form of resistance. Strategies to address resistance should be a integral part to the execution of the implementation plan. Change management should include, but not limited to, proper management of the politics of change, management of multi-stakeholder interests, strategies for disrupting resistance, and frequent adjustments to the implementation stratey (Trader-Leigh, 2002).

Change is a continuous process consisting of three main phases – readiness, adoption, and institutionalization. Lack of change readiness is the primary reason for organizations failing in their change management initiatives (Armenakis & Harris, 2002). In order to create change readiness and prevent reaching high levels of resistance, an organization which goes through change processes needs to develop capabilities for change (Meyer & Stensaker, 2006). In order to develop such capabilities, the change has to first be properly communicated with an emphasis on the reasons for the change and the rationale behind making a particular set of changes. Without proper communication, individuals in the organization are likely to interpret the changes in various ways while trying to figure out the meaning of the change, its effect on them, and their role in it. Furthermore, people who are affected by the change must be involved in the planning and implementation process. This can contribute in a better understanding of and greater commitment to the change. Involving organizational members from different parts and levels in the organization not only improves the discussion around the implementation process, but also facilitates change thus reducing the resistance to change (Meyer & Stensaker, 2006). One process which has historically helped people think about change, and reflect on their and others behavior and feelings is survey

feedback. Such feedback equips those who are affected by the change to deal with that change more confidently and competently. Additionally, this reflection process helps hidden conflicts to surface (Griffith, 2002).

## 2.4. Employee Communication during Change Initiatives

Effective employee communication is critical for the success of change management programs. In spite of that, many companies do not pay as much attention to employee communications as they give to the financial and operational aspects of the change initiative (Barrett, 2002). Lack of or inconsistent communication may result in misunderstanding of the goals to the change process. Such misunderstanding usually leads to demoralization and lack of commitment to the change among the employees (Gill, 2003). Table 2 demonstrates the perceived keys to successful change:

Table 2 – Keys to successful change:
Survey of 259 senior executives in the USA (Gill, 2003)

| | *% mentioning this as important* |
|---|---|
| Leadership | 92 |
| Corporate values | 84 |
| Communication | 75 |
| Teambuilding | 69 |
| Education and training | 64 |

According to Gill (2003), despite the apparent importance of communication only a small fraction of the total communication in organizations is dedicated to the change vision.

Barrett (2002) emphasized the importance of management involvement in assuming responsibility for facilitating communication across the organization. Most importantly, the communication has to be direct in order to be most effective. There are five primary objectives for effective and meaningful employee communication during change (Barrett, 2002):

1. Ensure clear and consistent messages of the company's change vision.
2. Motivate employees to support the company's new direction.
3. Encourage higher performance.

4. Prevent misunderstandings that may decrease productivity.
5. Align employees behind the company's strategy and change goals.

Barrett (2002) suggested a framework for using strategic employee communication during major changes in the organization. The first step is to form a strategic communication team. After which, the team needs to assess the current communication within the organization. This can be done through interviews with a cross section of managers and employees. The next step consists of holding workshops in order to communicate the organization's change vision and strategy. Lastly, the team needs to monitor the results of the communication. During the monitoring stage, the communication team has to assess the employees' level of understanding of the changes occurring in the company. Additionally, the team should recognize the employees' most frequent sources of information. Following this framework should help organizations use strategic employee communication to facilitate change (Barrett, 2002).

## 2.5. Lean Methodology

Lean thinking promotes value stream thinking – the organization has to stop looking at a collection of activities and start looking at all the specific actions needed to produce specific products or to perform specific services. Then it needs to challenge the actions which do not add value for the customer, whether it is the end customer or another department within the organization. Another principle of Lean thinking is achieving perfection through endless improvement steps. All employees should constantly strive to solve production or process problems and implement improvements (Womack & Jones, 1996).

If managed successfully, Lean can be a philosophy that unites the organization in a constant drive for improvement (Atkinson, 2004). According to Atkinson (2004), there are several reasons as to why organizations commit to Lean thinking. These include:

- Need for a cost reduction
- Quality or delivery problems
- Requirement to reduce cycle time
- Launching new products or services

The four steps Atkinson (2004) describes for successfully implementing Lean strategies are:

1. Communicating the Lean philosophy with emphasis on the results and benefits of Lean rather than on the use of specific tools.
2. Achieving senior management psychological commitment to Lean implementation.
3. Designing projects which involve all of the significant players who take part in the production or service process. The people who actually do the work probably have a large percentage of the solutions.
4. Selling the benefits of Lean thinking, highlighting the value for the participating team members who are working on problems previously assigned only to management. Additionally, a benefit of Lean thinking is that it encourages close relationships between functions, meaning the breaking of silos. (Atkinson, 2004)

Two important Lean tools, standard work and visual management, were introduces during this project, and are described below.

### 2.5.1. Standard Work

Lean thinking involves changing and improving processes to make the system more stable and less variable. In order to achieve that the Lean implementation team should not only fix things that do not work, but also standardize things that do (Motwani, 2003). Standard work is defined as a precise description of each activity, specifying both cycle time and specific tasks. One element of standard work is defining the sequence of operations in each process. Standard work instructions allow operators to observe the process with an understanding of how the different activities are to be performed. Standard work instructions can also serve as an excellent training aid (Rooney & Rooney, 2005).

In order to standardize work, the process has to first be analyzed for its steps, key points, and reasons for the key points (Feng & Ballard, 2008). While the steps include all the operations needed to advance the work, the key points include anything in a step that can either injure the worker or make the work easier to do. There are five types of key points: safety, quality, productivity, special techniques, and cost control. Feng and Ballard (2008) further defined four types of work: Routine

work which has low task variety but high analyzability; technician work which has high task variety and high analyzability; craft work which has low task variety and low analyzability; and non-routine work which has high task variety and low analyzability. Routine tasks are composed of repeatable steps, while non-routine tasks can have many ways of completion. Standardized work is not aimed to make all tasks highly repetitive, but is aimed to characterize the best ways to perform a task and to reduce variation in the work method (Feng & Ballard, 2008).

Standardization and workflow formalization also lead to simplification of the work procedures. Standard workflow aims to eliminate the barriers between the stages in the process such that work flows directly from one stage to the next without buffering. Additionally, detailed standardization of a process not only reduces the process variability but also enhance the process visibility (Mehta & Harshit, 2005).

### 2.5.2. Visual Process Management Tools

Visual tools are defined as any devices that help operators to quickly estimate the process status at a glance. Visual controls should include progress indicators and problem indicators to help see when process is ahead of, behind, or on schedule (Rooney & Rooney, 2005). Visual controls should also be used as communication tools, as they can provide immediate feedback to the employees who perform the task on hand (Motwani, 2003).

In many organizations the availability of information is not the primary difficulty; it is the communication of the information that is not sufficient. Lean methodology utilizes simple visual communication tools in order to effectively bring information to both employees and managers. Good visual aids should clearly reveal problems and errors and should include graphics, pictures, symbols, and color coding (Parry & Turner, 2006).

One of the most common visual control tools in Lean production is 5S (Parry & Turner, 2006):

- Sort – distinguish what is needed from what is not needed and should be taken out of the work space.

- Simplify – organize the work space logically to make it easier for everyone to find and return to place needed tools.
- Sweep – keep things clean.
- Standardize – maintain and improve the clean and organized work environment.
- Self-discipline – constantly improve the first 4S.

Parry & Tumer (2006) discussed the case study of implementing a visual communication system at Rolls Royce. This system, which consisted of a large process board (Figure 4), was put in place to communicate the production schedule to the shop floor, as well as to track the progress of the process.

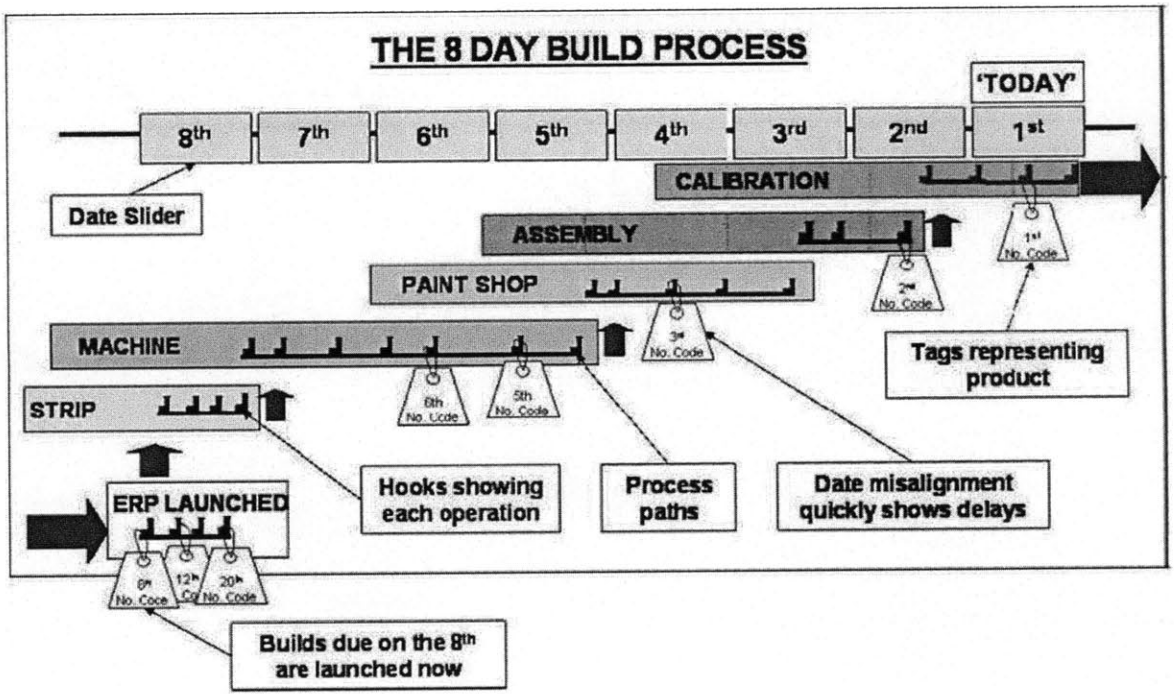


Figure 4 – Visual control board. Used to communicate the production schedule and process flow to the shop floor (Parry & Turner, 2006)

On the board, the value stream is running from left to right and hooks represent each operational stage. All of these stages are of a known duration. The timeline along the top of the board shows the current date on the far left. When the product moves through the process, a tag which represents this product moves from one hook to the next. Each tag also shows the anticipated completion date for the product. When a tag reaches the end of the flow, its finish date

should match the time on the date line. If the dates do not match, it is quickly visible that a problem occurred (Parry & Turner, 2006).

The visual tool described above was developed by the operators, thus it had complete buy-in. Additionally, such a system is very cheap to build and maintain. The benefits achieved from this visual control system include process transparency, transfer of the process ownership to the operators, a mechanism on which to base process reviews, and focus on continuous improvement. Visual boards are not static. They should be used as dynamic forms of data communication. Two other important elements in implementing a beneficial visual system are ensuring full support from senior management and ensuring that all team members have input and control over the board. Finally, holding regular meetings around the board will guarantee that the board evolves into a useful tool for data communication (Parry & Turner, 2006).

# 3. Hypothesis

The turnaround process (described in section 1) is a very complex process. There are numerous activities needed in order to complete this process and also a large number of different departments participating in it. The large variability of the turnaround process cycle time, as well as insufficiently effective and clear communication around handoffs (between shifts and between different groups), were identified as two of the main contributors to the complexity of the process. A hypothesis was suggested, bringing forth the idea that an improved training program, standardization of the process flow and enhancing the communication around the process would help resolve the aforementioned issues, and make the turnaround process more manageable. This hypothesis was first tested in the Facilities Engineering group, which performs the preventative maintenance (PM) activities of the turnaround process. Additionally, the study looked into time saving opportunities around the pressure-hold tests.

## 3.1. Cycle Time Variability

Due to the large variability in the duration of the PM process, a significantly larger amount of time is scheduled to complete the turnaround process than should be required in actuality. Two of the major reasons for this variability are inconsistent technicians' training around specific turnaround activities, and a non-standard work flow for the PM process. The variable training consistency leads to the bioreactor sitting idle for substantial durations, waiting for the next shift of trained personnel to arrive. The lack of standard flow leads to performing the PM process in a different order each time, which reduces the manageably and repeatability of the process.

## 3.2. Clarity of Handoffs Process

Since the PM process flow is not standardized, during shift changes, the leaving technical group has to verbally explain to the arriving technical group which activities were completed and which still need to be. Moreover, at times when more than one department is performing turnaround activities

in the production site the different schedules are not clear enough across departments. This may cause shifts in the planned schedule due to space constraints.

### 3.3. Time Saving Opportunities

During a pressure-hold test, the pressure reading is greatly affected by the vessel temperature and ambient temperature. Due to the stringent standards for passing a pressure-hold test, such temperature effects might extend the pressure-hold test cycle time significantly. That also leads to greater variability in the pressure-hold test duration. Hence, by finding a method to account for the effects of the temperature changes, it would be possible to significantly reduce the duration and variability of the pressure-hold test. This theory was first tested on the Media tank pressure-hold test.

# 4. Research methodology

## 4.1. Data Collection

Four strategies of data collection were used throughout the research: Interviews, direct observations, questionnaires, and use of secondary data. Interviews were conducted with technicians, operators, and managers in order to understand the different stages of the turnaround process and to assess the key issues faced by the participants in the process. Additional interviews were used to evaluate the impact of the implemented changes.

Direct observations were used to study the PM process and to conduct time studies on the PM activities. One common problem with observations is the reaction of the participants to the observer which may cause them act differently then they usually do. Thus, it is critical to create an environment where people will feel comfortable enough to act naturally despite the presence of an observer (Tashakkori, 2003). In order to create such an environment, a significant period of time was spent with the group both before and after the observations took place.

Questionnaires were used to complement the time data gathered through observations. They were filled out by both experienced and inexperienced technicians who participate in the turnaround PM process. Secondary data in the form of official documents and electronic database was used to further study the turnaround process with an emphasis on the pressure-hold test.

## 4.2. Framework Development

A framework was developed for improving the turnaround process by implementing and sustaining standard work flow and communication improvements between floor workers and management. This framework is illustrated in Figure 5.

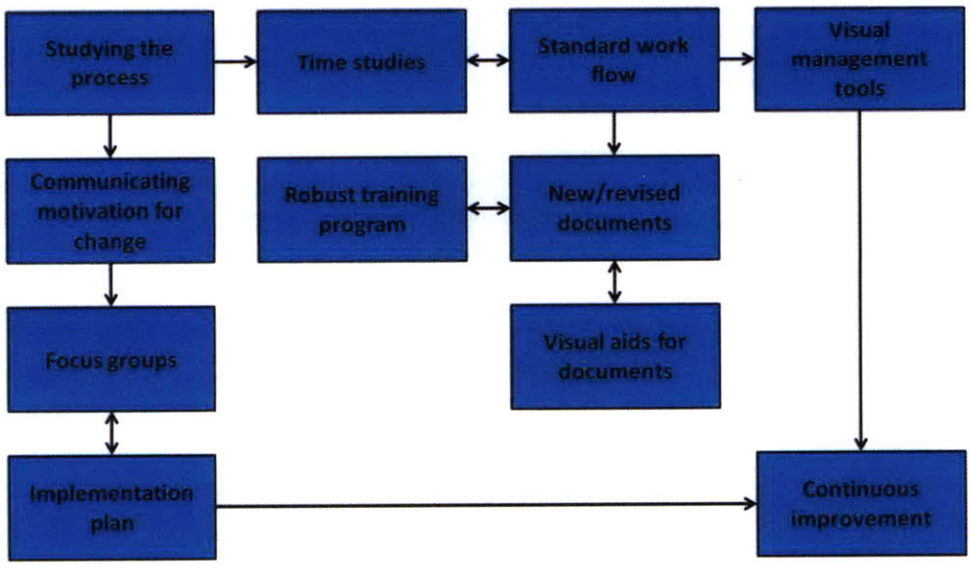


Figure 5 – Framework for implementing and sustaining standard work flow and improving communication

The implementation process began by studying the process and by explaining the goals of the project to the participants. Communicating the motivation for the project was deemed necessary in order to get those associated with the project on board and to eliminate some of the initial resistance to the changes. Another crucial step was the holding of focus groups comprised of both floor workers and managers. The purpose of the focus groups was threefold: discuss and gain further understanding of problems in the process, generate an implementation plan for some of the improvement ideas, and involve a maximum number of people in the process improvement efforts. Next, a standard work flow for the process was developed based on the data collected through the interviews and the time studies. Different process steps were grouped into activity blocks and a specific order was set to these blocks. These activity blocks were then incorporated into the official documentation and training program. In order to further track this new work flow, a visual management tool in the form of a process tracking board was implemented. The board has an additional purpose of improving communication between shifts and among the different departments involved in the turnaround process. Furthermore, the implementation plan generated through the focus groups was presented on the process board with the purpose of achieving a continuous improvement methodology; by reviewing the plan and constantly adding new suggestions for further improvement.

## 4.3. Data Analysis

Pressure and temperature data was collected from seven independent media tank pressure-hold tests. Since the media tank pressure-hold tests are performed while the tank is at a significantly higher temperature than the ambient air, the temperature drop has a significant effect on the vessels' pressure. Thus, the pressure data was plotted against the temperature data for each of the test to look for possible non-temperature related trends in the pressure change. This will be further explained in chapter 5.

# 5. Findings and Discussion

## 5.1. Case Study: Improving the Turnaround PM Process

The purpose of this case study is to demonstrate how the framework described in chapter 4 was applied to the turnaround PM process.

### 5.1.1. Facilities Engineering and the Preventative Maintenance Process

The technicians working in the Facilities Engineering department have a crucial role in the turnaround process – they perform all of the required PM work during the turnaround, a process which may account for up to 20 percent of the overall turnaround cycle time and has a significant impact on the turnaround process.

During the PM work, all of the gaskets and diaphragms on the bioreactor, media tank and harvest tank are replaced, and any removable stainless steel parts are stripped from the vessels and undergo a rigorous cleaning routine. Other parts of the vessels are tested for their integrity. The purpose of this process is predominantly to prevent contaminations and mechanical problems during the production cycle. One of the most critical steps of the PM process is the rebuilding of the vessel. If the vessels are not built correctly then it will likely not be able to pass the pressure-hold test and the turnaround process will be delayed.

The cycle time of the PM varied, ranging from four eight-hour shifts to seven eight-hour shifts. Some of the variability resulted from the variance of each of the discrete activities, which was mostly due to a non-standardized workflow specific to PM turnaround activities and variability in the availability of trained personal. However, some of the variability resulted from the transition times; from one activity to the next. This was due to an ambiguity around the shift change process and, again, due to variability in the number of trained personal across shifts.

Another issue with the turnaround PM process was that this process was not transparent to the other departments participating in the process. As a result, the people present in the production

suite did not have enough clarity regarding what stage the PM process is on, and whether or not it is progressing according to the planed schedule.

### 5.1.2. First Stage: Studying the Turnaround PM Process

The first step was studying the turnaround PM process. This was done mainly by examining official documents, interviewing technicians and managers, and conducting direct observations. However, it was crucial to first gain credibility and buy-in from the group, especially since the technicians' help was needed in order to conduct the time studies properly. Due to the long cycle time of the PM process relative to other turnaround activities, the Facilities Engineering department was deemed as a priority in cutting both time and variability. Numerous time-reduction projects have been launched and aborted in a relatively short period of time, and the workers were frustrated at the inconsistent follow through. In order to overcome this hurdle it was important to explain the motivation and goal of this new change initiative. When talking about the PM process improvement plan, the benefits to the workers' from the changes were emphasized. The main benefit from improving the turnaround PM process was to make the work more manageable for the technicians. This communication helped establish the technician's buy-in, which was crucial in order to move ahead with the next stages of the framework.

### 5.1.3. Second Stage: Focus Groups

Three main concerns came up during the first implementation stage: first, the communication between the technicians and the managers was suboptimal and not frequent enough, which led to concerns around the change initiative. Second, the technicians and supervisors were not directly involved in previous improvement efforts, which left them to feel that the changes are forced on them from above and are not for them. Moreover, despite the fact that the technicians provided the occasional feedback on the PM process, very little was accomplished by management to implement their ideas. Third, although some of the issues with the PM process were reoccurring, their root cause was never addressed. All of these concerns were addressed through the focus groups.

The focus groups facilitated in producing in-depth discussions which were aimed at revealing the root causes of a number of repeatable turnaround PM problems. The root cause analysis focused on the points that added to the long cycle time and variability of the turnaround PM process. Issues that were identified during the focus groups are presented in a cause-and-effect diagram, commonly referred to as fishbone diagram (Figure 6). In this diagram, the box on the right hand side represents the problem that is being examined, while the main body of the diagram contains the potential causes to this problem, grouped into categories.

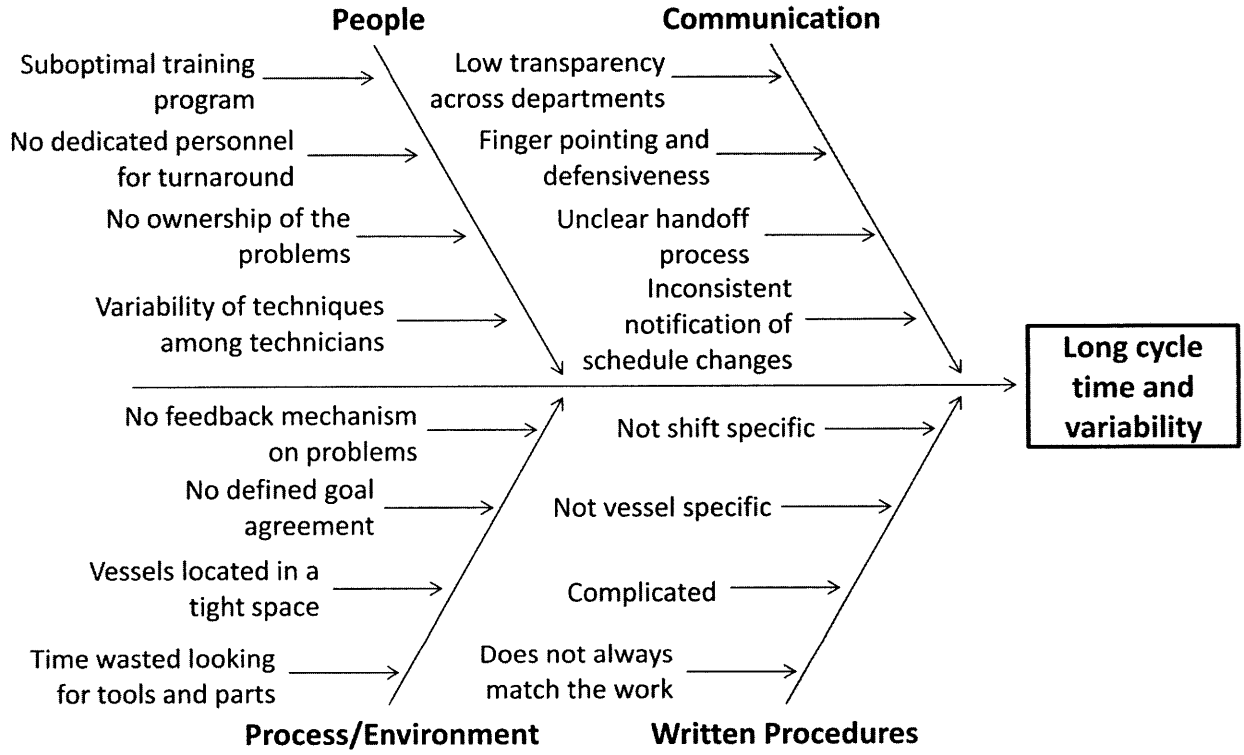


Figure 6 – Cause-and-effect diagram

**People:** The people factor contributes a great deal to the variability in the PM process. Due to variability in training around specific turnaround activities, which results from a less than optimal training program, different PM processes were completed in different amounts on time – depending on whether or not well trained technicians were on shift. Additionally, since PM dedicated personnel do not exist, the technicians would on occasion be called off the production suite to attend to other issues throughout the facility, which effectively caused unplanned delays in the process. The technicians felt no ownership of problems that occurred during the PM process, thus

they nearly never tried to improve the process in order to eliminate these problems. Another contribution to the process variability resulted from lack of consistency in the techniques used among the technicians, as each did things the way he/she found right.

**Communication:** Low transparency across departments and unclear handoff process between departments led to unanticipated delays in the overall turnaround cycle time. For instance, when one department completed the work in the production suite, the next department's workers did not always know when they could start their work. Communication across the departments was commonly through ineffective finger pointing and defensiveness, which led to additional delays. Additionally, the workers did not always receive notifications on a change of schedule, which led to both delays and frustration.

**Process/Environment:** The technicians did not always receive official feedback regarding their work process and results, thus they did not address and try to resolve repeated problems. The department that took ownership of the turnaround process was the Cell Culture Operations department. However, they did not precisely define a goal agreement with the Facilities Engineering department in order to define what a successful and acceptable PM process is. Due to that, there was variation in the results of different PM processes. Additional factors which increased the cycle time of the turnaround PM process were the time spent looking for tools and parts, and the fact that the work was performed in a tight space that required slow and calculated movements.

**Written procedures:** Another time consuming issue was the official documentation needed to be filled out. These documents were very long and complicated and did not lay out clearly the work that needed to be done. Additionally, time was wasted when the workers had to continuously go back and forth through the paperwork while working in the production suite as the documents were not vessel or shift specific.

The focus groups did not only help in analyzing the root causes of some of the PM process issues, but also got the technicians and supervisors involved in the process improvement efforts. The group came up with a number of possible solutions to the issues presented in Figure 6, and generated a detailed implementation plan. Since the technicians and supervisors are the ones who

came up with the aforementioned issues and possible solutions, they felt accountable for the plan`s success. Moreover, each action item on the implementation plan had at least one of the technicians as an owner, increasing the involvement of the workers in the improvement process. The focus groups also improved the communication between the workers and the managers through the close interactions which took place. The experience helped the managers realize the importance of the technicians' feedback, and they continued along that path throughout the other implementation stages.

### 5.1.4. Third Stage: Standard Workflow

The next stage included generating a standard workflow for the turnaround PM process in order to make the process more manageable and less variable. Additionally, the standard workflow was used to improve the official documents and the training program, and to set reasonable expectations for the PM duration as part of the overall turnaround process. The direct observations and time studies helped with grouping the different activities of the PM process into discrete blocks of activities, commonly referred to as PM modules. The modules were determined such that each shift could start with a new module, and a certain number of modules could be completed during a shift. That way, unfinished work or documentation will not have to be passed over from one shift to the other. The bioreactor PM modules are presented in Figure 7. The error bars represent the current variation, represented as one unit of standard deviation from the norm, of each of the PM modules, as was recorded from the various time studies and questioners.

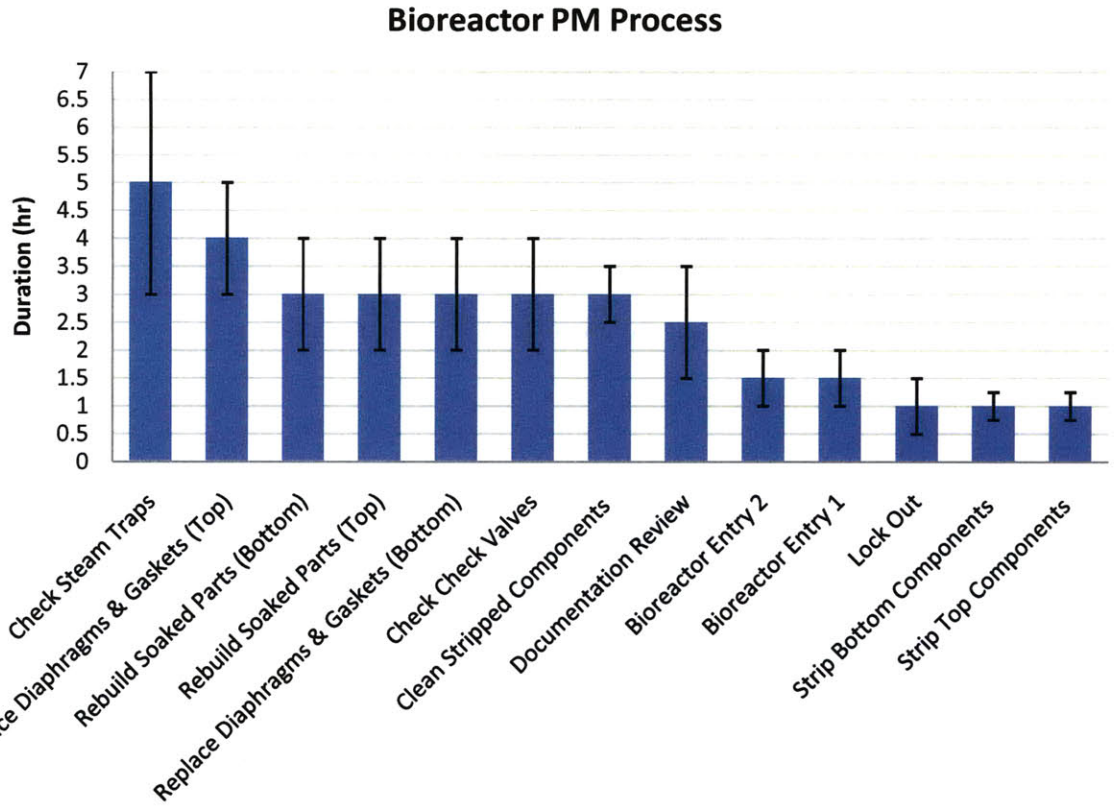


Figure 7 – Key activities of the bioreactor PM process. Error bars represent the standard deviation of each discrete activity

Next, the paperwork was revised to reflect these newly determined PM modules. The previously long and complicated PM documents were changed such that each one of the modules had its own section, written for simplicity in the form of a check list. In order to make a number of the documents even more robust, visual aids were incorporated into them. Since much of the time variability of each individual module resulted from the inconsistent cross-shift trained personnel, the modules were incorporated into the training program. A matrix was prepared; depicting which technician is fully trained, and hence certified, on what module. By assigning only trained personnel to each module, the mean and variability is expected to decrease. Additionally, this will enable proper tracking of the training progress of the technicians.

In order to verify that the new standard workflow is sustained, and to further improve the communication around the PM process, the final stage of the framework was implemented.

### 5.1.5. Fourth Stage: Visual Management

The visual management tool that was implemented to track the new workflow of the turnaround PM process was a process tracking board. A process tracking board gives a snapshot of the current progress of the process. It also allows transparency of the outstanding issues and facilitates visibility across functions and communication. Additionally, the process reviews can be based around such a board. The turnaround PM process board was also used to improve the scheduling of the different turnaround PM activities and to enable rapid responses to problems. This board is shown in Figure 8.

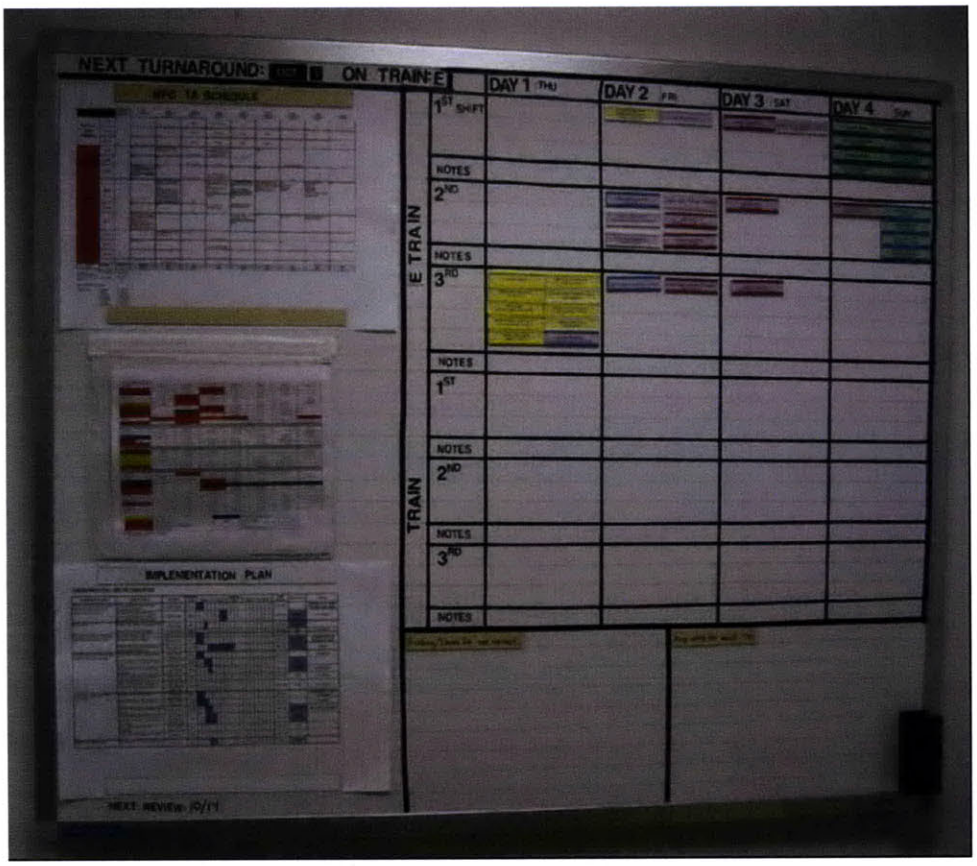


Figure 8 – Turnaround PM process tracking board

The main parts of the board include the overall turnaround schedule, Facilities Engineering schedule, improvements implementation plan, and the PM modules.

The overall turnaround schedule is generated by the Cell Culture Operations department, and includes all of the turnaround activities which are performed by the participating departments. This schedule was included in the process board so that both the technicians and supervisors could be aware of the entire turnaround process, with an understanding of how each and every discrete PM activity fits into this schedule. The facilities schedule is the work schedule of the technicians and supervisors. This schedule was included in the process board for the benefit of the technicians and supervisors. This would give them knowledge pertaining to who is participating in the turnaround PM activities during each shift of each day.

The implementation plan includes tasks that need to be executed in order to improve the PM process. It also presents who should perform each task, when the due date is, when the next review is, and what the current status of each task is. The purpose of the implementation plan is to achieve continuous improvement of the PM activities and involve all of the technicians, supervisors, and managers in the improvement initiatives.

This plan should be reviewed frequently. During each and every review, the progress of each task needs to be evaluated and problems with the implementation should be addressed. Additionally, the technicians and supervisors should come up with new improvement initiatives based on issues revealed during the turnarounds, in a manner similar to the focus groups. It is extremely important that each task will have an owner and a review date. This is aimed to ensure that the implementation progresses and improvements are continuously made.

The PM modules are arranged in a matrix of days and shifts. Inside each square, the modules that should be performed on a specific day during a specific shift can be found. Additionally, the modules are color coded according to the different vessels. The supervisors are the ones who assign the modules for each shift according to the duration of the modules and the technicians available on each shift. The goal was set to assign a reasonable number of modules per shift so that all of those modules will be completed by the end of that shift. This is aimed to improve and shorten the shift changes duration. The supervisors should also make sure that the work is done according to schedule, and to update the board in case of schedule changes. Both technicians and supervisors should be in charge of keeping notes to explain delays, problems or even reasons for being ahead of

schedule. Additionally, if a certain module in consistently completed before of or after its estimated time, the supervisors should update this module's duration accordingly.

In order for there to be an effective communication and tracking tool, the process board should be reviewed during each shift change by the supervisors and technicians of the leaving and entering shifts. The emphasis of the review should be on addressing problems and rearranging the modules as needed. Constant reviews of the board and the implementation plan would help facilitate the continuous improvement efforts.

## 5.2. Pressure-Hold Test Model

The first pressure-hold test of the media and harvest tank is conducted while these vessels are at a higher temperature than the ambient air, right after the cleaning process. In order to pass a pressure-hold test, the operator must record a pressure loss no greater than 0.1 psi over a period of four hours (approximately $7x10^{-3}$ atmospheres/4h). However, since the pressure reading is being done manually by the operators, they cannot tell apart a pressure loss that occurred due to temperature changes or fluctuations and a pressure loss that occurred due to an actual leak. This increases the duration of the pressure-hold test, as the vessels rarely pass the test before they significantly cool down to the ambient temperature. After analyzing data from past media tank pressure-holds tests, a numerical model was generated suggesting that automating the pressure reading and analysis during a pressure-hold test will allow a large reduction of the pressure test time. The model accounts for the pressure differences which occur due to temperature changes/fluctuations, hence prevents the majority of the false pressure test failures and helps insure that no false positives occur.

After analyzing data from seven different media tank pressure-hold test, a distinct trend was discovered, as can be seen from Figure 9. According to the data, after one to two hours the pressure stabilizes and then starts to drop linearly as the temperature drops. It is important to note that in all the examined cases the temperature dropped as time progressed (data not shown). If the pressure drops below a certain level before passing the test, the vessel is vented and then re-pressurized. This can be performed as much as three times for one pressure-hold test.

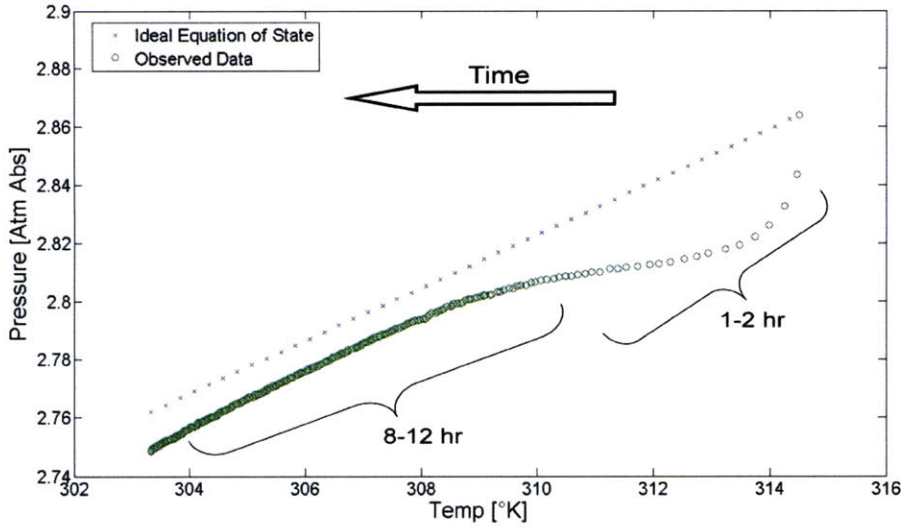


Figure 9 – Data analysis of media tank pressure-hold test.

After identifying this trend, it was necessary to estimate the pressure drop which occurs due to temperature changes. This was done using the Ideal Gas Equation of State. The Van der Waals and Redlich-Kwong equation of state were also tested and yielded similar results (Figure 10) as expected given the range of pressures and temperatures.

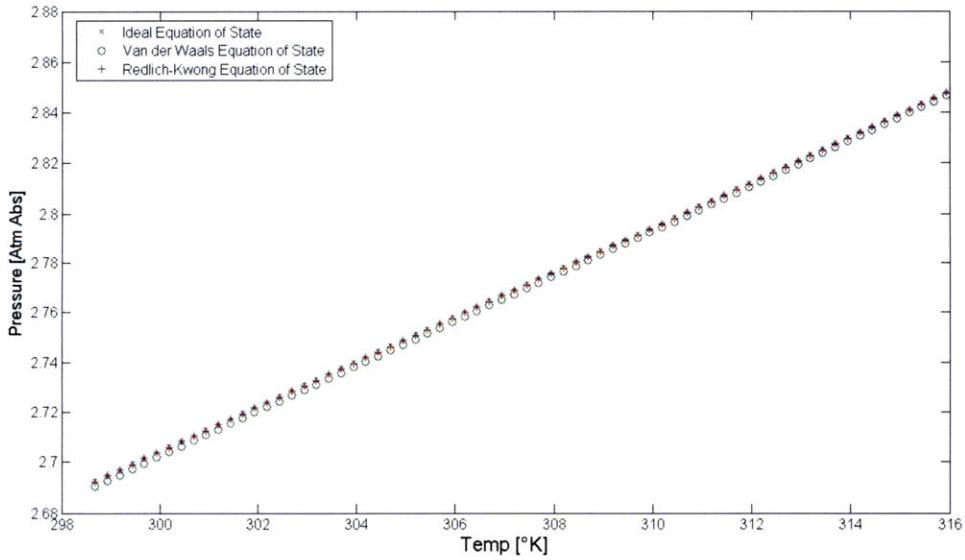


Figure 10 – The Ideal Gas, Van der Waals and Redlich-Kwong equation of state in the pressure tests ranges of temperature and pressure.

The Ideal Gas Equation of State was plotted at the beginning of each pressure-hold test using the following equations:

(1) $PV = nRT$

(2) $n = {P_0 V}/{RT_0}$ ($P_0$, $T_0$ – at the beginning of the test)

(3) $P_{i,ideal} = \left({nR}/{V}\right)\Delta T_i$

(4) $Slope_1 = {\Delta P_{ideal}}/{\Delta T}$

Where P is the absolute pressure in atmospheres, V is the volume of the vessel in liters, n is number of moles of gas, R is the universal gas constant, and T is the absolute temperature. Since the actual initial pressure and temperature values were used for each test, the slope of the Ideal Equation of state is the actually the pressure change due to temperature change for each test. An example of a fitted Ideal Equation of State can be seen in Figure 9.

The next step in the model development was to fit a first order polynomial to the observed data (after the first 1-2 hours of temperature stabilization) of each pressure-hold test (Figure 11). After the initial temperature stabilization, a window of 4 hours was chosen and tested. A linear fit was tested for the slope, or the rate of change of pressure as a function of temperature, which can be well correlated through documentation with time. It should be noted that it is a requirement that the slope of the observed data be larger than the theoretical slope as the theoretical slope incorporates only the change in pressure which occurs due to the change in temperature, where the observed data incorporates both the pressure loss due to the change in temperature and due to the leak which is what the pressure hold-test intends to ascertain. It is with this method, graphically discussed in Figure 11, which will reduce the dead time from >8 hours to exactly 4 hours. One assumption that was used in generating this model was that the leak rate was independent of the pressure change – this allows us to assume that the leak is therefore in fact related (linearly) only to the duration of the test.

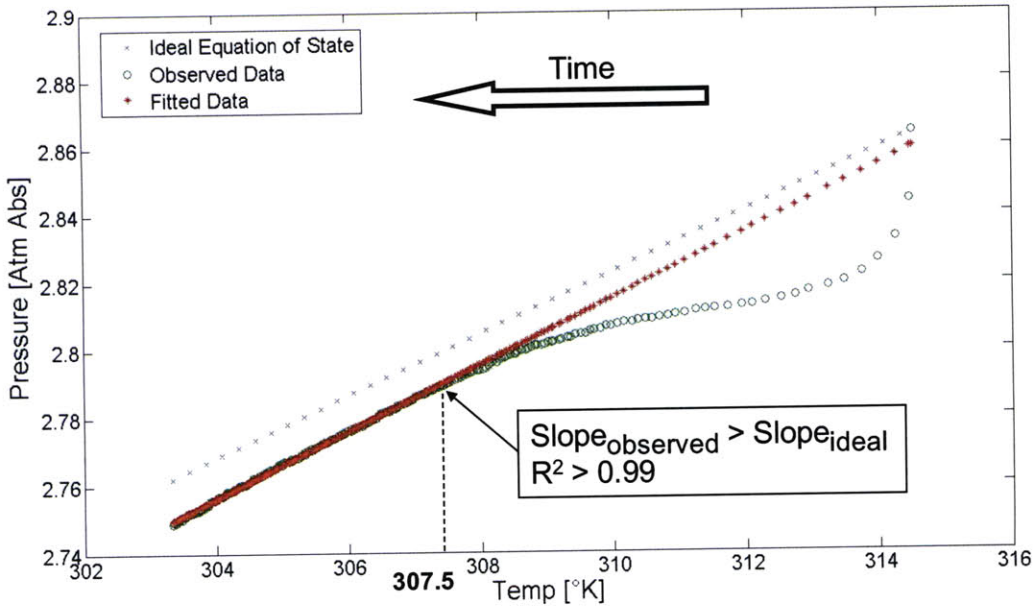


Figure 11 – Linear fit for the observed pressure data.

The last step of the model was to calculate the pressure drop that occurred due to an actual leak and not due to temperature changes. This was done by simply subtracting the ideal equation slope from the fitted line slop for each pressure-hold test:

$$(5) \quad \Delta P_{leak}/\Delta T = \left(\Delta P_{observed} - \Delta P_{ideal}\right)/\Delta T$$

As discussed above, since the automated system also records the time elapsed, by knowing $\Delta P_{leak}/\Delta T$ over a time span of four hours, we can also know what the pressure drop due to leaks was over four hours, which is the criteria for passing a pressure-hold test. In order to correctly predict the leak rate, a number of conditions needed to be met. Firstly, the slope of the observed data needed to be larger than that of the ideal one – this is in fact trivial as if it was in fact lower this would indicate that the pressure leak was negative. Secondly, all data achieved $p < 0.05$ and an adjusted $R^2 > 0.99$ for a leak rate of less than 0.1psi/4h.

After analyzing seven data sets using the aforementioned model, it was proved that the media tank pressure-hold test duration could be shortened from an average of 35 hours to an average of 11 (table 3). Furthermore, we also see a 30% decrease in the variability of the pressure-hold test duration. Thus, automating the pressure-hold test analysis during a pressure test will take into account the pressure changes which occur due to slight temperature fluctuations, and this will enable approximately a 24 hour reduction in the total press-hold test time.

Table 3 – Durations of seven media pressure-hold tests with and without the automated pressure reading model.

| Test | Actual Time Required (hours) | Time Required with New Model (hours) | Δt (hours) |
|---|---|---|---|
| 1 | 27.75 | 4.75 | 23 |
| 2 | 35 | 5.25 | 29.75 |
| 3 | 52 | 10 | 42 |
| 4 | 34 | 12 | 22 |
| 5 | 29.5 | 22 | 7.5 |
| 6 | 29 | 10 | 19 |
| 7 | 38 | 12.25 | 25.75 |
| Average | 35.04±8.35 | 10.89±5.74 | 24.15±10.51 |

Although in its current form, the model cannot be applied to the bioreactor pressure-hold test (as the bioreactor is placed under a temperature control system) slight modifications to this model can remedy this. As the ambient temperature fluctuations still affect the bioreactor pressure readings, the bioreactor pressure-hold test could also benefit from automating the pressure reading process, although a slightly different model will have to be used.

## 5.3. Organizational issues

One of the most challenging aspects of the process improvement initiative resulted from the fact that several departments actively participate in the turnaround process. This required not only high degree of coordination, but also overcoming barriers and differences among the departments when implementing changes. An analysis of the organizational issues encountered throughout the project is presented below.

### 5.3.1. Strategic Analysis

It is without doubt that the Cell Culture Operations (CCO) department is the owner of the turnaround process, as this department is responsible for the cell culture manufacturing stage. Throughout the entire turnaround improvement project the strategy of the CCO department was to invest time and resources in increasing the capacity, productivity, and quality of the biologics manufacturing in order to provide a sufficient amount of quality drugs to Genzyme's patients worldwide.

Formally Genzyme's Allston Landing site is designed as an organization of separate departments and groups for different manufacturing and support functions. This structure can hinder the improvement efforts when the turnaround project involves many different departments. On the other hand, the fact that each department is fundamentally independent allowed piloting implementations for one group with minimal impact on others. This later helped facilitate benchmarking within the manufacturing site.

In order to overcome the problems presented by this organizational structure, a project manager was assigned to coordinate and manage the overall turnaround project across all of the relevant departments. However, the project manager was brought on by the CCO department thus he was not optimally supported by all departments. In order to be able to significantly improve the turnaround process with an emphasis on the coordination between the different departments participating in the process, some form of structural change is recommended. One possibility is to have dedicated turnaround coordination and scheduling group which will work with all of the departments participating in the turnaround process and will not report to only one of the groups but to a higher level of management.

### 5.3.2. Political Analysis

Various stakeholders of the turnaround project had different interests, which tend not to coincide. While the CCO and Facilities Engineering departments were aware of the need to change and were acting to implement improvements, other departments did not see anything wrong with

their current operations and were hesitant to take part in certain improvement initiative. Additionally, while the CCO department sees the turnaround as the most important process which should be prioritized, other departments see this process as yet another activity among the vast number of activities taking place daily throughout the manufacturing site. That led to several problems with the turnaround project. The most obvious one had to do with scheduling of turnaround activities. The CCO department was focused not only on reducing the turnaround cycle time but also on creating a more manageable process. In order to do so, they had started to schedule the turnaround activities of all the departments involved in the process. While the people from the different departments who are involved in the scheduling process tried to accommodate the CCO department's scheduling team, they were not always willing to change their department's priorities in order to do so. These conflicts did not allow for an effective problem solving regime within the time frame of the project.

In addition to the scheduling issues there had been other disputes around the turnaround project as initiatives for process improvement were accepted by one department but were rejected by others. In one specific case, one department went ahead and started a new process implementation without updating the project manager. When this came to the knowledge of the project manager, he intervened to stop the implementation, worrying it would have an adverse affect on the turnaround process. Only after assuring him that the implementation would not adversely effect in any way the turnaround process was this resolved. It should be noted that throughout the turnaround process all opinions and suggestions were welcomed.

### 5.3.3. Cultural Analysis

The turnaround cycle time reduction project included, over a span of over two years, a number of different initiatives for process improvement. Many of these attempts began and ended without conclusive results, which left many frustrated and unwilling to try new and innovative ideas. Many were fed up with process improvements programs, and that made the implementation of the new process improvement initiative very challenging. In order to overcome this problem it was crucial to achieve buy-in for this initiative by explaining the purpose and goals of the process improvement to all of the participants. Another hurdle that had to be resolved regarded the follow-through on

projects. Although feedback was both requested and expected from employees, only a small portion of the ideas were implemented or piloted. Additionally, it was extremely difficult to achieve commitment to task completion dates and/or to regularly review implementation plans in light of multiple complex tasks already ongoing at the site.

The current state of the turnaround process was to focus on reaching the end point on time, regardless of what happens on the way there. That resulted in lack of standardization. Thus, introducing Lean principles required a significant cultural change on the department's end.

The turnaround project in general and the implementation of standardization and other Lean tools in particular, created an overall atmosphere of change. Although that atmosphere fit well into Genzyme's dynamic and innovative environment, most of the people involved in the turnaround process have been employed at Genzyme for a number of years and changing the way they do things required a more personal cultural change. On the other hand, Genzyme's most imbedded value is its patient wellbeing orientation. Since the turnaround project was aimed to increase capacity, hence increase the number of drugs delivered to its patients worldwide, it related perfectly to this most important value and reinforced it. Indeed, the main message that was communicated to all about the turnaround project was the opportunity to deliver more life improving drugs to patients.

Another aspect to the Lean element of the turnaround project was that in essence the project was but a fraction of a wider Business Process Improvement (BPI) initiative that Genzyme recently initiated. The BPI group is aimed at introducing Lean concepts and practices throughout Genzyme's different sites hoping that that would eventually result in a system wide cultural change.

Although the organizational structure created functional silos, the lateral relationships were very dominant. Many of the participants of the turnaround process had known each other for years and the unofficial communication at that manufacturing site was extremely important for knowledge exchange, and process updates. Additionally, although people tend to be mentored by the more experienced personnel most decisions were data-driven rather than experience driven. Thus, it made sense to start with a pilot implementation of a few key Lean tools and then the data gathered from the pilot could be used to drive a broader and more in depth implementation program.

# 6. Conclusions and Future Work

There are number of key factors which are crucial for the success of a process improvement effort in general, and Lean implementation in particular (Duque & Cadavid, 2007):

1. Preparation and motivation of the people: Elaborate communication to clarify and emphasize the need for change and the purpose of change.
2. Roles in the change process: There is a need not only for active leadership, but also for employees' involvement in each and every step of the improvement project.
3. Methodologies for change: Using process improvement and Lean tools to demonstrate immediate and visible improvements.
4. Environment for change: Leadership should constantly reinforce the guiding principles of the improvement initiative such as mutual trust between workers and managers and across different departments.

All of these factors existed during the turnaround process improvement project. That without doubt set the stage for successful process improvement pilots and implementations for a highly convoluted process such as the turnaround process.

The greatest challenge with implementing changes in the Facilities Engineering department resulted from the fact that most of the technicians and supervisors had worked there for years, and were accustomed to the existing processes. However, with the successful implementation of the standard workflow and process tracking board, it proved that it is possible to implement changes in this environment. There is no doubt that communicating the motivation for the changes and involving all of the employees in the improvement efforts were the keys for the success.

## 6.1. Communication

The communication between the managers and the Facilities technicians improved as the technicians were incorporated into the improvement efforts. As a result of the focus groups, the technician learned that their feedback was valuable, and increased the amount of feedback and

improvement ideas for the managers. The communication also improved between shifts as the use of the process tracking board picked up.

Although the communication across departments improved with the implementation of the detailed turnaround schedule and the involvement of all the departments in the improvement efforts, more work is still needed. Part of this could be achieved by clearly defining the expectations when the turnaround process passes from one department to the other. Additionally, it is believed that by implementing an overall turnaround process tracking board, the adherence to the turnaround schedule will be increased. Another possible outcome from implementing such a visual management tool is better communication within the turnaround process as all departments participate in shift changes.

## 6.2. Standardization

The implementation of the PM modules that was discussed in section 5.1.4 was the first attempt at standardizing the workflow of the PM process. These modules were successfully used both to increase the clarity of the PM process and to simplify the PM paperwork. While in the old paperwork the technicians received a long and unorganized list of activities which needed to be completed, in the new paperwork each PM module is presented as a separate check list. This not only simplifies the paperwork, it also significantly shortens the time it required to properly address it.

The standard workflow was implemented both in order to make the PM process more manageable and to reduce the large variability of this process. While the PM process indeed became more manageable and reproducible (as verified through interviews and focus groups), additional work is needed in order to significantly reduce the time variability. This can be done by further standardizing the different activities which compose the PM process. Moreover, the variability can be further reduced by creating a structured and standard training process which incorporates the standardized work procedures.

## 6.3. Visual management

As was mentioned before, the process tracking board which was piloted in the Facilities Engineering department helped improve the clarity of the PM process across departments and the communication across shifts. However, this process board also allowed the tracking of the PM process during turnarounds and addressing problems as they occurred. This was achieved through constant reviews of the board during, as well as before and after shift changes. Employing this methodology of quickly addressing problems and ensuring all workers are involved in the process improvement efforts is critical in process improvement.

Future work should include the sustaining of the process tracking board and the numerous reviews of the implementation plan. Therefore, it is crucial to assign one or two of the Facilities department supervisors as the owners of the board. These supervisors would be in charge of assigning PM modules during a turnaround, gathering all employees around the board during shift changes, and tracking the implementation plan. Furthermore, it is important to reward the employees who contribute a great deal to the improvement process. Given the employees' valuable input, this cannot be stressed enough.

The turnaround process would also benefit greatly from implementing another visual tool: 5S. Implementing this visual tool will reduce the time it take the workers locate the relevant parts and tools. It would additionally allow the workers to ascertain whether they have all of the necessary equipment with them before setting foot into the production suite.

## 6.4. Pressure-Hold Test Model

The numerical model that was developed for the pressure-hold test showed a potential reduction of over 65% in the test time required for the media and harvest tanks. Therefore it is possible to state that by using an automated pressure reading to eliminate the effects of the room temperature fluctuations on the pressure, the amount of time required and its variability for the pressure hold test can be significantly cut back. This could potentially drastically reduce the bioreactor pressure-hold test time, which is a part of the turnaround critical path. The bioreactor

system is slightly more complex than the media tank by way of a temperature controlled system. While intuitively it would be possible to assume that this system is more stable, in fact quite the opposite is true. Due to the temperature feedback mechanism, temperature fluctuations that arise due to the ambient air variations (flow and temperature), and inaccurate readings make the data fitting less accurate. Despite this, one could easily envision a model which would take the temperature feedback into account and hence extrapolate the real loss due to leak though a similar first order polynomial fitting. The experiments that would need to take place include monitoring the ambient temperature in the production suite during a pressure-hold test, ascertaining the feedback controller response, and then analyzing this data against the bioreactor pressure readings that were recorded during the same time span. Given the relatively high accuracy of the instrumentation, fast communication between the feedback controller and the system, and the high level of accuracy achieved in the media tank pressure-hold test – one would assume that solving this technical issue is quite straightforward and hence feasible.

## 6.5. Organization

The existence of departmental silos challenged the turnaround process improvement project. To overcome this challenge it was critical to bridge among the different departments. This was achieved by involving all of the departments which take part in the turnaround process in the improvement efforts. However, this was not a simple task, as not all of the departments were committed to the turnaround project. Due to senior management involvement, though, it was possible to achieve a site-wide participation in the turnaround project. Furthermore, the new turnaround scheduling process helped with the involvement of all of the groups in the turnaround project.

The turnaround process, as well as many other production processes that require high degrees of coordination across departments, would benefit greatly from a change in the organizational structure. Enhanced cross-department workflow could be achieved by creating a matrix structure where the departments are cross linked with specific process groups. Additionally, the turnaround process could be better synchronized with a uniform shift structure across all of the participating groups. Currently, while some departments work with an eight-hour shift structure, some have a

twelve-hour shift structure. This causes additional complications with the handoffs process during a turnaround.

As was mentioned before, scheduling turnaround activities encountered difficulties as the turnaround schedule did not include other daily activities going on in the production site. Although the scheduling process improved with time, the schedule was still not accepted by all which resulted in low adherence to the planned schedule. This problem may be resolved by having a separate scheduling group that will consider all of the daily activities being performed by all of the different departments when scheduling the turnaround activities.

The turnaround project achieved the required buy-in from the majority of the participants despite the fact that many of the employees were fed up with process improvement programs. The acceptance of the project was achieved thanks to constantly explaining to the involved employees what the motivation for the change was and where they fit into the improvement efforts. Involving all of the workers in the implementation process also contributed to the success of the project. The detailed implementation plan that was generated during the focus groups helped maintain management follow-through for the improvement project. However, during the reviews of the implementation plan it was still difficult to get a commitment for task completion dates. This issue was partly resolved by assigning smaller milestones to the implementations rather than committing to one distant completion date.

During the implementation of Lean principles some cultural changes were achieved. The Facilities Engineering department workers, for example, started questioning additional legacy processes as they saw it is possible to execute the turnaround PM process better with less effort. Moreover, the workers became more involved in the improvement efforts and contributed many improvement ideas to the implementation plan. They also constantly attempted to find solutions to problems.

## 6.6. Performance Metrics

Currently, the only metric used to track the performance of the turnaround process is getting to the predetermined end date on time. However, this is the wrong metric to use since this date is reached almost 100 percent of the time. The question that needs to be asked is whether this end date was reached by a well organized and manageable process or by hectic work around the clock. Poorly designed performance metrics may have dire behavioral impact. People modify their behavior in order to achieve positive performance measure, and that can at times involve inappropriate courses of action (Neely, Richards, Mills, Platts, & Bourne, 1997).

Measuring for the sake of measuring is worthless. The purpose of the measurement metrics should be to help the team estimate its progress (Parry & Turner, 2006). Metrics should also be used to build control charts and to determine periodical improvement goals (Duque & Cadavid, 2007). Neely el al. (1997) generated some guidelines to designing performance metrics:

1. Measure: the title of the metric should be self-explanatory and explain what the measure is and why it is important.
2. Purpose: the rationale behind the metric should be specified.
3. Target: it is important to specify the level of performance that needs to be achieved.
4. Frequency: the frequency with which the metric should be recorded.
5. Who measures: the person who should collect the data should be identified.
6. Source of data: the source of the data needs to be consistent in order to compare performance over time.
7. Who acts on the data: the person who should act on the data should be specified.
8. Action: it should be clear that if needed, corrective actions need to take place.

Metrics should be aligned with employee incentives. On the one hand, the metrics should provide incentives for the team to act in a way which improves the process or product (Hauser & Katz, 1998). On the other hand, the employees should be rewarded for successful metrics measures. Moreover, employee incentives should be aligned with the company's strategic goals so that employees would make decisions that are in the best interest of the company (Hauser & Zettelmeyer, 1996).

One important measure for Lean manufacturing is achieving continuous improvement. Measures of continuous improvement should include a number of improvement suggestions per employee and percentage of suggestions that get implemented. It is also important to measure cross training by means of the number of employees capable of performing several different activities. Other Lean measurements include the frequency with which information is given to employees and the frequency of process boards updates (Duque & Cadavid, 2007).

In order to effectively track the performance of the turnaround process, the metrics which are presented in Table 4 were suggested:

Table 4 – Performance metrics for the turnaround process.

| | **Metric** |
|---|---|
| CCO | 1. Pressure-hold test duration and time variation |
| | 2. Start/stop times as scheduled (for handoffs between groups) |
| | 3. Cross training (number of employees able to rotate across activities) |
| Facilities | 4. PM work duration and time variations |
| | 5. Number of equipment rebuilding problems that were discovered after PM completed |
| | 6. Number of improvement suggestions per employee |
| | 7. Cross training (number of employees able to rotate across activities) |
| | 8. Number of procedures documented (standard work, visual aids) |
| | 9. Frequency of updating process board and implementation plan |

These metrics include both time measurements (metrics 1, 2, and 4) and Lean metrics (metrics 3 and 5-9). The time measurements are important in order to monitor the cycle time and time variability of the turnaround process. The Lean metrics have two purposes. First, they should be used in order to achieve continuous process improvements and quick problem resolution. Second, they should be used to monitor the effectiveness of employee training programs. While the target level of performance of the different metrics should still be defined, the frequency of the measurements should be determined for every turnaround process that takes place in the production site. While the first three metrics should be measured by CCO operators and supervisors, the next six measurements should be performed by Facilities Engineering technicians and supervisors. These measurements should be reported to and reviewed by management; however it is up to both

workers and managers to determine the right course of action that need to take place and act upon them. This would help in maintaining the atmosphere that was achieved during the turnaround project of cross-level involvement in the improvement efforts.

## 6.7. Summary

Process improvement initiatives are fundamentally difficult to achieve as there are a number of personal, non-data guided barriers to overcome. However, the rewards of a properly designed process improvement methodology are too great to overlook. These difficulties, if met with a proper planning regime based on past experiences and innovative thinking can be circumvented in order to achieve buy-in from the workers up to senior management. The work presented here, presents an interesting case study of process improvement in the biotech industry. As was described earlier, process improvement in the biotech industry, while incorporating the difficulties of more traditional manufacturing sites, is a more complex system due to the inherent convoluted nature of an interdisciplinary field such as biologics manufacturing. While difficult to properly quantify, the changes to standardized workflow and the implementation of visual management tools did reduce turnaround duration and variability as was ascertained through interviews and final focus groups. However as mentioned above, proper metrics need to be assigned and evaluated in order to achieve a more quantitative analysis. Automating the media tank pressure-hold test was proved to be remarkably relevant for the initiative, far more than was originally anticipated. While originally the duration and the variability of the test were anticipated to decrease, the vast decrease was not expected. It is important to note that a more robust model will likely further decrease the test time. More to the point, this simple example is a direct example of the level of inefficiencies that do exist in current manufacturing processes which increase costs and cycle times. It is these inefficiencies which can and should be sought out. Genzyme, with its world renowned corporate responsibility for placing the interest of its patients high on its priority list, sought to achieve a system-wide process improvement through the BPI program. Creating a sense of striving to achieve a greater good was made significantly easier within Genzyme's culture. The flexibility that was shown throughout Genzyme in going away from legacy processes and the breaking of old habits is no doubt a sign of the devotion to excellence that is embedded in Genzyme`s culture.

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