Augmenting Drug Process Development Capacity through Applications of Lean Principles and High Throughput Technology

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Abstract

The long development lead time and high R&D costs for biologics drugs makes it imperative to eliminate delays and inefficiencies. Limited process development capacity can lead to delays in the availability of life-saving drugs and a large opportunity cost for biopharmaceutical companies. This study investigates the combined viability and impact of two approaches, namely applying lean principles and using high-throughput technology to increase capacity and productivity in pivotal biologics drug process development. Specifically, the project will explore a framework for improved handoffs and work design, and propose management systems to sustain implementation. In parallel, the study tests the sensitivity of the process development cycle to various resource constraints through a discrete event simulation and develops heuristics for the effective use of high-throughput equipment in upstream and downstream processes to increase process development capacity. The two approaches identified a potential increase in throughput of 2.75X (+175%) in preparation for an anticipated 2.3X (+129%) growth in biologics program demand in pivotal process development.

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"If I have seen further than others, it is by standing on the shoulders of giants." - Isaac Newton

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<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AS</td>
<td>Attribute Sciences</td>
</tr>
<tr>
<td>ASTL</td>
<td>Attribute Sciences Team Lead</td>
</tr>
<tr>
<td>cGMP</td>
<td>Critical Good Manufacturing Practices</td>
</tr>
<tr>
<td>CPD</td>
<td>Commercial Process Development</td>
</tr>
<tr>
<td>CPP</td>
<td>Critical Process Parameters</td>
</tr>
<tr>
<td>CQA</td>
<td>Critical Quality Attributes</td>
</tr>
<tr>
<td>DEA</td>
<td>Data Envelopment Analysis</td>
</tr>
<tr>
<td>DIA</td>
<td>Drug Information Association</td>
</tr>
<tr>
<td>DOE</td>
<td>Design of Experiments</td>
</tr>
<tr>
<td>DS</td>
<td>Drug Substance</td>
</tr>
<tr>
<td>DSTL</td>
<td>Drug Substance Team Lead</td>
</tr>
<tr>
<td>FAL</td>
<td>Functional Area Lead</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FIH</td>
<td>First-in-Human</td>
</tr>
<tr>
<td>FTE</td>
<td>Full-Time Employee</td>
</tr>
<tr>
<td>GCSF</td>
<td>Granulocyte Colony-Stimulating Factor</td>
</tr>
<tr>
<td>HTPD</td>
<td>High Throughput Process Development</td>
</tr>
<tr>
<td>HTT</td>
<td>High Throughput Technology</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>KPI</td>
<td>Key Performance Indicator</td>
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<tr>
<td>LPE</td>
<td>Lab Process Excellence</td>
</tr>
<tr>
<td>NBE</td>
<td>New Biological Entity</td>
</tr>
<tr>
<td>NME</td>
<td>New Molecular Entity</td>
</tr>
<tr>
<td>NPV</td>
<td>Net Present Value</td>
</tr>
<tr>
<td>PAT</td>
<td>Process Analytical Technology</td>
</tr>
<tr>
<td>PC</td>
<td>Process Characterization</td>
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<tr>
<td>PD</td>
<td>Process Development</td>
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<tr>
<td>QbD</td>
<td>Quality by Design</td>
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<tr>
<td>QTPP</td>
<td>Quality Target Product Profile</td>
</tr>
<tr>
<td>SKU</td>
<td>Stock-Keeping Unit</td>
</tr>
<tr>
<td>UF/DF</td>
<td>Ultrafiltration / Diafiltration</td>
</tr>
<tr>
<td>WIP</td>
<td>Work-in-Process</td>
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Chapter 1  Introduction

This section provides a background on the productivity and capacity issues in the biopharmaceutical industry and Amgen, highlighting the importance of capacity management methods. Two approaches are proposed with the goal of testing their combined efficacy on program throughput. The overall research methodology, conceptual framework and limitations of the thesis are also discussed.

"We firmly believe that both good process and good science are not only compatible, but together will yield the greatest return on R&D investments and thus, have the greatest impact on R&D productivity." - Paul, et al. [1]

1.1 Background of the Study

1.1.1 Productivity and Capacity Issues in the Biopharmaceutical Industry

One of the defining characteristics of medicine is the long period of time required for its development. A typical biologics drug can take 10 to 15 years to develop and release into the market [2]. For rampant illnesses like cardiovascular disease, which kills 34 people across the world every minute [3], the timeliness of drug availability is essential. This high potential to save human lives places increased pressure on the $163 billion global biopharmaceutical industry with over 7000 medicines currently under development but with only an average of 32 successful Food and Drug Administration (FDA) approvals each year since the year 2000 [4].

Several factors make it imperative to eliminate time delays and inefficiencies in the drug development process. First, rising healthcare costs as a result of an aging population is increasing pressure on biopharmaceutical companies to deliver drugs at a lower cost and higher efficiency. This is particularly true for biologics or large-molecule drugs which are roughly 22 times the daily cost of small-molecule drugs [5]. Second, despite a compounded annual growth rate of 8% [6], biologics have experienced increasing R&D (research and development) costs as a result of declining clinical approval success rates (Figure 1-1). Total capitalized costs have increased at an annual rate of 8.5%, well above price inflation, and R&D costs have increased to above $2.5 billion per drug. These are due to rising costs in the clinical phase (contributing 57% increase in the total cost) and labor costs increasing by 8 to 9% annually [2]. On average, only 12% of drugs entering the clinical trial phase result in an approved medicine [4]. The low productivity of biopharmaceutical drug development has increased pressures on companies to reduce costs [7].

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Third, patent expirations and the prevalence of biosimilars now threaten the market competitiveness of biopharmaceutical companies. Every month of delay presents a valuable opportunity cost to the developer. Being first-to-market for a New Biological Entity (NBE) could grant a company a 6% market share advantage over later entrants [8]. These impacts highlight the importance of improving efficiency and productivity in drug development.

**Figure 1-1**: Declining R&D expenditure-to-approval ratio over time [9]. Reprinted by permission from Springer Nature: Nature Reviews Drug Discovery, *Diagnosing the decline in pharmaceutical R&D efficiency*, J.W. Scannell, A. Blanckley, H. Boldon, et al. © 2012.

Accounting for an uncontrollable ten months of FDA review and a trial success rate that is difficult to predict, companies must turn to endogenous factors that can increase productivity. Pursuing a larger pipeline of parallel research programs increases chances at yielding success, factoring in standard rates of attrition [10], [11]. However, this large volume of work will only be possible with sufficient R&D and manufacturing capacity throughout the different phases of drug development. Insufficient resource capacity can lead to delays in the development of life-saving drugs. While there may be a tendency to operate at capacity, building sufficient slack equips an organization with the flexibility to adjust to pipeline variability, whether due to changes in strategy or due to actual technical roadblocks. Building sufficient capacity also protects a company against firefighting scenarios [12].

Much of existing literature have investigated capacity improvement methods solely for commercial drug manufacturing and provided high-level overviews for R&D as a whole. The drug development process is summarized in **Figure 1-2**. The process begins with drug discovery, which can take between two to ten years. Several proteins, compounds, antibodies or substances are generated and tested until a target is selected, based on the desired properties and characteristics
that are critical for a disease. Lead candidates are then compared with each other until a molecule is selected to advance into development. Pre-clinical and first-in-human (FIH) process development follows by generating cell banks and a fit-for-purpose FIH process. The drug then enters clinical trials (Phases 1 to 3), each phase corresponding to a different patient group size and testing purpose. During these clinical trials, Pivotal Process Development occurs whereby a commercial drug manufacturing process is developed and tested for robustness. Once the drug passes all three phases of clinical trials, all pertinent document is filed to the FDA for review and approval. Once approved, the drug can proceed to commercial manufacturing and launch.

**Figure 1-2: Overview of the drug development process**

Limited, granular research is available on capacity management and productivity improvement at the Pivotal Process Development phase of large-molecule drugs. Pivotal Process Development, the phase during which the manufacturing process of a drug is designed and tested for robustness, is performed during Phases II and III. In a deeper analysis of 60% of the global R&D spend in pharmaceuticals, Phase II has the highest attrition and vulnerability among all drug development phases. Trends between 2008 to 2010 also reveal that although efficacy is the primary reason behind program attrition (51%), purposeful suspension due to strategic reasons (29%) is the second driver [11]. The poor risk–reward ratio and market pressures cited earlier prompt biopharmaceutical companies to be more selective in their portfolio management and allocation of resources to programs. To add to this, process changes often occur within Phase II itself, increasing demand on the limited resources available in a shortened timeline [13]. Given these trends and research gaps, there is an opportunity to explore capacity management methods in the biopharmaceutical industry's process development realm.

**1.1.2 Business Context: Process Development Capacity at Amgen**

Amgen, Inc. is a global biopharmaceutical company that has focused on developing medicine for six therapeutic areas, most of which are diseases with limited treatment options. Since its
foundation in 1980, Amgen has successfully commercialized 15 drugs and currently has the industry's largest toolkit with 13 modalities across its pipeline and marketed products. At present, Amgen has publicly disclosed 33 preclinical and clinical targets under development with strong genetic support. With its increasing pipeline and resource utilization, Amgen has realized the need to augment its process development capacity to meet program demands.

From an organizational perspective, Pivotal Process Development (PD) at Amgen is a combination of R&D and Manufacturing, with primary activities involving lab experimentation by Upstream and Downstream project teams. Since these experiments are not pressured by scale, full-time employee (FTE) resources are the primary constraint or capacity-defining resource. As shown in Figure 1-3, Amgen is expecting a 129% (2.3X) increase in the number of Pivotal PD biologics programs over the next three years, but relatively static FTE capacity. Although the chart indicates that Pivotal PD is operating above 100% of its planned capacity (and has been validated as doing so by activity trackers and resource management platforms), this has been managed by the cancellation and spreading out of programs. Although throughput has not waned, the situation presents a risk of entering and remaining in a firefighting condition which may impair future productivity. Past process improvement projects have been made within the Drug Discovery stage, specifically in Therapeutic Discovery and Medicinal Chemistry [14], but similar initiatives have yet to be conducted for Pivotal Process Development (PD), hence the proposal of this study.

Figure 1-3: Amgen's planned FTE capacity vs. program demand from 2017 to 2020
1.2 Problem Statement and Objectives

Amgen can take several approaches to augment pivotal PD capacity to at least match its growing pipeline. As illustrated in Figure 1-3, the anticipated rate of increase in the number of programs is approximately 129% (2.3X), therefore the objective of this study is to increase the current program throughput of the pivotal PD process by at least 2.3X. However, considering queuing theory and a recommended productivity capacity utilization of 80% to minimize blocking as program demand approaches capacity, the target throughput increase should be at least 2.8X. In selecting which approaches to take, we can revisit the R&D productivity formula introduced by Paul et al [1], which will be discussed in greater detail in Chapter 2. Isolating the variables that are more readily controllable in the formula, we arrive at a translation of Little’s Law popularized by Hopp & Spearman [15]:

\[
\text{Throughput (λ)} = \frac{\text{Work-in-Process (WIP)}}{\text{Cycle Time (CT)}}
\]

Equation 1-1: Manufacturing expression of Little’s Law [15]. Throughput or the average output of a production process is a function of the WIP (inventory of products during a process) and cycle time (the time a product spends as WIP) [16].

Based on this equation, increasing throughput may be done by optimally manipulating the number of programs (WIP) and cycle time (CT). The ability to estimate the resources required to achieve the desired throughput and to balance both WIP and CT is defined as capacity management [1]. Capacity management is important to minimizing any potential delays that may arise as a result of having insufficient FTE resources available to work on program demand, which may consequently affect speed to market. Given the relatively static FTE capacity against the growing program demand in the coming years, continuously improving the number of programs that FTEs can complete within a given time period ("efficiency") without incurring significant additional risk is also important to maintaining the productivity of the Pivotal PD organization. To address resource constraints and to guide future investments in Amgen Pivotal PD capacity, there is a need to determine the combined viability and impact of the two Amgen-proposed approaches on overall FTE capacity and throughput:

1. working faster by using lean principles ("Lab Process Excellence" or LPE) to reduce cycle time, and
(2) doing more by investing in high throughput technology (HTT) to run more programs, thereby increasing WIP and also decreasing cycle time.

The goal of the study is to perform this investigation and to provide heuristics or recommendations to augment Pivotal PD capacity for biologics. Specifically, the study will explore a framework for optimized work design, and propose management systems to sustain implementation. In parallel, the project will test the sensitivity of the process development cycle to various FTE resource constraints and develop heuristics for the effective use of high-throughput equipment in upstream, downstream and analytical lab processes. The study also seeks to fill an identified gap in the available research on the combined impact of both process and technological improvements in the PD realm of large-molecule drugs.

1.3 Research Methodology and Conceptual Framework

The research methodology uses the two approaches defined in the problem statement with the goal of providing process development scientists and key decision makers with useful tools and insights to increase their program throughput. As summarized in the conceptual framework in Figure 1-4, the study seeks to answer one question: How can we do more projects and go faster with a finite set of resources? Each approach tackles the two variables driving throughput, based on Equation 1-1: work-in-process (the number of biologics programs per year) and cycle time (how fast each unit operation and drug development phase takes). There are several factors that can potentially limit both variables. The rate at which equipment can process samples is one factor to consider, but its use is also dictated by the availability of FTEs to run the equipment. Aside from this, beginning an actual experiment also relies on FTEs to plan and design the experiment. Therefore, in a hierarchy of constraints, human resources are the primary rate-limiting resource for drug development [17]. The two approaches proposed in this study also seek to free up FTE capacity. It is important to note that increased FTE capacity does not necessarily translate directly into increased throughput since FTEs are not used for the entirety of the PD process.
How can we do more projects and go faster with the resources that we have?

\[ \frac{\text{Work-in-Process}}{\text{Cycle Time}} = \frac{\text{Throughput}}{\text{FTE Utilization}} \]

LAB PROCESS EXCELLENCE (LPE)
1. A playbook and implementation plan for process design improvements in Process Development
2. An estimate of potential cycle time and capacity freed

HIGH-THROUGHPUT TECHNOLOGY (HTT)
1. A simulation tool that estimates the impact of different HTT scenarios on throughput and FTE utilization
2. Heuristics (a strategy) on the right use and combination of HTT

Figure 1-4: Conceptual framework of thesis study

In the first approach (Lab Process Excellence), a framework is developed for applying lean principles through optimized work design, then supported by a proposed set of management systems and tools. The goal of this approach is to define the optimal experiment design for process development. Interviews of experienced scientists are used to identify the root causes of limited throughput and high resource utilization. The study investigates three components to work design: (1) defining the optimal type and number of experiments required, (2) establishing systems that will enforce the use of prior knowledge for continuous learning and reduced experimentation, and (3) streamlining program phases. A hypothesis is generated on the potential cycle time and throughput improvements that can be gained from improved work design. Given the absence of active biologics programs for testing and the limited research period, the study relies on a retrospective exercise where a recent program’s actual experiments are fitted into the proposed framework, and the potential savings that could have been realized are quantified.

In the second approach (High Throughput Technology), the different applications of high-throughput technology (HTT) in upstream, downstream and analytical lab unit operations are reviewed based on their viability and load capacity. The goals of this approach are to quantify the potential impact of HTT on process development capacity and to provide a simulation tool that can be used to test the system’s sensitivity to a hierarchy of constraints. Test scenarios are developed based on select technologies and tested on a discrete event simulation that is designed and validated for accuracy. To isolate the effects of HTT, the simulation follows the new process design proposed under Lab Process Excellence. The simulation takes into account portfolio
scheduling, FTE resource availability, cycle times, scale-up method, load sizes and equipment capability to model end-to-end unit operations in Pivotal PD. Hypotheses are generated based on a theoretical cycle time and throughput calculation using cycle time data recorded from time-and-motion studies. These hypotheses are then tested using the simulation. The insights gained from both approaches form recommendations for further implementation and research.

1.4 Scope and Limitations

The scope focuses on large-molecule (biologics) pivotal PD which is the phase performed in parallel with Phase II and III clinical trials where the manufacturing process for a biologics drug is tested and qualified for effectiveness and robustness. Figure 1-5 summarizes the research scope in the context of the drug development process. There are currently two stages:

(1) Commercial Process Development (CPD) - the stage where a manufacturing process is developed and tested for its ability to produce the targeted drug at a smaller scale

(2) Process Characterization (PC) - the stage where process developed in CPD is tested for robustness.

![Figure 1-5: Research scope within the drug development process](image)

The same program team is responsible for conducting both CPD and PC, implying labor constraints. The program team can be divided into two groups:

(1) Drug Substance (DS) - the scientists that conduct upstream and downstream experimentation (i.e. expression, scale-up and purification)

(2) Attribute Sciences (AS) - scientists with expertise in assay method development, qualification and analytical lab testing activities
Although both groups are involved in pivotal PD, this thesis focuses mostly on the DS team due to their sponsorship of this research.

The detailed limitations of the LPE and HTT approaches will be discussed in their corresponding chapters, but the following limitations govern the overall study:

- The study will focus on process development for traditional fed-batch processes for large-molecule drug development. The development of perfusion or continuous manufacturing processes will not be considered in this thesis but is proposed for further research as Amgen and the rest of the industry gain more experience with this for process development. The details and differences between these two processes are discussed further in Chapter 2.
- The effects of the LPE and HTT improvements will not be studied outside the Pivotal Process Development phase for large-molecule drugs.
- Small-molecule applications will not be considered.
- Design of Experiments studies to assess the full capabilities of the HTT will not be explored in this study. The discrete event simulation will focus on unit operations, not the mechanics of the equipment.
- No new equipment will be sourced or developed outside Amgen's existing portfolio.
- Due to a limited research timeframe and the absence of active programs for pilot tests, the validation of the proposed solutions is constrained to retrospective studies and simulation runs.
- The proposed changes might not be applicable to all modalities. Hypothesis testing is restricted to monoclonal antibodies (mAbs) and bi-specific T-cell engagers (biTEs) due to wider availability of historical data.

1.5 Thesis Overview

The study lays its foundation on literature reviews on lean applications in the biotech or pharmaceutical industry and high-throughput technology, ongoing technology development initiatives at Amgen, interviews with scientists, process mapping exercises and collection of cycle times and load sizes from past experiments. These reviews and calculations of theoretical cycle time and FTE capacity savings generate the study's hypotheses under the two approaches.
Chapter 2 provides an overview of the drug development process for large molecule drugs to guide further discussion. It then examines the latest trends that are driving productivity and speed-to-market in the biopharmaceutical industry, both from the aspect of process improvement and from the use of high throughput technology. Gaps in existing literature on the use of lean principles and simulation modelling are also discussed, which builds the case further for this study.

Chapter 3 provides an overview of the dual-approach methodology that is used by the study and the analysis that was done to narrow down the focus areas for both approaches. Results from shadowing scientists, interviews and a broad assessment of HTT initiatives at Amgen are funnelled into specific actions for the succeeding experiments.

Chapter 4 details the first approach which employs lean principles to improve process development. It addresses three areas of interest, resulting in a proposed pivotal process design, supported by a set of tools and management systems that can enable its successful implementation.

Chapter 5 details the second approach which employs high throughput technology (HTT) to release FTE capacity and increase overall pivotal PD throughput. It discusses the model used in the simulation exercises, the hypotheses to be tested and the actual results of the tests. The last section is used to test a high throughput system’s sensitivity to other variables such as equipment failures, experiment run size and team size, then establishes further heuristics for the appropriate use of HTT as a result of these tests.

Chapter 6 summarizes the conclusions from the study, assesses the combined impact of the two approaches relative to total pivotal PD throughput, FTE utilization and financial value. It ends with recommendations to continue the work that has been started and to conduct further research.
Chapter 2  Literature Review

This chapter defines the gaps in existing literature that this research aims to fill. It gives a brief overview of the process development in biologics drug development, examines trends influencing productivity in the industry, including past research conducted on the application of lean principles, high throughput technology and simulation modelling to increase process throughput.

2.1 Introduction

New biological entities (NBEs) have been studied to have a higher chance of success compared to small-molecule drugs [1], hence the expansion of several pharmaceutical companies into biologics. The growth of proportion of pipeline dedicated to specialty products and biologics exceeded 10% between 2010 to 2014 [18]. With the growing competition in the market but the low approval rates of drugs, there is a need to increase productivity in biopharmaceutical companies. As Federsel summarizes, the increasing pressure from the market to reduce the cost of medicine, the upcoming expiration of several drug patents and the significant opportunity costs to be incurred from failing to be first-to-market have increased the awareness within the biopharmaceutical industry of the importance of process R&D [13]. Process development, sometimes called process R&D in other organizations, is responsible for developing the manufacturing process for a drug. In this phase, the process parameters are not only developed, but are also tested for robustness. Two logical approaches to increasing productivity would be (1) achieving speed-to-market through faster process development and (2) reducing costs by streamlining the production process for drugs [19].

Some suggestions from previous research to improve productivity are to involve a more data- or evidence-based approach to decision-making and aligning information with Quality Target Product Profile (QTPP), seeking expertise during decision-making, and reducing cycle time and operational costs [20]. Reducing process development times, adopting a fail-fast approach given the low success rate of candidate drugs during trials, enhancing protocol design and control and boosting productivity are all necessary to maintain competitiveness in the biopharmaceutical industry [21]. Nfor et al. [22] summarize four rising techniques in process development: (1) heuristic or knowledge-based process development, which relies on the building up of prior knowledge and
experience for parameter selection and optimization, (2) process optimization through mathematical models to increase understanding of unit operations, (3) high throughput process development with the assistance of automation and data processing, and lastly, (4) a hybrid of all techniques. Literature reviews identify multiple articles for each technique individually, but very few highlight the effectiveness of a hybrid of techniques. This presents an opportunity for further research.

2.2 The Large-Molecule Drug Development Process

A biologics or large-molecule drug, as defined by the FDA, is a complex product that is derived from a natural source or living organism, typically Chinese hamster ovary (CHO) cells or E-coli. Biologics bind to cell receptors that are identified with a specific disease. Because of the complex behavior of biologics, they undergo a different drug development process, divided into upstream and downstream processing.

In upstream processing, the cell line for a protein is generated, cultivated or scaled up in media over several days, then harvested for further processing or filtration. Upstream processing is time-sensitive since the drug substance degrades over time in a bioreactor system. There are two dominant methods of cell culture used in the industry: fed-batch processing and perfusion. In a typical fed-batch process, a vial of drug substance is thawed over a few hours, pipetted into a shake flask with media addition for increased yield, then undergoes culturing over time, moving from a shake flask to eventually inoculating a bioreactor for production of large volumes. Centrifugation or filtration is then used to harvest the desired material for downstream filtration. In perfusion processes, the vial of drug substance undergoes the same process steps as those in fed-batch production, media is continuously added to the cell culture while harvest is done in parallel for material containing the desired protein. Fed-batch processes last up to two weeks while perfusion processes can run between one to two months [23]. This timing is influenced by the growth rate of cells during expansion and the expression rate of cells during production.
Downstream processing takes the cultivated material and purifies the desired protein through several filtration steps. Xenopolous [25] and Hanke & Ottens [26] provide templates for a typical downstream process for a monoclonal antibody (mAb), which consist of a Capture step via affinity chromatography for Protein A (ProA), the chemical inactivation of viruses, further filtration through two Polishing steps that use different types of chromatography, depending on the desired protein. Some examples of chromatography techniques used in these stages by industry are cation exchange (CEX), anion exchange (AEX), hydrophobic interaction (HIC) and mixed-mode chromatography (MMC). Alternatively, polishing steps may be separated by viral filtration steps. In some processes, gradient elution is used, followed by Viral Filtration, another flow-through chromatography process step, then a final filtration using Ultrafiltration / Diafiltration.

Both upstream and downstream processes provide samples that are used for further statistical analysis. These samples can undergo different assays which are lab tests that are conducted to qualitatively and quantitatively measure specific parameters for the target protein. These further contribute to the total process development lead time for a drug. In the 2016 High Throughput Process Development (HTPD) Conference [27], a more critical area for improvement cited by attending biopharmaceutical companies is the inconsistency in workflows when transferring samples from PD to analytics highlighting the need for coordination of the two to meet PD needs.
2.3 Trends in the Biopharmaceutical Industry Influencing Speed-to-Market and Productivity

2.3.1 Process Analytical Technology (PAT)

Several FDA guidelines and industry practices have been proposed in response to the growing need for increased productivity and cost competitiveness in the biopharmaceutical industry. One of these guidelines was Process Analytical Technology (PAT) which was proposed in 2004 as a response to a call for more innovative and risk-taking means of promoting more efficient production methods for as long as they maintain product safety [19]. The PAT framework proposes the use of in-line measurements to ensure compliance with quality standards, reduce production cycle time, increase capacity, reduce rejects and manage variability. The goal of PAT is enable process understanding to thereby control variability in the process. Some of the tools proposed under PAT include the use of at-line process analyzers and measurement systems, process control tools, multivariate tools for design and analysis, simulations and other tools that are capable of multivariate analysis and rigorous statistics [28]. With the increased use of continuous manufacturing processes, PAT is also needed to continuously monitor changes in critical quality attributes (CQA) [29]. Other recognized advantages of PAT include faster process optimization, reduced cycle times and FTE resource requirements due to the reduced need for offline sampling, increased process control and therefore increased quality.
As shown in Figure 2-3, Undey et al. [30] view PAT as integrating into biopharmaceutical PD in its collection of data in real time and timely optimization of the process to achieve desired product specifications. Simon et al. [31] reviewed existing applications of PAT in the industry, most notably in bioreactor monitoring, in focusing the realm on PD. Cramer & Holstein [32] also present principal component analysis tools for the prediction of protein A chromatography. While PAT applications continue to grow for PD, there is also a growing need for sufficient training among scientists for PAT techniques but also increasing potential for large data sets to be processed and analysed within the same or shorter period of time, with the help of software and in silico runs. This emphasizes the need for sufficient automation and capacity support for analytics in PD.

2.3.2 QbD (Quality by Design)

In 2005, the FDA also introduced Quality by Design (QbD) guidelines under the International Conference on Harmonization (ICH) as a means of designing quality into the manufacturing process of a drug. As defined by the FDA, QbD refers to “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [33].” Adoption of QbD would require more statistical rigor and appropriate risk-taking [34]. Under QbD, the Quality Target Product Profile (QTPP) and critical quality attributes (CQA) are first defined, comprising of the quality characteristics of a drug product that must be achieved, considering safety and efficacy [33]. The design space, which is a collection of DOEs to test the
interaction of critical process parameters (CPPs) and their effects on CQAs, is then defined, together with a control strategy and risk assessment that will ensure that the design space is met. Process validation and filing are then performed, followed by continuous monitoring of process robustness. The wider operating ranges contrast with the traditional process of finalizing a process within very tight operating ranges and ensuring that products are only manufactured within those ranges. The goal under QbD is to be able to develop a manufacturing process that produces the targeted product quality consistently.

As illustrated in Figure 2-4, QbD has a significant impact on Process Development, influencing the targets set within PD and the control strategy to ensure that the product meets the design space. In the 42nd Annual Meeting for the Drug Information Association (DIA), Amgen highlighted QbD as the “umbrella over the connection between Process Development, Process Characterization and Process Validation [35].” In this presentation, QbD was also described as an application of Juran’s principles for quality control, which are often used in conjunction with six sigma and lean practices. There are, however, limited studies that explore process improvements within PD performed in conjunction with QbD practices and tools.

![Figure 2-4: Quality by Design milestones](image)

Figure 2-4: Quality by Design milestones [36]. Reprinted by permission from Elsevier: Trends in Biotechnology. *Quality by Design (QbD)-based process development for purification of a biotherapeutic*, A. Rathore. © 2016.

Significant benefits from QbD have been estimated by past studies. Rathore [36] compared a QbD-based biosimilar (granulocyte colony-stimulating factor or GCSF) downstream purification process with the traditional process. The QbD-based process produced a larger operating range, enhanced process robustness, higher overall yield, a 3X reduction in process cycle time and 10X
improvement in productivity. A previous study conducted within Amgen [37] identified several potential throughput improvements that could be gained within Process Development as a result of QbD practices and corresponding management support. In one of the Amgen business cases examined for PD, a potential 80% reduction in cycle development time was identified per lyophilized stock-keeping unit (SKU).

The emphasis on creating a design space, control strategy and risk assessment by leveraging multiple data points, prior knowledge and design of experiments strengthened not only the need for PAT but also high throughput process development (HTPD) platforms that would enable the testing and analysis of multiple CPPs especially in a resource-constrained organization [38]. As more parameters are tested to define an operating range, more PD capacity will be needed for these DOEs. HTT is therefore viewed as a critical enabler for reaping the benefits of QbD.

2.4 Lean Principles in Drug Process Development

2.4.1 Measuring R&D Productivity

Since R&D processes do not produce an exact or standard product, several studies have attempted to define R&D productivity in a more quantitative and objective manner. Shimura et al. [39] define R&D productivity as a function of both efficiency and effectiveness, where efficiency measures the cost efficiency of developing a new molecular entity (NME) and effectiveness is the average value generated by the NME. In their 2014 study, scores were assigned to various biopharmaceutical companies for both efficiency and effectiveness. High numerical scores in efficiency translated into high efficiency while low numerical scores translated into high effectiveness. A data envelopment analysis (DEA) model (a method of gauging distance from the efficient frontier) is then used to translate the distance between efficiency and effectiveness scores into productivity. A highly productive company would therefore have a shorter triangular distance or low DEA score. Although there were limitations to the study, especially in the predictability of a drug’s marketability, the study showed Amgen as having a relatively high productivity score compared to its peers. There are opportunities to improve productivity by both increasing the number of NMEs explored, thereby requiring more efficient processes and development, and maximizing NME value through speed-to-market.
An alternative approach to defining R&D productivity is to use a translation of Little's Law, which is summarized in Equation 2-1. Paul et al. [1] adapted this and defined productivity as "the medical and commercial value created by a new medicine and the investments required to generate that medicine." The translation of this concept into R&D throughput as it relates to process cycle times, the actual number of programs in the pipeline, the potential value of the drugs, the likelihood of failure and the costs of development, are summarized in Equation 2-2.

\[
L = \lambda W 
\]

**Equation 2-1:** Little’s Law as presented by Little & Graves [16]. L refers to the average items in a queue or system, \( \lambda \) arrival rate of items per unit of time, and W the average waiting time in the system.

\[
P = \frac{WIP \times p(TS) \times V}{CT \times C} 
\]

**Equation 2-2:** R&D Productivity Equation as proposed by Paul, et al. [1]. R&D productivity (P) is a function of work in process (WIP), the probability of a program's technical success (p(TS)), the market value of the program if successful (V), the cycle time (CT) and program cost (C).
Equation 2-2 presents several levers that can be targeted to increase productivity. The probability of a target's success \((p(TS))\) and market value \((V)\) are difficult to predict and control, making the number of programs \((WIP)\), cycle time \((CT)\) and cost \((C)\) the key levers. Reducing cycle time and consequently cost through process improvements or process optimization could increase productivity. Other methods they suggested include waste reduction (lean) and six sigma practices on the critical path of development, introducing automation for rapid sample processing, use of information systems, reducing non-value adding wait times between development and, similar to other studies' suggestions, adopting a fail-fast approach by performing trials quickly to establish probability of technical success. Alternatively, it would be possible to increase the number of programs or WIP in the pipeline. Based on their model and failure rates (approximately 96%) and not considering market value, a typical biopharmaceutical company would have to maintain between 9 to 11 NMEs to successfully yield a single NME launch per year. Increasing WIP would, however, require sufficient development capacity and as identified by Paul et al., lack of capacity would result in a detrimental effect on cycle time, especially if available resources transform into the bottleneck [1]. In line with capacity management, careful portfolio selection and management would also be helpful in scheduling programs that have significant promise and appropriate timings relative to the resources available. For this reason, the authors recommended further research on estimating resources required and optimally balancing programs throughout the different phases of drug development.

2.4.2 Capacity Management Paradigms in New Product Development

Repenning & Sterman define net throughput as the rate at which inputs are successfully converted into outputs [40]. Throughput goals are actually endogenous and controllable by a firm’s management. When faced with a shortfall in throughput, their study has suggested three options: (1) expanding capacity, (2) using existing capacity more intensely (i.e. working overtime) and (3) repairing defective output. Since there is no way to repair the output in the case of PD, only the first two options seem viable. There are, however, consequences to each option, and both present a risk of unbalanced capacity and demand.

Because organizations that consist of R&D or new product or process development activities rely heavily on human capital, majority of R&D strategy issues have historically related to the management of human resources. Weil et al. [41] described the common issue of "workflow
bunching” where workload oscillates or is sub-optimally distributed across a workforce. In such situations, the organization experiences periods of undercapacity, followed by periods of overutilization. The periods of undercapacity are shown to increase backlogs and subsequent constraints on sequential downstream activities. When unanticipated problems occur in these situations of undercapacity, scarce resources must then be allocated or work overtime to complete tasks and solve these problems. Repenning’s study [12] describes this situation as “firefighting” which is a self-reinforcing phenomenon that imposes several additional costs, a higher chance of errors, burnout and a higher chance of missed deadlines. In the study, which made use of a system dynamics model to determine the effects of firefighting on overall performance in new product development, it was found that a temporary shock to the product development organization (e.g. overloading researchers with work), if large enough, could push the system beyond a tipping point that will lead to a permanent decline in performance. As FTE resource utilization increases, smaller shocks are needed to push the system beyond the tipping point and into the self-reinforcing loop of firefighting. The study also emphasized the need for capacity that is greater than the work that needs to be performed especially in the earlier stages of product development (e.g. concept development, design), since an organization that is at capacity will have little allowance for shocks that can push it over its tipping point. Moreover, building in some buffer capacity will allow an organization to take in more disruptions to the system, such as unplanned project cancellations, reprioritization or unexpected changes.

There is no universal policy for capacity management in R&D, especially since trade-offs to be made in one or more critical variables are ultimately dependent on management discretion. Weil et al. and Repenning therefore recommend conducting a study on understanding the combinations of factors producing workflow bunching and firefighting, and how the interactions of different policies may influence overall throughput. Such studies are currently limited in the realm of biopharmaceutical PD. Given the rising FTE requirements as the PD role becomes more active in the drug development process (Figure 2-6), it is important to manage programs so that FTE utilization is well balanced.
In response to managing workload in a PD organization, some studies have highlighted portfolio management and scheduling as a powerful means of addressing the root cause of workflow bunching and firefighting. Sax et al. [20] used the productivity equation presented by Paul et al. [1] to demonstrate the impact of focus on careful planning of experiments, focus on QTPP, portfolio management and restriction of data points to be collected on overall productivity. Based on their study, data-driven experiment planning and design have high potential to increase the value that can be gained from a drug over time (by speed-to-market) and reducing the cost (by gained efficiencies). Konstantinidis et al. [42] also demonstrate how strategic assay selection can help reduce the likelihood of analytics becoming a bottleneck for PD.

2.4.3 Cases of Lean Process Improvements in the Biopharmaceutical Industry

Lean process improvements are common proposals to improve productivity and are associated with reductions in overall waste, primarily through reduction in lead times and improvement of flow [43]. A framework proposed by Bellm [44] shows operational excellence as
stemming from a series of cooperating elements which include management commitment, a strategy for continuous improvement, empowerment and training of people, sufficient maintenance, quality control, standardization and visual management in manufacturing, portfolio clustering or scheduling, employing a pull-driven process, and transparency of key performance indicators (KPIs). These elements are visible throughout several existing cases on productivity initiatives and lean applications in the biopharmaceutical industry, but very few shed light on their application to an R&D process.

The applications of lean in the biopharmaceutical industry are varied, with majority of prior literature focusing on commercial manufacturing. Chowdary & George [45] enumerate some of the integrations of lean through a case study of a local manufacturer and distributor of pharmaceutical and non-pharmaceutical products. Through the use of tools such as value stream mapping, 5S and quality control, they managed to reduce non-value added time by 64% and WIP inventory by 86%. They also doubled workforce capacity and reduced floor space consumption by 38%. They also hypothesize that the slow adaptation of lean in pharmaceutical manufacturing is due to a mismatch between critical GMP (cGMP) practices and lean manufacturing practices, since cGMP promotes heavy inspection and quality control in the process. In another case presented by Federsel [46], continuous improvement at Merck resulted in a greater than 98% reduction in cost of steroid cortisone drug to treat rheumatoid arthritis within six years of its introduction to the market. In this study, he also emphasized the importance of finalizing the drug process as early as possible to reduce rework down the line.

Sewing et al. [47] proposed a toolbox of further lean tools that could be used to transform pharmaceutical R&D operations. Their toolbox includes the application of lean and six sigma tools to lead optimization in biopharmaceutical R&D. They suggest the parallel execution of projects and sharing of resources, thus balancing the utilization of costly equipment, and the implementation of a unified business process that will drive consultation of experts and discipline among teams, 5S and kaizen projects. Beyond the typical lean tools, they also suggested standardizing work to improve consistency, without sacrificing creativity. This was demonstrated through execution in Pfizer's Primary Pharmacology Group (PPG), specifically by employing generic liquid handling programs instead of scientists writing their own programs, resulting in reduced equipment downtime because programs were only written to the equipment capabilities.
The error rate on the liquid handling machines was monitored for 90 days and found to be consistently reduced after implementation of the standardized programs. As they summarized, "Greater than 90% of problems are because of ill-defined, unclear processes and a lack of training [47]." This focus on work design has been demonstrated to have significant improvements on productivity.

Similar approaches have been taken at the Broad Institute’s [48] genomic sequencing process which was in a constant state of “busy-ness” (firefighting) with no time for innovation. The researchers proposed the implementation of dynamic work design which is defined as the reconciliation of intent and activity, or matching work to the capabilities of the team implementing it. This consisted structured problem solving, setting optimal challenges or targets, and connecting the human chain by improving handoffs. Some notable improvements were a reduction of genomic sequencing of samples from 120 to 21 days (82.5%), improved machine utilization and line balancing from 50% to 85% by using a pull system for processing of samples and using visual management to match intent with work activity, reducing workload of staff by 50%. Rapid feedback also allowed them to maintain continuous improvement.

Amgen has adapted operational excellence in laboratory environments under what it calls “Lab Process Excellence (LPE)” which is a framework based out of the DMAIC (Design-Measure-Analyze-Improve-Control) model. Similar to DMAIC, the framework involves diagnosing a problem, mapping the process and collecting data, identifying improvements and implementing them with the support of management systems, then sustaining the gains while collecting data for analysis. In 2016, one Amgen project in the Medicinal Chemistry group focused on the optimization of the small-molecule Drug Design Cycle. Continuous improvement methodologies resulted in a 64% reduction in cycle time per compound. In 2017, the LPE team implemented standards for assay submission and processing for Attribute Sciences to support PD activities. The guidelines standardized formats for both physical and electronic handoffs (i.e. submission of assays) and assigned fixed schedules for specific programs to submit samples, thereby allowing them to phase upstream operations and manage capacity. Initial results showed at least a 55% increase in on-time assay turnaround despite some level of staffing attrition. The results paved the way toward increased interest in LPE initiatives within Pivotal PD.
2.5 High Throughput Technology in Drug Development

2.5.1 High Throughput Technology and Its Perceived Benefits

Resource allocation is interwoven with technology strategy [41]. Given this, existing literature has also recommended automation as an enabler for increased productivity. High throughput process development (HTPD) has been defined as “the combination of data processing and experimental techniques” [26] and “the combination of high-throughput screening techniques and fast analytics that is steadily augmented with methods of mechanistic modeling, process simulation and data processing tools [49].” Equipment and automation that enable this rapid processing of samples and data can be called high throughput technology (HTT).

The basic concept of HTT which will also be used in this study is illustrated in Figure 2-7. In the current state, a set of 24 loads would require 24 sets of runs on a low-throughput machine which can only take one load at a time and would require operation by one scientist, resulting in 24 work days and very high FTE utilization. A high throughput version of this process could ideally run multiple loads in parallel, resulting in a reduction of required FTE hours and time to just three workdays and therefore reduced utilization. HTT therefore has the potential to reduce cycle time and free up FTE capacity, which are crucial for rising demands on PD.

Figure 2-7: Conceptual FTE resource and cycle time benefits of high throughput technology

Aside from parallelism, other forms of HTT also enable high-volume processing whether through miniaturization or simple automation [38], complementing the introduction of PAT and QbD which require more rigorous and data-intensive statistical analyses. Larger DOEs and multivariate data analysis be performed with the help of HTT, enabling the generation of a larger
database of knowledge for future experimentation and potentially predictive analytics. As a result of this, the effectiveness of HTT is dependent on the availability of sufficient analytical support which is viewed as an area lacking sufficient advancements and, as a result, a typical bottleneck in automated systems [27][50].

### 2.5.2 Past Applications of High Throughput Technology

**Figure 2-8:** History of high throughput screening (HTS) in Pfizer [51]. Reprinted by permission from John Wiley and Sons: British Journal of Pharmacology, *Origin and evolution of high throughput screening*, D.A. Pereira & J.A. Williams. © 2007.

HTT has been used by several companies in the biopharmaceutical industry from as far back as the 1980’s. **Figure 2-8** illustrates a brief history of high throughput screening (HTS) applications at Pfizer until the 2000’s. Pfizer has used HTS techniques since 1986, beginning with the Drug Discovery group, which needed to increase screening capacity tenfold [51]. They used 96-well plates and miniaturized assay volumes compared to traditional methods which required 1 mL samples in individual test tubes, thus limiting capacity to a maximum of 50 compounds per week. This was supplemented by automation using robotics, resulting in increased process speed and decreased labor requirements. HTS produced hits for 40% of the Discovery portfolio, making it an essential part of the entire process. Similar to the identified gap in current advancements, Pfizer also struggled with data capture and analytics upfront. Bensch et al. [52] further emphasized the inverse relationship between the number of samples and the analytical effort and time required.
to process these samples (Figure 2-9). HTT is seen a means of balancing this relationship while capturing the same quality and amount of data.

![Figure 2-9: Correlation between experimental design and analytical effort](image)


HTPD studies that have benefited from HTT range from media screening, culture studies and QbD studies to process characterization. Publicized technologies are varied and include microwell plates, miniaturized samples in deep well plates, small-scale bioreactors, and integrated liquid-handling platforms for resin screening and chromatography [38]. Specifically, in PD for biologics, a number of studies and biopharmaceutical companies have shared their current investments in HTT.

Due to the relatively fixed cell culture lead time, upstream operations have focused on process characterization of several factors under complex DOEs. A typical upstream PD program uses six to eight lab-scale bioreactors with several rounds of DOEs that evaluate up to 10 parameters. The total duration of an upstream operation could take up to twelve weeks for CHO cell drug substances [53]. Since a single scientist may not be able to operate all bioreactors at once, this upstream process can become very labor intensive and costly. One of the most discussed HTTs in this operation is a miniaturized, 250-mL disposable bioreactor system which has been studied to be capable of completing 96 samples over an 18-hour period, which would normally have taken three shifts (or approximately 24 hours) in a manual system [54]. Shorter setup times were also observed as a result of the use of disposable bioreactors while automated sampling reduced labor intensity by up to 66% [53]. Several studies and biopharmaceutical companies have documented their use of this technology [30], [53], [55].
Advances in technology have shifted the focus of productivity efforts to other parts of the drug development process. Higher cell culture titer as a result of optimized media and improved techniques have shifted the “bottleneck” to downstream processing [32][38]. Much of the recent work on HTPD has focused on chromatography [32] which has proven to be challenging due to its multi-stage nature (bind-wash-elute) and the challenges of parallel workflows [50]. Loading is considered the most time-consuming step in continuous chromatography and although this may be done across several machines simultaneously, it increases capital costs and labor requirements [56]. HTT can resolve this problem through miniaturization of loads and columns, resin-containing micropipette tips and batch adsorption [32]. These, combined with a robotic liquid handling station, not only reduced cycle time and FTE requirements (three weeks for the work of one person in a study by Diederich, et al. [49]), but also reduced material required. In another study by Farrell et al. [57], 900 samples were processed in 24 hours.

Other HTT include the use of resin slurry plates to map the behavior of the target protein based on a wide range of key parameters on chromatography resins. This has been used for solubility and excipient testing as well as sample handling and preparation. Merck & Co, Wyeth, Genentech and Eli Lilly have all been documented to use this type of HTT for purification [27]. Bergander et al. [58] also identified a similar application of this technology combined with predictive mathematical models for the study of dynamic binding capacity (DBC) as part of downstream purification. The resulting comparison of DBCs predicted significantly reduced cycle time and experimentation, reducing time required tenfold and samples required by 50X.

Advances in technology for analytics has not been as prolific with analytics now viewed as the major bottleneck that relies on the effectiveness of the use of samples and subsequent generation of insights [32][52]. One notable technology is the adoption of UPLCs (ultra-high performance liquid chromatography) as a faster separation technique that uses higher operating pressures, smaller packings, automation and miniaturization of solid phase extraction. This is combined with offline parallel processing using automated solvent extractors, sampling robots [59]. Automated data capture and encoding in an electronic lab notebook still remain to be challenges across the industry and an area for improvement, especially if the use of HTT shifts to capturing larger data sets for prior knowledge development.
It should be noted that automation and the use of HTT should be done while considering the impact on maintenance costs, overall utilization of the equipment and resource allocation, especially if training will be required [27]. In some cases cited by Pollard et al. [27], a significant investment is often required to train either a specialized team of super-users or the entire PD team in general to use the new HTT. Specialized headcount for the operation of HTT was recommended as an effective means of overcoming the activation energy required for adoption of HTT. In a study conducted in Novartis' Drug Discovery group [60], automation was used in plate preparation, tool production, drug discovery screening and toxicology screening, minimizing human intervention but requiring engineers to run HTT full-time. The interactions of HTT with other policies within the PD organization must therefore be evaluated.

2.6 Applications of Simulation Modelling in the Biopharmaceutical Industry

Beyond the definition and management of capacity, the successful implementation of HTT relies on an understanding of the detailed workflow needed to run it [57]. Identifying the repetitive tasks that may potentially add delays to the overall workflow and anticipating their impact on the effectiveness of HTT is a necessary exercise in the implementation of HTT. Moreover, identifying bottlenecks in the workflow will aid the correct identification of appropriate technologies. Considering the process in its entirety and the human effort required to perform tasks can guide decision making, product selection and overall time savings [57]. Hanke & Ottens [26] have emphasized the importance of providing guidance for process development engineers or scientists through computerized "expert systems" that provide heuristics on approaching a process flow sheet. This need has been recognized in the development of multiple simulation models to evaluate not only of HTT but of other process improvement initiatives.

Process workflow simulation has been applied in several ways for biopharmaceuticals, each with limitations. Weil et al. developed a system dynamics model on DYNAMO that attempts to define the combination of factors that would produce workflow bunching. The simulation considers the skill levels of researchers involved and seeks to answer several questions:

- What is the appropriate allocation of human resources across programs?
What are the heuristics dictating the use and mastery of new technology before it is incorporated into a standard process?

What are the implication of speeding up the R&D process?

What are the interrelationships between technology and productivity?

Thedinga [61] developed a Monte Carlo simulation model to forecast FTE and production capacity requirements for Novartis. The simulation provided a high-level overview of the entire production process, focusing mostly on manufacturing and not on PD. A standard estimate of FTEs required for each process was used, instead of trying to obtain actual FTE requirements based on individual process cycle times of each unit operation. Any future process improvements such as the application of lean techniques would require significant reprogramming of simulation, therefore leaving an unsustainable solution and tool. Varma et al. [62] took a similar Monte Carlo approach to determine the effect of resource allocation and scheduling on portfolio performance for pharmaceutical R&D, but considered all possible resources including contract research and contract manufacturing organizations. The simulation only explored the cycle times for the high-level processes and success probabilities for Phases I to III, not showing a breakdown of unit operations. In this model, all programs competed for the same pooled resources, including PD, which is not necessarily reflective of actual scenarios. Rajapakse et al. [17] developed a similar model on a different simulation package, but conducted an extensive scenario analysis to determine the influence of both external (e.g. market share captured, drug pricing, competition, clinical trial time) and internal factors (e.g. contract manufacturing time, quantity of material, batch size, personnel available) on the total net present value (NPV) of a drug. As shown in Figure 2-10, FTE unavailability has a significant influence over a drug’s potential value, highlighting the importance of capacity management. Farid et al. [63] similarly developed a tool to properly allocate operators in a manufacturing facility for cell culture with the objective of maximizing worker utilization. Aside from focusing on commercial-scale manufacturing, the model only provided a high-level view of manufacturing with no model validation.
Figure 2-10: Tornado diagram detailing the influence of various factors on an NPD’s value [17]. Reprinted by permission from John Wiley and Sons: Chemical Engineering & Technology, Modelling of the biopharmaceutical drug development pathway and portfolio management, A. Rajapakse, N.J. Titchener-Hooker, S. S. Farid. © 2005.

An alternative approach to capacity management is to manage the product portfolio and timing of its experimentation. A study conducted at Novartis [64] built a simulation model to predict the probability that a drug program will transition from one phase of the drug development process to the next, but only provided a high-level overview of these processes without understanding the FTE resources required for each transition. A number of simulation-optimization models were also built to improve program pipeline management and resource allocation. Little research exists for similar approaches applied to process design and production planning decisions [65]. In the mixed integer linear programming model and Monte Carlo simulation developed by Marques et al. [65], the focus was on small molecule drugs. A major limitation of the model was that it assumed that capacity expansion would occur to meet demand, without elaborating on how this would be done. This study, however, successfully emphasized the strong influence of process design configurations and scale-ups on the success of clinical trials, which provide the information necessary to advance decision-making regarding process selection and risk mitigation. Subramanian et al. [66] and Gatica et al. [67] adopted a different approach by treating profit maximization rather than throughput maximization as the objective function of their deterministic integer linear programming model for R&D pipeline management. Although this model allowed appropriate scheduling to maximize potential financial gain, it allowed FTE resource capacity to be overbooked, therefore leaving issues of firefighting or bunching unresolved.
Perez-Escobedo et al. [68] approached portfolio management of new products in the pharmaceutical industry by developing a discrete event simulation to appropriately select and schedule programs to populate the drug pipeline while managing the uncertainty of success at each phase of development. This particular study introduces PD in two phases (similar to Amgen’s use of CPD and PC), explores fed-batch processing for biologics and estimates PD as taking 600 to 1000 days or roughly 6.7 to 11 quarters. Similar to the study by Paul et al. [1], the study also recommends nine concurrent drug programs as the standard quantity. However, the simulation looks at drug development from a very high level perspective, using triangular distribution for the estimated time required for each phase due to lack of available data on actual lead times. The simulation also does not consider the impact of automation technology nor other process improvements that may potentially increase productivity. The design of simulation models in existing literature therefore point to gaps in analyzing high throughput technology and lean improvements, and how they may interact with other factors that contribute to productivity.

Although this extends beyond the scope of this research, the impacts of mechanical failures and material selection for specific target profiles’ cycle time requirements and success rates. To understand these dynamics better, companies can use mechanistic and in-silico models to predict performance, minimizing material and FTE resource wastage [32], [69]. With the growing use of continuous manufacturing processes in biopharmaceutical companies, there will also be an increased demand for models that can test process sensitivity to various disturbances and trace potential causes of failure for further intervention [70].

Although available simulation models provide powerful tools for biopharmaceutical companies to assess factors and predict performance, current studies are limited to demonstrating the simulation’s effectiveness with little suggestion on potential heuristics or policies based on the results derived.

2.7 Gap Analysis from Literature Review

This review of existing literature has identified several opportunities for further research that this thesis can expect to explore:
• **Refocus of scope on pivotal process development for large molecule drugs:** Existing studies discuss process improvement in the context of commercial manufacturing for small molecule drugs, though biologics have a higher growth rate in the industry, and failure risks and higher costs are incurred during process development and drug development phases. There is therefore an opportunity to conduct research on this phase of the drug development process.

• **Exploring interactions between lean process improvements and high throughput technology relative to PD productivity:** Past studies have treated maximization of a drug's market value or a company's profitability as the objective function of simulation models and productivity initiatives, though insufficient PD capacity has been demonstrated as a significant factor influencing drug NPV. While limited studies already exist which explore lean tool applications and high throughput technology separately, no research exists examining the combined impact of the two on a PD organization for biologics. Specifically, studies have yet to use increased program throughput and balanced FTE utilization as their primary metrics of success.

• **Capacity improvement and resource management beyond outsourcing and capital investment on facility expansion:** Existing studies focus on new statistical methods, portfolio scheduling, outsourcing to contract research organizations (CROs) or contract manufacturing organizations (CMOs) and simply investing on more capacity (i.e. hiring more staff, expanding a facility). There is an opportunity to explore the optimization of an internal system to generate additional capacity, instead of relying on external entity.

• **Methodology of combining lean process improvements, process design and process flow simulation with a granular focus on unit operations:** Most literature approach productivity improvement with a high level review of drug development phases, rather than examining the limitations and opportunities for improvement in individual unit operations, and their sensitivities to various internal and external system factors.

• **Heuristics for effective use of high throughput technology:** Various high throughput technology applications have been suggested across unit operations in process development, but factors that may influence their effectiveness in a PD system have yet to be explored.
Chapter 3  Current System Analysis

This chapter sets the stage for the two approaches that will be undertaken to address the problem under study. It details the diagnosis of the root causes behind the problem of insufficient pivotal PD capacity and based on their classification into waste types, prioritizes the lean principles to apply to address the causes. An evaluation of current process cycle times and available high throughput technologies is presented to illustrate the need to evaluate the potential efficiencies to be gained from their application.

3.1 Problem Diagnosis and Root Cause Analysis

3.1.1 Organizational Evolution of Process Development Operations

To better understand the dynamics behind the current pivotal process development (PD) organization, we must revisit the recent history of its formation. Pivotal PD is the result of the merger of two previously separated organizations. Commercial Process Development (CPD), which is the process by which the manufacturing process is defined, was formerly an R&D activity, while Process Characterization (PC) or testing the robustness of the process, was under Operations. After a major organizational transformation across Amgen, the two phases were merged into one, which would fall under the new group called “Process Development.” Although program teams now work on both phases, several issues still arise from the lack of alignment between the two culturally different and formerly separate entities. The adjustment to the new work dynamic, combined with a gradual development of prior knowledge and experience in various modalities has led to this initiative to explore process improvements within the new Pivotal PD organization.

3.1.2 Diagnosis, Results and Root Cause Analysis

Macroscopic and microscopic approaches were taken to diagnose the root causes behind the problem of insufficient capacity in pivotal PD which manifests itself through symptoms of constantly busy FTEs and a consistently high level of utilization (>100%). In the macroscopic approach, interviews and focused group discussions were scheduled with twelve upstream and downstream scientists to understand the various factors delaying completion of CPD and PC. Scientists with over ten years of experience working in two key Amgen Pivotal PD sites in more than one type of modality were selected to capture more long-term and recurring problems. An interview questionnaire was designed with the purpose of describing the current method of
designing and executing experiments, and identifying pain points within the process that contributed to the key problem. The questionnaire can be found in the Appendix. Responses were compiled and classified into an Ishikawa diagram which was then used to derive the root causes. To thoroughly investigate the root causes, the Why-Why method was integrated with the Ishikawa diagram, determining the “why” or reason behind each cause until the root cause is found. The repeated questioning and brainstorming during interviews of scientists enabled this analysis.

**Problem Definition:** Pivotal process development requires a long lead time and FTE resources.

**Material**
- Some experiments have to be repeated due to contamination or failed tests.

**Root Cause #1: Material unavailability.** Input material is not always readily available, requiring additional experiments to support downstream experiments. Lab associates consequently have to accelerate process times and multitask to meet deadlines.

**Man**
- There are insufficiently trained lab staff available to conduct experiments and available lab hands can take more time to conduct experiments.

**Root Cause #1: Insufficient training references.** Scientists are not fully aware or tend to forget the standard process steps when actual experimentation begins. Training for CPD and PC is only performed once, at the beginning of onboarding, before any actual experimentation occurs.

**Root Cause #2: Insufficient or variable standards for experiment design.** Experiments are designed freely by FALs and DSTLs with no standard format. There are limited guidelines and varying standards for the typical CPD and PC process. Prior knowledge reports are not updated following organizational changes.

**Method**
- Experiments generate more data than what is actually required for Quality Target Product Profile (QTPP) or for filing.
Root Cause #1: Insufficient or variable standards for experiment design. There are unclear and unstandardized guidelines on the appropriate number of runs, standard process steps and timelines. Varying standards lead to different program timeline estimates which may be arbitrarily set and not reflective of the minimum amount of time required.

Root Cause #2: Insufficient means to leverage prior knowledge. Prior knowledge is not used as a source of data when designing experiments. Prior knowledge reports are not updated and there are insufficient guidelines on how to access prior knowledge. There are no established "subject matter experts" within the organization and scientists rely on their familiarity of the network and organization when seeking advice.

Root Cause #3: Unclear guidelines on standard experiments that define a typical pivotal PD CPD / PC program. Many ad-hoc or additional experiment requests are made to both DS and AS, and it is unclear which to prioritize with respect to new product filing.

Root Cause #4: Lengthy decision-making process. There is a lengthy decision-making and issue resolution timeline since the forum to raise these concerns occurs once a month.

- Scientists spend a lot of time writing experiment reports.

Root Cause #1: Insufficient standards and lack of compliance in data entry. The electronic lab notebook (ELN) that was recently implemented has opportunities to improve in usability. There are no standards or templates for use during reporting, so formats and content can vary across program teams.

- There are delays from the time of sample drop-off and experiment start and actual assay processing.

Root Cause #1: Distance or unnecessary transportation. The DS experiment is not co-located with the assay required, requiring shipment of samples to another Amgen PD site. At one PD site, the DS scientist must make at least two trips up and down a flight of stairs to retrieve media and samples for upstream processing.

Root Cause #2: Undefined information handoffs and requirements. AS is not always aware of what upcoming DS requirements are and are consequently unable to schedule resources accurately. Similarly, analytical method development is not always completed on time since FTE resources to develop the method are either unavailable or dealing with a high workload.
Root Cause #3: Multiple information handoffs. There are multiple information handoffs regarding assay requirements and these handoffs vary across programs. In some programs, questions regarding assay requirements can be passed four to five times before a response is obtained.

Machine

- Some equipment breakdowns and bioreactor failures can affect experiment success rates.

Root Cause #1: Equipment age or obsolescence. Some equipment has already exceeded its useful life and needs replacement.

Root Cause #2: Waiting on third-party maintenance. Equipment repair times can be slow due to no in-house technician available. These can lead to delays in the maintenance of the equipment, despite the establishment of preventive maintenance schedules.

- Scientists have to perform several runs on one machine multiple times.

Root Cause #1: Limited equipment capabilities. The equipment used is only capable of running a limited set of samples at a time. Scientists would have to multitask across multiple machines to complete several runs at once.

3.1.3 Problem Classification and Prioritization

Instead of addressing the issues individually, the root causes were grouped according to the seven wastes proposed by Toyota [43] with the objective of proposing broader solutions. The seven wastes refer to (1) Waiting, (2) Overproduction, (3) Transportation, (4) Processing, (5) Inventory, (6) Defects and (7) Motion. During the classification exercise, the root causes could only be classified into five of the seven wastes. The results are summarized in Table 3-1. Although there are some opportunities in the organization of the lab to reduce unnecessary motion and transport of materials (6S) and reduction of equipment failures (preventive maintenance), these are smaller improvements that Amgen has already begun to explore with its Environment, Health and Safety team.
<table>
<thead>
<tr>
<th>Waiting</th>
<th>Overproduction</th>
<th>Transportation + Motion</th>
<th>Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Material unavailability</td>
<td>• Insufficient or variable standards</td>
<td>• Distance or unnecessary transportation</td>
<td>• Equipment age or obsolescence</td>
</tr>
<tr>
<td>• Lengthy decision-making process</td>
<td>for experiment design for CPD/PC</td>
<td>• Multiple information handoffs</td>
<td>• Waiting on third-party</td>
</tr>
<tr>
<td>• Undefined information handoffs</td>
<td>• Insufficient means to leverage prior</td>
<td>• Non-compliance with data entry</td>
<td>• Maintenance</td>
</tr>
<tr>
<td>• Waiting on third-party</td>
<td>knowledge</td>
<td>standards</td>
<td>• Limited equipment</td>
</tr>
<tr>
<td>maintenance</td>
<td></td>
<td></td>
<td>capabilities</td>
</tr>
</tbody>
</table>

Based on the root cause analysis, there appears to be a more fundamental issue in the actual process design and definition of value to the customer. In the case of pivotal PD, the customer would be manufacturing, which will then adopt the process designed into a large-scale operation. With majority of the wastes concentrated in waiting, overproduction and processing as a result of poorly defined guidelines and standards, standardizing then optimizing experiment design is recommended as a first step to addressing the problem of limited capacity. As suggested by Womack and Jones, specifying value and forming “a clear view of what is really needed,” is the first step to lean thinking [43]. Beyond the definition of value, there is also a need to create a structure to support decision-making around changes to this work design over time, especially when things do not go according to plan. Defined as “dynamic work design” by Dodge et al. [48], this process of designing work to match the capabilities of the organization and creating structures to support changes to this work, can enable improvements in organization efficiency. This aligns with the LPE framework outlined in Figure 3-1 and the focus of this study of long-term process changes over quick wins.

**Figure 3-1:** The Lab Process Excellence (LPE) framework
3.2 State of High Throughput Technology Implementation

3.2.1 Process Flow Mapping and Results

Limited equipment capabilities, especially in terms of batch size, were also identified as a root cause behind delays in experimentation. To better understand the impact of these limitations, a quantitative approach has been taken to identify bottlenecks in the actual CPD and PC process steps, then match them to available high throughput technologies that may potentially address limitations in capability. Due to the absence of accurate timestamps for the start and end of individual process steps within unit operations, data points on cycle time were collected through time-and-motion studies of process steps within experiments and interviews of downstream and analytical operations leads. A separate data collection was also made for touch time or FTE hours spent on each process step, which will be useful for determining the potential impact of high throughput technology on the process. Table 3-2 illustrates which process steps contribute the most to the total cycle time of each unit operation and therefore the bottlenecks of upstream and downstream operations. Process steps contributing 70% of the cycle time are highlighted as the focus areas for improvement. An assessment of available high throughput technologies can therefore be made based on their ability to address these bottlenecks.

Table 3-2: Summary of process cycle times across unit operations in pivotal PD. Highlighted process steps represent ≥ 70% of cycle time while steps in red are currently exploring high throughput technologies that can influence cycle time. The red process steps have not yet implemented high throughput technology (HTT) and therefore do not yet reflect the effects of HTT.

<table>
<thead>
<tr>
<th>Process Phase</th>
<th>Upstream (Cell Culture)</th>
<th>Downstream (Purification)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Val Thaw</td>
<td>Scale-Up</td>
</tr>
<tr>
<td>% of total phase</td>
<td>1%</td>
<td>17%</td>
</tr>
<tr>
<td>Material Preparation</td>
<td>58%</td>
<td>5%</td>
</tr>
<tr>
<td>Equipment Setup</td>
<td>16%</td>
<td>22%</td>
</tr>
<tr>
<td>Initiation</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Processing</td>
<td>5%</td>
<td>66%</td>
</tr>
<tr>
<td>Sample Handling</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Data Handling</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Cleanup</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>11%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>4%</td>
<td>11%</td>
</tr>
</tbody>
</table>

As detailed in Chapter 2, there are several ways by which an organization can benefit from high throughput technology which include reducing total cycle time by performing multiple runs in parallel, reducing total FTE touch time requirements (thereby freeing up capacity), and
allowing collection of more data points, thus building up prior knowledge which can potentially be used to reduce experimentation in the future. As shown in Table 3-2, the current HTT being explored do not account for the entire unit operation, mostly covering material preparation until sample handling. This therefore means that the total cycle time benefits that may potentially be realized may not be directly translated into 100% of the unit operation in which the HTT is implemented. The same principle applies to the potential reduction in FTE touch time that may be obtained from the use of HTT.

### 3.2.2 Upstream Operations

![Figure 3-2: Breakdown of process cycle times in upstream operations](image)

Upstream operations, whether fed-batch or perfusion, are constrained by the naturally long lead time to culture cells. As shown in Figure 3-2, majority of the upstream unit operations are defined by a "monument" processing step. Other potential areas for improvement include the vial thaw process which is still significantly manual in nature and in the equipment setup. Vial thaw typically requires only one scientist for the operation but takes a long period of time for material preparation due to the gradual thawing required for the material. Vial thaw, however, only comprises 1% of the total upstream operation cycle time, therefore improvements to this process will have minimal impact. The focus should therefore be on the actual scale-up activity which can consist of several scale-up "N-steps." Scale-up activities do not differ much between CPD and PC.

Amgen is exploring a demo system of two disposable, single-use 250-mL bioreactors capable of fed-batch and perfusion process development and characterization for both mammalian and
microbial profiles. Once fully qualified, the demo unit is expandable to the full 12 and 24-vessel system with an automated liquid handling and sampling, and process-control software integrated into the system, allowing one scientist to control all bioreactors simultaneously instead of relying on the help of two or three more scientists. The key benefits that can be derived from this system are in the number of FTE hours required to perform each process task and the scale of factors that can be studied in DOEs within the same period of time.

In the standard system, a smaller set of larger bioreactors is used to run a smaller set of parameters in the same period of time. This setup requires two to three scientists for equipment setup and monitoring, and relies on several hours of cleaning time after use, which is currently outsourced to a third party service provider. The larger volume in the current bioreactors also presents a higher risk of material wastage in the event of contamination or equipment failure, which consequently impacts cost. With its scaled-down setup, this bioreactor system aims to address the high FTE requirements and costs. Internal studies have estimated at least a 30% reduction in material costs and a 60% reduction in cleanup time conducted by the third party. It should be noted, however, that scale-up or processing times remain the same, since the technology does not actually accelerate cell culture, but enables collection of more data points. Limited alternatives are currently being explored and expertise has yet to be developed for upstream continuous manufacturing practices. For this reason, the focus of this study will be on the miniaturized bioreactors.

3.2.3 Downstream Operations

Downstream operations can be conducted in parallel, but still consist of several experimental runs, some of which using similar technology. As discussed by Hanke, et al. [26], Capture and Polishing steps generally use similar chromatographic separation technologies, depending on the types of impurities to be removed. Viral inactivation remains a manual process performed using a stirring rod and beaker, while filtration activities (Viral Filtration and Ultrafiltration/Diafiltration) can be run on a similar machine. A single scientist is assumed to perform a single experiment and complete the necessary documentation for it. This means that a single scientist will perform Capture end-to-end, instead of having multiple scientists step in during the process. As shown in Figure 3-3, downstream processing activities contribute the most to total cycle time, followed by sample handling and equipment setup. A closer examination of
process steps reveals that this is driven by the large number of samples and runs that have to be set up and purified individually. Unlike upstream operations, the CPD and PC time requirements are different for downstream because of the larger set of parameters being explored for robustness (Table 3-3). As a result, the benefits of HTT will be best realized in PC, primarily through parallelism and processing larger run sizes for the same number of FTE resources.

![Figure 3-3: Breakdown of process cycle times in downstream operations](image)

**Table 3-3: Comparison of average CPD and PC run sizes**

<table>
<thead>
<tr>
<th>Downstream</th>
<th>PC increase in number of runs from CPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capture</td>
<td>25%</td>
</tr>
<tr>
<td>Viral Inactivation</td>
<td>0%</td>
</tr>
<tr>
<td>Polishing 1</td>
<td>100%</td>
</tr>
<tr>
<td>Polishing 2</td>
<td>150%</td>
</tr>
<tr>
<td>Viral Filtration</td>
<td>0%</td>
</tr>
<tr>
<td>UF/DF</td>
<td>100%</td>
</tr>
</tbody>
</table>

For Capture and Polishing steps, Amgen is currently generating data to support the qualification of an automated liquid handler and parallel chromatography system that can be operated by one person and is capable of running multiple packed resins and eight times the number of loads compared to the current system. The system is currently being studied for different types of purification techniques, ranging from resin batch binding, flowthrough chromatography to bind-elute chromatography. Experience in the use of this equipment has been
developed in the past 5 to 7 years, with scientists using the same technology to high-throughput screening activities on multiple well plates and cell culture handling. The oldest among the HTT being explored, this technology has the highest level of readiness and also influences more than 75% of the cycle time for purification steps through parallelism. Because of its ability to process multiple resins in parallel, this allows one scientist to purify multiple loads in the same period of time, reducing overall cycle time as a result of fewer runs, and freeing up FTE capacity.

Another high throughput technology being explored is for a parallel filtration system for UF/DF operations. Amgen is currently training scientists on the use of a multi-train normal flow filtration device which allows operation of up to five trains in parallel with a single control system, enabling one scientist to operate all trains simultaneously. Data collection is centralized in a single graphical user interface and initial feedback from scientists undergoing training is that the usability of this new system is better than that of the current. The system has a smaller footprint and also uses disposable pressure sensors on the feed lines of filters which makes pressure data collection and calibration easier. Like the chromatography system, this HTT provides benefits through parallelism, especially in process characterization where there are larger run sizes. This has the potential to influence equipment setup and processing which constitute 81% of the total cycle time for UF/DF processes.

3.3 Summary of Focus Areas for Dual Approach Investigation

Given the limited timeframe for analysis, an assessment of the current system allows us to focus the study and process improvements on specific aspects in Pivotal PD under the two approaches. The qualitative root cause analysis and classification performed highlights the need to prioritize more fundamental process design changes over the typical application of lean tools like 6S and equipment maintenance. These make the Lab Process Excellence (LPE) framework an ideal approach for resolution of long cycle times and limited FTE capacity. The focus of the first approach will therefore be on the specification of optimal work design, driven by the application of standard work and the creation of support structures to manage process changes and risks.

The quantitative analysis of high-level bottlenecks paves the way for a closer examination of where high throughput technology (HTT) benefits can be gained. In the assessment of current HTT initiatives in Pivotal PD, upstream operations are likely to benefit more in the form of freed
FTE capacity, while downstream operations have the potential to improve in both cycle time and FTE capacity, as a result of parallelism of runs. Operations that have significant increases in runs under Process Characterization (PC) also have a high potential of benefiting from HTT. It is evident that these benefits are not directly transitive and are likely to be influenced by other factors that should be explored in greater depth under the second approach of HTT.
Chapter 4 Working Faster: Lab Process Excellence in Experimental Work

This chapter discusses the application of three principles to optimizing experimental work design with the objective of reducing cycle time and increasing FTE capacity. The development of a rightsizing tool, management system and streamlined process are described. In the absence of active programs for pilot testing, a retrospective study was performed using past program experiments to assess the potential impact of the proposed tools. Simulation is also proposed as a means to validate the streamlined process.

4.1 Defining Optimal Experimental Work Design

4.1.1 Current Method of Experiment Design

Interviews were conducted with functional area leads (FALs) and other scientists involved in program experiments to determine how they currently plan and design experiments. Scientists can use different formats and documents for outlining experiment details, ranging from Excel to Word files. These files can be stored in a shared folder accessible to teams or communicated over e-mail. Quick reviews of these records indicate that the number of runs and parameters tested in upstream and downstream operations have opportunities for some level of standardization or guidelines in specifications such as the number of runs, time requirements and prioritization of experiment types.

Although there is no standardized process for accessing prior knowledge from past experimentation or a formal set of updated playbooks on designing CPD and PC experiments, several touchpoints have been established between program team members and stakeholders to maintain regular updates and immediately resolve any program issues. Discussions on experiment design and program issues occur between DS team leads and the FALs through one-on-ones which are scheduled weekly or as needed to discuss. Full program team meetings are scheduled as needed. A monthly team meeting is organized by the project manager, who belongs to the life cycle management group. This meeting is attended by the DS team lead, AS team lead and FALs to discuss specific program issues which may potentially impact the program timeline. Issues that are unresolved or which require management review, guidance or approval are compiled in a deck and presented in the pivotal portfolio review meeting which is held once a month. Senior PD
management, resource planners and scientists join this meeting to provide their insights and make decisions to address any issues raised. A “hot topics” meeting has also been scheduled as a means to gain regular updates and to quickly escalate any critical issues. Ad hoc meetings can also occur to immediately resolve issues that may derail program timelines. These touchpoints illustrate a management system that can be leveraged to support any process improvements or changes.

The interviews have demonstrated that program team leads and members have a range of experience and history with Amgen which is manifested in a spectrum of practices related to experiment design, record-keeping, use of prior knowledge, report development and information handoffs. When combined with limited forums where they can share knowledge and align best practices, this variety of practices can potentially result in longer cycle times and other forms of waste which can be reduced by optimizing work design. To address these opportunities in improving pivotal PD experimental work design, several principles under the Lab Process Excellence approach can be explored which do not just focus on simple lean improvements but also revisit some fundamentals of experiment design.

4.1.2 Key Principles for Optimizing Experimental Work Design

Despite the many other improvement areas identified in Chapter 3, the focus of the first approach of Lab Process Excellence is on the design of experimental work itself as the root cause behind limited resource capacity. Optimal experiment design aims at maximizing information gained from a set of experiments [52]. There were three principles proposed to optimize experimental work design in pivotal process development (Figure 4-1):

1. Rationalize or rightsize the number of experiments: Developing tools to help scientists prioritize experimentation with some amount of risk-taking.
2. Leverage prior knowledge: Enforcing the access and use of prior knowledge gained from past experiments.
3. Streamline select processes between CPD and PC: Combining select processes to reduce overall cycle time.

To enforce discipline behind all of these principles, there must be continued support from top management through an established form of governance or management system. Womack and Jones [43] proposed installing business systems to promote lean thinking and to ensure that any process improvements become self-sustaining.
The theme of the principles suggested in Figure 4-1 aligns with a previous study on the dynamics of process improvement where Repenning and Sterman [40] documented a series of improvements made to New Product Development process of a company with the goal of increasing the speed of development and increasing throughput by 50%. In the paper, three changes were made to the product development process which were intended to result in “working smarter”:

1. Provide a detailed documentation of customer requirements.
2. Propagate learning through a “bookshelf” of past learnings and establishing a "wall of innovation" project gate where the bookshelf will be used, instead of spending time and resources to create something new.
3. Increase discipline by using a stage-gating system to enforce the wall of innovation.

In this framework, we can see the proper definition of customer value, the collection of only the right amount of data to provide this value, and the development of management systems to enforce the access of this data. A similar framework was suggested by Spear [71] under the four capabilities of a high-velocity organization, which include:

1. Designing work to capture existing knowledge and reveal problems
2. Containing problems to build new knowledge
3. Sharing new knowledge throughout the organization
4. Securing management support to lead and develop the first three capabilities

This creates a properly enforced system that will sustain the flow of programs and consequently the throughput of the process development organization.
4.2 Rightsizing Process Development Work

4.2.1 Development of Rightsizing Template

Sax et al. alluded to the importance of having a clearly defined set of experiments and a clear definition of requirements from any clinical trials based on the Quality Target Product Profile (QTPP) [20]. In anticipation as well of the use of high throughput technology, data templates would provide scientists with guides for optimized experimentation and analysis of data [27]. The objective of rightsizing is therefore to develop a sustainable and usable tool that could be integrated into the current and future management system. The following factors were considered while designing the templates:

- **Work design**: Based on past, “model” programs, what are the typical upstream and downstream experiments conducted, and corresponding analytical assays used?

Standardization is a key lean principle applied to reduce variability in the number and type of experiments. We defined a standard set of experiments that would be performed in each program, leaving room for scientists to propose additional or ad hoc experiments, if needed. This would therefore shift the mindset from performing all desired experiments to managing by exception. Process development reports from exemplary programs were taken from the quality management database and used as references to generate an initial list of proposed upstream and downstream experiments to be conducted. This initial list was then placed through multiple reviews by experienced scientists who provided additional insights on essential, value-adding experiments to add to the list.

- **Information handoffs**: What information does each program team member need to receive in order to keep the process flowing?

As Spear suggests in the design of complex work systems, once the objective (i.e. the program, experiment and purpose) and pathway (i.e. the scientists responsible for delivering the output) are defined, the next step is design the connections between process steps [71]. In this stage, we must determine the triggers that signal someone to start or stop his or her work, and what form the information must take during handoffs. Since a parallel initiative has already tackled physical sample handoffs between DS and AS, the focus of this rightsizing tool is to define the information that AS would need from DS to fulfil its work effectively and efficiently. Since the intention is to
minimize handoffs and opportunities for error and variability, this information should be stated upfront, with a single handoff of this filled-in rightsizing template. Figure 4-2 breaks down the generic process steps within AS and the corresponding details required at each phase. All of the information collected by AS is essential to the allocation of analysts, the maintenance of an assay cadence or program submission schedule, and the monitoring of assay turnaround times for performance improvement initiatives.

Figure 4-2: Information handoffs within Attribute Sciences (AS) process steps

- **Information handoffs:** What information will allow senior management, resource planners, program team leads and project managers to make effective decisions?

Similarly, information handoffs by DS to key managers and team leads need to be defined to inform future decisions. This must also be defined upfront in a single template since there is only a single handoff point (the Pivotal Portfolio Review meeting) available each month for this. Table 4-1 summarizes the various stakeholders in that meeting, their objectives and required information. The information points were compiled into the same template used to define DS to AS handoffs.
Table 4-1: Information required for handoffs during pivotal portfolio review meeting

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>DS and AS Team Leads</th>
<th>Life Cycle Management Planners</th>
<th>Senior PD Management (Directors, Executive Directors)</th>
</tr>
</thead>
</table>
| **Objectives** | • To secure approval and resources to proceed with program  
| | • To gain further guidance on program implementation | • To manage the timely implementation of concurrent programs  
| | | • To properly allocate limited resources available | • To review all incoming and ongoing programs, their statuses, risks and overall impact to targeted completion timelines or objectives |
| **Information Required** | • Approval to proceed with program start  
| | • Potential risks and/or improvements | • FTE resources required  
| | | • Estimated experiment duration  
| | | • Number of experiments | • Rationale for ad-hoc experiments  
| | | | • Anticipated experiment risks  
| | | | • FTE resources required  
| | | | • Estimated experiment duration |

- Data management: *How should the data be presented so that it can be easily harvested in the future by machine learning and data management tools?*
- Usability: *What format would require a minor learning curve and can easily integrate into the current and future information and management systems?*

Instead of creating delays due to a learning curve, it is appropriate to use tools that most team members are familiar with. An examination of the current tools used by scientists to plan their experiments narrowed down to Excel, JMP (a statistical platform), the electronic lab notebook (ELN) and Word files. Excel was selected due to its ability to be converted into a variety of searchable formats. Significant learning curves were involved for JMP and ELN, while Word files left too much flexibility for customization.

Excel templates were generated from the combined inputs, which are proposed to be made available through one of the existing online platforms being used by scientists. Figure 4-3 shows an example of a rightsized experiment template with each "Focus Area" representing an experiment under each unit operation. Four templates were prepared for CPD and PC upstream and downstream, then presented to experienced scientists, top management and the actual
scientists who would be filling out the templates. Feedback received from all parties was used to improve the templates to an ideal state for pilot testing. Significant improvements can still be made to the overall usability of the form by adding dropdown menus or linking the form to a database of past experiments. These features can be explored once the templates are incorporated in the current document management system.

<table>
<thead>
<tr>
<th>Unit Ops</th>
<th>Focus area</th>
<th>Objective of work if including or rationale if excluding</th>
<th>Number of bioreactor blocks</th>
<th>Start Date</th>
<th>End Date</th>
<th>Duration (wks)</th>
<th># other samples</th>
<th># Product Quality (PQ) samples</th>
<th>PQ assays (Assay 1, Assay 2, etc.)</th>
<th>Total # PQ samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-1 / N-0</td>
<td>Standard Focus Area 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upstream</td>
<td>Standard Focus Area 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-0</td>
<td>Standard Focus Area 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-1 / N-0</td>
<td>Standard Focus Area 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-0</td>
<td>Standard Focus Area 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-1 / N-0</td>
<td>Standard Focus Area 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expansion stages / N-0</td>
<td>Standard Focus Area 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expansion stages</td>
<td>Standard Focus Area 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-0</td>
<td>Standard Focus Area 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4-3: Sample of a rightsized template for upstream experimentation. See Appendix for the other templates developed.

4.3 Leveraging Prior Knowledge in Experiment Design

4.3.1 Proposed Management System

The templates generated enforce a “checklist” style of experiment design where scientists not only run through the typical experiments that need to be conducted, but also ask themselves whether they have reviewed all possible sources of prior knowledge. To enforce the discipline of accessing prior knowledge to potentially reduce experimentation, a form of governance needs to be used with support from top management.

Figure 4-4 illustrates the proposed process that enforces the use of the rightsizing templates and the consultation of experienced managers and scientists in the organization for potential risks, advice from past experiences and improvements. DS Team Leads will fill out the templates with their functional area leads (FALs) to provide a full list of experiments and requirements. Any assay or analytical requirements will be filled out together with the AS Team Lead to ensure that all assay expectations are aligned. The templates will be compiled and
submitted to the monthly pivotal portfolio review meeting where senior managers in PD, the resource planners, project managers and team leads discuss the templates, highlighting any exceptions. During this meeting, DS and AS Team Leads have an opportunity to access prior knowledge through the expertise of senior management in attendance and by learning about useful references or documents they can access from past experiments that can provide helpful guidance for their experiments. This process therefore enforces some discipline into this review of prior knowledge. Team leads therefore obtain feedback on potential improvements or risks in their proposed experiments in a single setting rather than a repetitive and tedious back-and-forth review of experiments. Once all revisions have been made, the pivotal portfolio review meeting is also used to align on resource requirements for a program with the resource planners, who have visibility of the program timeline, milestones and available capacity. Presenting the templates will allow them to assign resources at a more granular level, rather than using a blanket to cover total resource requirements. The meeting concludes with a formal approval to proceed with experimentation and resourcing by all key stakeholders.

Figure 4-4: Proposed review process incorporating the rightsizing templates

Further improvements can be made to this process throughout the pilot, namely to route the templates through an automated workflow that will allow all stakeholders to access the templates as a pre-read. Figure 4-5 illustrates this process which allows multiple reviews to run in parallel, thus reducing the delay from waiting for monthly reviews. Should any points require further discussion, the reviewer can mark an item with comments, then upload a summary onto the workflow. Once approved, the templates will flow to a resource planner who can then build out the final resource allocation and call out any capacity constraints. If there are no issues, the templates will flow directly into an approved state visible to the DS and AS Team Leads, which will then serve as the trigger for the program team to begin work.
4.4 Hypothesis Generation Testing

4.4.1 Statement of Hypothesis

Due to the lack of standardization in the listing and documentation of past programs’ experiments, it is difficult to estimate a number for the potential amount of experiment time and resources that can be saved by rightsizing. As a result, the hypothesis that we aim to test in the succeeding exercise is:

**H0:** The proposed rightsizing templates can effectively reduce experimentation in both upstream and downstream operations.

This statement has been generalized for overall PD since there is a potential to streamline CPD and PC operations.

4.4.2 Test Methodology

Due to the limited availability of active biologics programs starting from CPD, a retrospective exercise was conducted to test the hypothesis. In this exercise, we asked scientists to list CPD upstream and downstream experiments from two past biologics programs in the proposed rightsizing templates. Experiments that go beyond the standard focus areas are labelled with their corresponding justification. The goals of this test are:

1. Estimate the potential benefit to be gained from rightsizing experiments by identifying experiments that could have been de-prioritized in the interest of time and limited resources.
(2) Obtain feedback from the actual scientists who will complete the templates on potential areas for improvement.

It should be noted that the results of this test do not imply that past experiments were wasted or unnecessary efforts but, rather, aim to demonstrate the effects of rightsizing and leveraging prior knowledge.

4.4.3 Test Results and Analysis

Only two programs (one BiTE and one fusion protein) were available for this test since they were recently completed and had detailed records of past experiments. Table 4-2 summarizes the potential reductions in experimentation that could have been realized had the templates been enforced. The range of savings is not generalizable, but validates the hypothesis that the rightsized experiment templates could help reduce overall experimentation and consequently total cycle time and FTE touch time.

Table 4-2: Summary of experiment reductions across programs

<table>
<thead>
<tr>
<th>Program A (Fusion Protein)</th>
<th>Program B (BiTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPD Upstream</td>
<td>15%</td>
</tr>
<tr>
<td>CPD Downstream</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>33%</td>
</tr>
</tbody>
</table>

The additional experiments that could have been introduced at a later stage or at a lower priority were conducted with the following rationales:

- Material generation for other downstream processes: The material used for downstream analysis could have been sourced from previous phases of drug development.
- Elution tests and washes to ensure that all the equipment work: Runs to test equipment reliability and stability.
- Experiments performed as a result of major program decisions made at a later period: Repeated experiments due to a change in type of manufacturing process or cell line.
- Additional material generation activities for iterations on product quality: Culture expansion for product quality improvements.

Although these experiment types might not necessarily be present in other modalities and programs, their characteristics may be identified in other experiments. Majority of these
experiments can be anticipated by significant planning, resource allocation and decision-making made upfront. The potential reduction in experimentation and cycle time illustrate the importance of moving this decision-making upfront and therefore the effectiveness of the proposed templates and management system.

Aside from the rightsized experiments, the scientists remarked that the templates were clear easy to use and did not present any opportunities for confusion. In addition to the standard focus areas, the scientists also proposed the addition of one standard focus area for each downstream unit operation as a potential improvement to the templates. Given the limited data available and the lack of pilot programs on which these new templates can be tested, it is difficult to arrive at a conclusive test for the hypothesis. The initial results however suggest that there are indeed opportunities for improvement in PD experimentation with the use of the rightsizing templates.

| Hypothesis: | H0: The proposed rightsizing templates can effectively reduce experimentation in both upstream and downstream operations. |
| Result: | Additional testing required with pilot programs from planning stage. However, initial results indicate some effectiveness of the templates in optimizing experimentation. |

4.5 Streamlining Commercial Process Development and Process Characterization

4.5.1 Diagnosis and Data Gathering

As diagnosed during the interviews of PD scientists, one root cause behind variable cycle times is the inconsistency of the definition of process development steps and standards across the organization. The goal of this third principle and LPE improvement is to properly define the standards and work within the standardized timelines and set of finite resources without incurring significant additional risk. Amgen currently has a formal decision process for prioritizing critical, highly promising programs, allocating additional resources and accelerating specific processes to reduce overall development time. This designation of “fastlane” programs differs from the LPE streamlining of CPD and PC in its higher degree of risk-taking. Although some formal playbooks were available for specific process steps within PD, there was no single consolidated and aligned definition for CPD. The lack of consistency in the way past experiments were recorded made it
more important to arrange a workshop where all the involved scientists could discuss and align process definitions and expectations.

A one-day workshop was conducted with senior scientists with over 20 years of experience in upstream, downstream and analytical operations to define each phase of pivotal process development, then to identify opportunities for improvement in the process that could potentially lead to cycle time and resource usage improvements. This workshop was endorsed and presided over by senior executives from Process Development, Engineering and Attribute Sciences. The results of the workshop were then succeeded by smaller focused group discussions for each segment of the operation to further refine the proposed process. The resulting playbook of combined process improvements consisted of five main types of process improvements:

1. **Standardization**: Using the rightsizing templates and management system proposed and clearly defining the appropriate number of runs, bioreactor blocks and process steps for a standard experiment.

2. **Maximizing use of experimentation**: Using multivariate experiments to generate more data to reduce repeated univariate experimentation in process characterization.

3. **Parallelization**: Running process steps in parallel.

4. **Moving process steps and decision-making upfront**: Similar to the principles behind the rightsizing templates and management system, key processes and decision-making are moved upfront.

5. **Reducing report generation**: Consolidating into a one-time report generation step.

The proposed improvements are dependent on a number of assumptions or enabling factors:

1. First-in-Human process is the starting point for Pivotal PD. Material for upstream and downstream processing is readily available.

2. Processes are all defined and standardized in the Electronic Lab Notebooks (ELN) and the rightsized templates and governance process are fully enforced.

3. No significant facility fit issues: The product has the flexibility to be manufactured in a pre-determined facility.

4. The pilot plant will be available to conduct confirmation runs.
(5) Standard turnaround times for design of experiments plans and analyses will be followed by Quality Engineering.

(6) Standard turnaround times for qualified assays will be followed by AS. When multiple pivotal PD programs are running in parallel, product quality assays will be run following a pre-established schedule, rather than on an as-received basis for samples. Upstream experiment runs will be scheduled to meet these schedules. This “assay cadence” initiative is an ongoing initiative that has standardized physical and electronic handoffs between DS and AS, and resulted in up to a 55% increase in on-time assay turnaround, despite some attrition in AS analyst staffing.

In line with Spear’s recommended steps for system design [71], there is a need to define the system inputs and outputs. The provision of the inputs would signal the start of the process while the completion of the outputs would signal the end of the process.

4.5.2 Upstream Process

![UPSTREAM PROCESS DESIGN](image)

**Figure 4-6:** Redefined upstream process design with breakdown of process design experimentation

Figure 4-6 summarizes the redefined and streamlined process for upstream operations in pivotal PD. The decision to start the upstream process depends on the preparation of inputs from the resource planning and lifecycle management team (demand forecast, program timeline), AS (qualified assays), PD teams in previous processes (QTPP and quality attributes, process, working cell bank) and management (facility fit). The diverse sources of the inputs further emphasize the need to enforce a checklist and management system that will form part of experiment design (as
proposed in the first two principles tackled) and the awareness of all involved teams (DS and AS) of this trigger. In this redefined upstream process, some notable qualifications are the clear method development by AS prior to the start of experimentation, which would allow the analytical lab team to efficiently collect and run samples with minimal delays. This assumes readiness of methods before actual experimentation, rather than relying on methods to be developed in parallel, with the potential of delays. The experiment’s scope of work, risk assessment and product format are all identified at the beginning with the completion of these exercises targeted before the actual cell culture execution among bioreactors. The succeeding steps follow the standard process for upstream operations, which are the scale-up of material, cell culture by executing a block of several bioreactors and completing assays as a final analysis. Confirmation runs to validate the process robustness and other parameters, then final documentation follow. The rightsizing templates, called the “PD Justification document,” are constantly updated and presented in the pivotal portfolio review meeting to share progress and obtain feedback. The final outputs would include a completed upstream document and control strategy for the combined CPD and PC process.

The proposed process works on several assumptions:

- Bioreactors will be available for supply runs to generate material for experimentation.
- No media-related studies will be conducted to test whether the media is compatible with selected platform or for viral risk mitigation.
- The timing does not consider new technologies that can be implemented, but the process will be open to the use of high throughput technologies.
- No significant product quality challenges will be encountered which will require significant revision of the manufacturing process. Glycosylation does not introduce significant challenges.
- The DS program team and AS analysts assigned to process the assays will be co-located in the same PD site. This removes any delays associated with shipping samples between sites or transferring knowledge.
- The product’s fit to Quality Target Product Profile (QTPP) and Fit to Manufacturability or Testability are identified early on during experiment design and prior to the start of the pivotal process design.
The reductions in cycle time were mostly driven by the following accelerations in their respective process steps:

**Process Design Experimentation**

- **Standardization:** Sufficient resources will be allocated for new method development, particularly for methods that currently do not fit current target profile. The method development turnaround will satisfy a standard period of time.
- **Standardization:** No Pre-LIVCA (limit of in-vitro cell age) studies (studies performed to assess risk of LIVCA) for a specific mode of programs.
- **Standardization:** Combine CPD and PC studies for the N-0 bioreactor.
  - Limit study to the key parameters defined in the rightsizing templates.
  - Limit the bioreactor blocks for upstream studies to the standard defined in the rightsizing templates (one less than typical number conducted in the past).
  - Limit to X number of bioreactors for the perfusion process for the N-1 bioreactor.
    No need for CPD run for non-perfusion process.
- **Maximizing use of experimentation:** Platform media stability studies will be completed for greater than five programs.
- **Parallelization:** Risk assessment and format selection are conducted in parallel with the scaleup of the first bioreactor block.
- **Moving process steps and decision-making upfront:** No process changes once upstream processing has begun.

**Confirmation Runs**

- **Maximizing use of experimentation:** Confirmation runs incorporate LIVCA studies.
- **Parallelization:** Conduct technology transfer enabling studies during upstream confirmation runs, instead of running them separately.
- **Parallelization:** Harvest for Fed-Batch processes will conduct studies during Confirmation Runs.

**Documentation**

- **Reducing report generation:** No CPD-only reports. Process Design reports would all be stored in the centralized quality document management system and would combine CPD and PC information.
- **Standardization:** Electronic Lab Notebook (ELN) entries would all follow a given template. Pivotal PD process design documents would serve as a reference for new drug applications.

The overall upstream process reflects a cycle time reduction of 39.5% from the current standard and an increase in Pivotal PD DS capacity by 2.4X (+144%).

### 4.5.3 Downstream Process

**DOWNSTREAM PROCESS DESIGN**

**Inputs:**
1. Demand forecast
2. Plant-scale or equivalent First-In-Human process
3. Quality Target Product Profile (QTPP)
4. Qualified assays
5. Defined formulation
6. Program timeline and clinical milestone timing
7. Facility Fit Guidelines

**Outputs:**
- Completed documentation package

![Diagram of Downstream Process Design]

**Figure 4-7:** Redefined downstream process design with breakdown of early experimentation

**DOWNSTREAM PROCESS DESIGN (FURTHER BREAKDOWN)**

**Confirmation Runs**

- Parallel Processes during Confirmation Runs
  - 61. Confirmation prep
  - B1. Design Experiment
  - B2. Run Experiment
  - B3. Assay Samples
  - B4. Analyze Data

**Late Process Design Experimentation**

- Detailed Breakdown of Late Process Design Experimentation (13.6%)
  - Capture/Exp Design
  - Pol 1 Challenge
  - Pol 2 Challenge

![Diagram of Late Process Design Experimentation]

**Figure 4-8:** Further details of confirmation runs and late design experimentation for downstream
A similar approach has been taken for downstream operations, with a proposed design summarized in Figure 4-7 and Figure 4-8. The inputs to downstream operations are the same as those of upstream, with the addition of a defined formulation. Since downstream operations involve more runs compared to upstream, it is important to have decisions like facility fit and formulation made upfront. The same structure is followed for downstream operations but consists of several downstream unit operations which may be performed in series or in parallel. The steps are aligned with those used by the rest of the industry [26], whereby a capture step is followed by filtration, polishing and ultrafiltration / diafiltration steps. Similar to upstream operations, this proposed process assumes that AS develops all methods before the start of any downstream experimentation. Viral clearance is performed in parallel with confirmation runs, which then provide inputs to the late process design experimentation. The delineation between an early process and late process design experimentation show how CPD (process qualification) and PC (tests for robustness) are integrated into the new proposed process. The rightsizing templates are maintained as live documents which are updated and shared through the management system throughout the entire process. The downstream operations are considered done once all the reports are completed.

The proposed downstream process is based on the following assumptions:

- Bioreactors will be available for supply runs to generate material for experimentation. First-in-Human (FIH) in-process material is available for use.
- Select a platform that is already existing or established within Amgen.
- No significant changes in impurity profiles resulting from upstream work.
- The timing does not consider new technologies that can be implemented, but the process will be open to the use of high throughput technologies.
- No significant product quality challenges will be encountered which will require significant revision of the manufacturing process. Glycosylation does not introduce significant challenges.
- The DS program team and AS analysts assigned to process the assays will be co-located in the same PD site. This removes any delays associated with shipping samples between sites or transferring knowledge.
• The product’s fit to Quality Target Product Profile (QTPP) and Fit to Manufacturability or Testability are identified early on during experiment design and prior to the start of the pivotal process design.

• All downstream designs of experiments follow the rightsized experiment design which includes the standardized durations, number of runs and resources allocated. The rightsizing templates and management system are used to support these designs.

• Material sourced from Confirmation Runs will undergo specific stability and challenge runs with a defined number of columns. One scientist will be allotted for these runs. If the team wishes to deviate from the standard or request for additional resources, they must do so through the pivotal PD portfolio review.

The following accelerations drive the overall improvement in cycle time downstream:

**Early Process Design Experimentation**

• **Standardization**: Sufficient resources will be allocated for new method development, particularly for methods that currently do not fit current target profile. The method development turnaround will satisfy a standard period of time.

• **Parallelization**: Risk assessment and format selection are conducted in parallel with the first downstream experiment designs.

• **Standardization**: There is a standardized range of factors that will be tested in each of the Design of Experiments (DOE). Any deviation from the range must be identified in the rightsizing templates and discussed during the pivotal PD portfolio review meeting.

• **Maximizing use of experimentation**: Use DOE center points, reuse runs, and any other applicable data already being generated for other purposes to eliminate the need for separate studies in select downstream operations. (Example: This method could potentially eliminate three runs per column for UFDF).

• **Maximizing use of experimentation**: When capture load ranges are not changed, use FIH viral clearance instead of running a separate pivotal-enabling viral clearance.

• **Parallelization**: Scientists can run more than one instrument and experiment per day.
Late Process Design Experimentation

- **Reducing report generation**: No CPD-only reports. Process Design reports would all be stored in the centralized quality document management system and would combine CPD and PC information.
- **Standardization**: Electronic Lab Notebook (ELN) entries would all follow a given template. Pivotal PD process design documents would serve as a reference for new drug applications.
- **Maximizing use of experimentation**: Use the same columns and filters that were used for DOEs, in resin or filter lifetime studies.

The overall downstream process reflects a cycle time reduction of 36.7% from the current standard and an increase in Pivotal PD DS capacity by 2.3X (+130%).

### 4.5.4 Proposed Pivotal Process Design

![Figure 4-9: Summary of proposed pivotal process design](image-url)

When combined, upstream and downstream operations run in parallel, with the longer process dictating the cycle time of the proposed pivotal process design. In this case, downstream operations with a cycle time reduction of 36.7% define the new cycle time. This has the potential to increase throughput by 1.6X (+58%). Pivotal DS capacity is also increased as a result of the
streamlined process, resulting in at least 2.4X increase in capacity for upstream and 2.3X increase for downstream pivotal DS staff. Since significant process changes are involved, this proposed process design needs should undergo a pilot study to assess effectiveness. However, due to absence of active programs during the period of the study, the only ways to validate this are through simulation and actual pilots in the succeeding year. The simulation methodology will be discussed in greater detail in Chapter 5.

4.6 Key Findings and Recommendations

This first approach to augmenting pivotal PD capacity through the application of lean principles (LPE) has generated a number of improvements and insights:

(1) **Rightsizing PD work has the potential to reduce experimentation and consequently reduce cycle time and increase FTE capacity.** Using the lean principle of standard work, the proposed experiment templates provide a baseline for DOEs and enable key stakeholders to manage experiments by exception rather than by exhaustive reviews. By defining their specific experiment objectives and requirements, scientists will be able to request for resources more accurately and prioritize experiments that directly contribute to the final product filing.

(2) **Management systems can enable access to prior knowledge and reduce risk of rework or additional experimentation by moving decision-making upfront.** Complementing the rightsizing templates with the use of the pivotal PD portfolio review to solicit feedback from experts and stakeholders allows important program-related decisions (e.g. risk-taking, resource allocation, facility fit, process type) to be made upfront, thus reducing the potential for changes and therefore rework later on in the process. Similarly, the management system enforces a formal practice of reviewing past experimentation as a pre-requisite to program initiation. Obtaining management support is crucial for standardization of experiment designs.

(3) **Aligning and standardizing the definition of process steps across the organization can result in significant cycle time reductions and improvements in FTE capacity.** Specifying value and applying basic lean principles of standardization, parallelization and reprioritization of specific activities can focus experimentation on
results that directly contribute to new product filing and can reduce variability and potential rework in experimentation.

Although a pilot test was not feasible during this period, the second approach to augmenting pivotal PD capacity may lend some additional insight to the proposed pivotal PD process design.
Chapter 5 Doing More: Applications of High Throughput Technology

This chapter recaps the unit operations where high throughput technology (HTT) is currently being explored. It also details the results of the tests to assess the ability of HTT to close the anticipated capacity-demand gap, estimate the net benefit in FTE capacity and throughput due to HTT, and assess the benefit of cross-training Drug Substance (DS) staff. Lastly, the sensitivity of a HTT-implemented system to other constraints is assessed to generate additional guidelines for effective use.

5.1 Summary of High Throughput Initiatives and Assessment

Table 5-1: High throughput initiatives at Amgen Pivotal Drug Substance Process Development. The table also presents the unit operations, sub-processes and their current, low throughput contributions to the total FTE time required across upstream and downstream operations.

<table>
<thead>
<tr>
<th>Process Phase</th>
<th>Upstream (Cell Culture)</th>
<th>Downstream (Purification)</th>
<th>Filling or Ultrapurification (UF/DF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit Operation</td>
<td>Scale-Up</td>
<td>Harvest</td>
<td>Capture</td>
</tr>
<tr>
<td>i</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>FTE time required per operation as a % of total FTE time requirements</td>
<td>12.5%</td>
<td>3.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>FTE time required per sub-process as a % of total FTE time requirements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j = 1 Material Preparation</td>
<td>14.0%</td>
<td>20.7%</td>
<td>15.6%</td>
</tr>
<tr>
<td>2 Equipment Setup</td>
<td>71.1%</td>
<td>12.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>3 Initiation</td>
<td>3.6%</td>
<td>12.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>4 Processing</td>
<td>5.5%</td>
<td>15.0%</td>
<td>4.7%</td>
</tr>
<tr>
<td>5 Sample Handling</td>
<td>5.1%</td>
<td>24.9%</td>
<td>47.4%</td>
</tr>
<tr>
<td>6 Data Handling</td>
<td>0.7%</td>
<td>6.2%</td>
<td>11.8%</td>
</tr>
<tr>
<td>7 Cleanup</td>
<td>0.2%</td>
<td>8.2%</td>
<td>15.6%</td>
</tr>
<tr>
<td>8 Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Total DS FTE Time Required</td>
<td>50.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AS FTE Time Required</td>
<td>49.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With the implementation of data- and process-driven approaches like QbD and PAT, employing high throughput techniques and automation have been identified as powerful means to increase capacity and throughput in drug development [13], [38]. As summarized in Chapter 3, Amgen is currently exploring several high throughput technology (HTT) initiatives, many of which are commercially available, off-the-shelf solutions being explored by their peers in the industry. Table 5-1 provides a summary of all the unit operations in upstream and downstream phases
where HTT is being explored. It is important to note that implementing HTT does not automatically translate to all sub-processes of the operation and it might not immediately address the bottleneck. As shown in the table, the HTT being explored for upstream and downstream account for 39% of the total Pivotal PD FTE time required for Pivotal PD. Attribute Sciences (AS) currently has limited HTT but they tackle 4.3% of the total Pivotal PD FTE requirements. Due to their off-the-shelf availability and OEM support, the HTT have a high implementation feasibility. The goal of this second study is to ultimately assess the impact of HTT and generate insights that can guide future investments in this technology. This will be done through a combination of simulation modelling and theoretical factory physics calculations.

5.2 Hypothesis Generation

Using process mapping and basic cycle time and throughput formulas summarized in Chapters 2 and 3, we can hypothesize the potential cycle time and throughput improvements that can be gained from the HTT initiatives. There are three main areas that are of top concern to management: (1) the ability to accommodate the upcoming pipeline of projects, (2) the potential benefit that can be gained from HTT, thus determining investment worthiness, and (3) the potential benefit to be gained from pooling upstream and downstream scientists. The simulation therefore seeks to test the following hypotheses:

**H1: The proposed pivotal PD process design will allow Pivotal PD to complete all projected programs for the next three years without implementing high throughput technology.**

The proposed pivotal PD process design under Lab Process Excellence could potentially reduce the total cycle time by 40% and increase Pivotal DS throughput by 139% (2.4X). Assuming a CAGR of 32% over the next three years, we can therefore hypothesize that an immediate implementation of the proposed process design will generate sufficient capacity for Pivotal PD to complete all projected programs for the next three years even without HTT. Although the proposed process changes will likely require more time for a pilot test and, considering human and organizational factors, might not be realized immediately, this hypothesis is only for purposes of validating the potential benefit from the proposed process design.
H2: The combined high throughput technology initiatives can free up to 30% of Pivotal PD FTE capacity and increase pivotal PD program throughput by up to 42%.

\[
\text{Total Pivotal PD FTE capacity freed} = \sum_{i=1}^{7} \sum_{j=1}^{8} (S_{ij} \times r_i)
\]

**Equation 5-1:** Formula to calculate total FTE capacity freed based on Table 5-1 data. $S_{ij}$ refers to the FTE time required per sub-process as a % of total FTE time requirements. $r_i$ refers to the FTE time required per unit operation as a % of total FTE time requirements. Each upstream and downstream unit operation is represented by a number (i) while each sub-process within those unit operations is represented by a number (j).

Based on the data provided in Table 5-1, it is possible to estimate the potential capacity that can be freed by all the HTT initiatives. Using **Equation 5-1**, we arrive at the data summarized in Table 5-2 which estimate the total Pivotal PD DS FTE capacity freed as 32%. To account for some variability due to actual cycle times, shift schedules and portfolio timing, this estimate is reduced to a conservative estimate of 30% capacity freed. As a result of running parallel batches and higher output volume from HTT initiatives, cycle time reduction can also be estimated based on a calculation of the total process cycle time before and after HTT. Based on this calculation, we can hypothesize a cycle time reduction of 34% or a throughput improvement of 52% ($1.52X$). This method, however, does not consider availability of FTE resources, program queuing and shift schedules which can contribute to reductions in throughput. To account for these other factors, the estimate is reduced by 10% to a 42% throughput improvement ($1.42X$) and 30% cycle time reduction.

| Table 5-2: Summary of estimated FTE capacity freed by all HTT initiatives in Pivotal PD |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Capture         | Viral Inactivation | Polishing 1 | Polishing 2 | Viral Filtration | Filling or Ultrafiltration | Analytical Lab  |
| % of FTE time requirements with HTT | 85%             | 86%              | 86%          | 86%          | 100%            | 80%              | 9%              |
| % FTE time required freed       | 43%             | 75%              | 75%          | 75%          | 80%             | 2%               |                 |
| % of total FTE time requirements freed | 7%             | 4%               | 0%           | 6%           | 6%              | 0%              | 9%              |
H3: Cross-training upstream and downstream DS scientists can increase Pivotal PD program throughput by at least 10%.

Cross-training or ensuring that both upstream and downstream DS scientists have the requisite skillsets to perform any type of experimental work creates a common resource pool that raises the overall FTE time available for use within a program. Creating an inter-program pool is currently not a consideration at the company due to employee development plans, necessary expertise and other factors.

5.3 Simulation Design

5.3.1 Model Overview

As demonstrated in Table 5-1, the benefits of HTT cannot be estimated by a straightforward mathematical calculation. Similarly, waiting to test the HTT on pilot programs will not only be time-consuming but may also risk output quality and cost. Given the limited FTE resources and time available, it is important to establish the expected improvement in overall throughput as a result of HTT implementation in a specific unit operation before investing resources to train scientists to gain the necessary expertise to run the equipment. To manage risk and due to the complexity and number of interacting factors influencing cycle time and throughput, a simulation model was selected as a means of estimating the potential impact of various policies, which will be inputted as simulation scenarios. Since the research also has a business purpose of providing the company with a tool that can be used for gaining insights on capacity management policies that management wishes to develop, a simulation would provide management with a flexible solution for this purpose. ProModel was selected as the simulation software due to its visual interface, basic code (a customized version of C and VBA), reporting capabilities and maintenance support, making it a sustainable platform for future use by PD.

5.3.2 Model Process Flow and Construction

The scope of the simulation design focused on the upstream, downstream and analytical lab operations of Pivotal PD. Although each program and modality is unique in the way its process is designed, the unit operations were generalized to build a generic model. This generalized model is summarized by Figure 5-1 where upstream and downstream operations are shown to be
running in parallel, each followed by a standard set of analytical lab tests ("assays"). For purposes of tracking, the simulation is also divided into the standard pivotal PD phases: CPD, PC Planning, PC, Challenge Studies and MA Enabling Viral Clearance. As discussed in Chapter 2, CPD awaits the results from analytics before proceeding with the next experiment whereas PC allows the next experiment to begin without waiting for results. The conditions for programs to flow through each phase follow the proposed pivotal process design under Lab Process Excellence. Each unit operation and sub-process is defined by a series of logical statements that include cycle times, batching, FTE resource allocation and data recording. Cycle times were obtained by shadowing lab teams and performing time-and-motion studies. A triangular distribution was used to capture the various ranges of cycle times across program types. Interviews of experienced scientists were also used to estimate cycle times especially for downstream activities. Following the proposed process design, buffers between experiments were eliminated but waiting could still occur as a result of resource unavailability.

5.3.3 Assumptions and Limitations

The simulation was designed with several assumptions in mind which are detailed in the Appendix. The critical assumptions that should be considered throughout the analysis are:

- **Program Team**: Each program team is pre-determined and unchangeable throughout the run. The standard program team size may, however, be changed before a run.
- **Calendar and Run Time**: The standard Amgen business calendar is used for the assignment of holidays. This includes regular US holidays and two shutdowns during the year. Personal vacations or sick leaves are not considered in the base case. Since an average program takes more than one year to complete, a standard simulation run is two years (24 months).
- **Upstream N-Steps**: The number of N-steps in cell culture varies between programs. Although this setting can be manipulated to meet program needs, a standard or four N-steps (N-3 to N-0) is set for the baseline simulation.
- **Shifts**: The standard 8-hour work day of a scientist is split between experimentation and "other tasks" (i.e. administrative work, meetings, documentation, report generation, training).
- **Experimentation**: Program teams do not start the next upstream experiment until the previous experiment has entered the analytical lab phase. Downstream experiments, on the other hand, can run in parallel.
**Assay Cadence:** The implementation of assay cadence is simulated by collating then batching experimental run outputs before running their designated assays at the analytical lab.

**Workload:** Program teams can only work on one program at a time.

It is also important to note the other limitations of the simulation as a result of the software capabilities and the availability of data:

- A major limitation of ProModel is its ability to keep a record of all the individual process times for each sub-process and unit operation, and the FTE touch times. Timestamps were coded to record the cycle times for each unit operation while the built-in Output Viewer reporting tool of ProModel allows viewing of individual FTE utilization and FTE touch time. However, viewing a breakdown of wait times between sub-processes is not within the capabilities of the software.

- A detailed Trace file of all the events that occurred during the simulation is exportable, but extracting data and insights from the Trace file is tedious and not a universally applicable method across simulation runs.

- Program teams are pre-determined and fixed throughout the simulation run. This means that the scientists in Program Team A will always work with each other for succeeding programs. This setting was done just for simplicity of analysis, but in reality, teams can interchange members.

- Data on the likelihood of a program’s success or failure is not readily available. A separate initiative has been launched to track this data and use it for portfolio management.

- As is the case with several models, the simulation does not self-optimize or self-correct. Therefore, if it is more efficient to run a low throughput machine over a high throughput one, it will not do so unless told to by the user. The model is therefore designed for testing of pre-determined scenarios.

- Cost is not considered in the simulation, but can easily be added, provided that there is a standard labor or resource cost that Amgen wishes to track.

- Unit operations do not include the influence of other process parameters like media used, resin capacity and yield.

- Due to limited data available for programs representing each modality, specific differences between modalities such as additional process steps and cycle times are not considered. The model is generalized to represent the generic processes used to develop biologics drugs.
Figure 5-1: Generic process flow diagram used in simulation model
5.3.4 Simulation Parameters, Inputs and Outputs

The simulation was designed so that users can manipulate multiple variables and test their effects on cycle time, resource utilization and throughput. Figure 5-2 summarizes the various inputs and outputs for the simulation. Before a simulation run, the user inputs the desired portfolio of programs to run, their phase (e.g. full program starting from CPD, full program starting already from PC or partial program starting from CPD), program site (e.g. Cambridge, Thousand Oaks), start dates, number of upstream and downstream experiments and number of runs (“loads”) per unit operation. The user can also indicate whether a HTT application will be used for a specific unit operation. All of these inputs are captured in an Excel file that the model loads once the run begins. The final outputs are shown in three forms: (1) a display window indicating the number of CPD and PC programs completed per site, (2) standard resource utilization and usage time reports from ProModel and (3) an Excel file with the cycle times per unit operation based on the timestamps coded.

<table>
<thead>
<tr>
<th>Input</th>
<th>Input Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program Name and Start Date</td>
<td>Excel initialization file</td>
</tr>
<tr>
<td>Program Type and Phase</td>
<td>Excel initialization file</td>
</tr>
<tr>
<td>Number of upstream and downstream runs</td>
<td>Excel initialization file</td>
</tr>
<tr>
<td>Number of loads per run</td>
<td>Excel initialization file</td>
</tr>
<tr>
<td>Program Site</td>
<td>Excel initialization file</td>
</tr>
<tr>
<td>Use of high throughput technology or not</td>
<td>Excel initialization file</td>
</tr>
<tr>
<td>Number of FTEs (upstream, downstream, AS)</td>
<td>Manual entry into software</td>
</tr>
<tr>
<td>Shifts and Holidays</td>
<td>Manual entry into software</td>
</tr>
<tr>
<td>Process cycle times</td>
<td>Manual entry into software</td>
</tr>
<tr>
<td>Labor or FTE touch time</td>
<td>Manual entry into software</td>
</tr>
<tr>
<td>Equipment failure rate</td>
<td>Manual entry into software</td>
</tr>
<tr>
<td>HTT capabilities (max batch sizes)</td>
<td>External arrays (“assays” and “downstream”)</td>
</tr>
</tbody>
</table>

Figure 5-2: Summary of simulation model inputs and outputs

5.3.5 Simulation Validation

The goal of simulation validation is to test whether the cycle times obtained from the simulation for each phase and unit operation of Pivotal PD closely match the theoretical post-LPE cycle times of the Pivotal PD process. These theoretical post-LPE cycle times were obtained from the proposed process design for Pivotal PD described in Chapter 4 and assume that the improvements under LPE are implemented successfully (i.e. rightsizing number of runs,
streamlining processes). Since the purpose of the model is to estimate the potential, incremental improvements (deltas) in throughput and FTE utilization that can be gained from HTT, the simulation results were compared against the theoretical post-LPE cycle times.

The simulation was loaded with the planned number of pivotal PD programs and staffing for 2017 and validated against the theoretical cycle times if LPE improvements are implemented successfully. The simulation was tested with 15 randomized runs, resulting in cycle time outputs that were then tested for normality. Most of the data was non-normal, each set with different distributions. As a result, a non-parametric (Wilcoxon signed rank) test is used to test whether there is a statistically significant difference between the simulation results and the theoretical (target) mean for each unit operation. This test was also selected since the primary purpose of the simulation is to measure improvements or deltas in utilization and throughput. As shown in Table 5-3, the simulation produces cycle times that have a 7-12% deviation from the theoretical cycle time, which is a reasonable margin to proceed with for further hypothesis testing.

Table 5-3: Highlights of the simulation validation

<table>
<thead>
<tr>
<th>% Deviation</th>
<th>CPD</th>
<th>PC</th>
<th>PC Planning</th>
<th>Challenge Studies</th>
<th>MA Viral Clearance</th>
<th>Full CPD-PC Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>9%</td>
<td>0%</td>
<td>7%</td>
<td>11%</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

5.4 Hypothesis Testing

5.4.1 Hypothesis 1: Capacity for Upcoming Program Pipeline

For this hypothesis test, the full portfolio of upcoming biologics programs from 2018 to 2020 was loaded onto the Excel input file under the following assumptions, on top of the standard set of simulation assumptions stated in the Appendix:

- The proposed pivotal process design improvements are fully implemented immediately.
- Lab teams (DS and AS) are only supporting program-related experimentation. They are therefore not spending any other time on report generation, technology development, meetings and administrative work.
- Staffing levels as of Q4 2017 will not change.
- The projected programs and their designated start dates for the next three years will not change, as extracted from the internal project management system as of Q4 2017. Not all programs will begin from CPD at the start of the simulation period.
Assuming that the revised process design and rightsizing are implemented immediately, the simulation indicates that Pivotal PD can successfully complete all upcoming biologics programs at their designated sites within their scheduled timeframe, with no delays and within a manageable FTE resource utilization level throughout the entire period. As summarized in Figure 5-3 and Table 5-4, FTE resource utilization has remained below an operations standard of 80% throughout a steadily rising number of programs. With the absence of abrupt spikes in the number of programs, program teams have been able to focus their efforts on completing programs on time, even without HTT. The utilization also implies that a larger throughput is possible as a result of the proposed Pivotal PD process design, which will be tested in Hypothesis 2. The findings therefore allow us to accept Hypothesis 1 as true.

Aside from this, a “stress test” was performed on the simulation to determine the maximum possible throughput. This was done by increasing the number of programs entering the PD organization at the start of the year until the entire process is unable to fully complete all programs that entered the system (i.e. the simulation results in incomplete programs at the end of the simulation period), limited by the full utilization of one or more FTE resource groups (most often limited by AS FTE resources). Once this maximum limit was identified, we performed 10 randomized runs of the simulation to generate a distribution for this maximum threshold. The mean threshold shows an increase of approximately 2.7X against planned capacity, which is above the forecasted capacity increase of 2.4X.

**Table 5-4: FTE resource utilization for pipeline programs without HTT implemented**

<table>
<thead>
<tr>
<th></th>
<th>Upstream</th>
<th>Downstream</th>
<th>AS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Simulated Utilization</strong></td>
<td>22%</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Peak Utilization (monthly comparison)</strong></td>
<td>61%</td>
<td>38%</td>
<td>50%</td>
</tr>
</tbody>
</table>

91
In summary:

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th><strong>H1</strong>: The proposed pivotal PD process design will allow Pivotal PD to complete all projected programs for the next three years without implementing high throughput technology.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>Accept null hypothesis, considering assumptions mentioned.</td>
</tr>
</tbody>
</table>

5.4.2 Hypothesis 2: Total Impact of Current HTT Initiatives

This test consisted of two experiments. First, the model underwent a "stress test" to determine the full throughput potential of Pivotal PD if all HTT initiatives were fully implemented. Second, the model was initialized and run twice on the planned number of programs based on the original process design, to compare the FTE resource utilization before and after the implementation of all HTT initiatives. Both experiments use the same assumptions as those in Hypothesis 1, but also assume that there are sufficient HT equipment available for use on all unit operations or sub-processes with ongoing HTT initiatives.

The first "stress test" experiment showed a 37% (1.37X) increase in maximum throughput attributed to the combined HTT initiatives, which is lower than the hypothesized maximum improvement of 42% (1.42X) calculated using Equation 5-3 and Table 5-2 during the generation of Hypothesis 2. This could indicate that the effects of other constraints like some
processes running in parallel, cycle time variability, portfolio queuing and shift schedules could be greater than anticipated.

The second experiment runs a smaller number of programs compared to the first test. This smaller number of programs is not meant to represent or imply that Amgen has a small number of programs in its pipeline. Rather, it is intended to test the sensitivity of the effects of HTT on total PD FTE time and cycle time. To determine the total throughput increase, we may use Equation 5-2 which is derived from Equation 5-1:

\[
\text{% Throughput Increase} = \left(\frac{\text{LT cycle time}}{\text{HT cycle time}} - 1\right) \times 100
\]

**Equation 5-2:** Formula for throughput increase (%) where LT cycle time refers to low throughput cycle time and HT cycle time refers to high throughput cycle time.

The results show that HTT reduced total PD FTE time required by 17% (Table 5-5), driven mostly by downstream operations. However, the FTE capacity freed (20%) is lower than the calculated maximum of 30%, since the baseline, low throughput capacity was not at maximum utilization. The same effect is visible in Table 5-6 where total throughput improvement is only 12% (1.12X) compared to the hypothesized 42% (1.42X). The total cycle time reduction is also only 11% compared to the hypothesized 30%. Looking only at the average of the unit operations, this reduced effect further emphasizes the fact that the benefits of HTT can only be realized with large volumes of work. For any biopharmaceutical company that wishes to invest in HTT, it should note that a lower return on investment might be realized if HTT is implemented to a case with low FTE utilization due to a small number of programs or if the program pipeline is expected to remain sparse. Since the throughput reduction is shown to vary across unit operations, it is recommended that investments in HTT should be directed at operations with the greatest need so that the expected return on investment can be maximized.
Table 5-5: PD FTE time requirements and capacity improvements due to HTT

<table>
<thead>
<tr>
<th>Team</th>
<th>% Reduction (of total PD FTE time required)</th>
<th>FTE Capacity Freed per phase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upstream</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Downstream</td>
<td>10%</td>
<td>47%</td>
</tr>
<tr>
<td>AS</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td>17%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Table 5-6: Cycle time and throughput improvements due to HTT

<table>
<thead>
<tr>
<th>% Cycle Time Reduction</th>
<th>Throughput Increase (X)</th>
<th>% Cycle Time Reduction</th>
<th>Throughput Increase (X)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPD PC</td>
<td>CPD PC</td>
<td>Total</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Upstream</td>
<td>4% 9%</td>
<td>1.04 1.10</td>
<td>6% 6%</td>
<td>1.06</td>
</tr>
<tr>
<td>Downstream Capture</td>
<td>90% 88%</td>
<td>10.03 8.35</td>
<td>89% 89%</td>
<td>8.91</td>
</tr>
<tr>
<td>VI</td>
<td>35% 1%</td>
<td>1.55 1.01</td>
<td>19% 19%</td>
<td>1.24</td>
</tr>
<tr>
<td>Polishing 1</td>
<td>79% 85%</td>
<td>4.65 6.71</td>
<td>83% 83%</td>
<td>5.93</td>
</tr>
<tr>
<td>Polishing 2</td>
<td>73% 88%</td>
<td>3.77 8.10</td>
<td>84% 84%</td>
<td>6.28</td>
</tr>
<tr>
<td>VF</td>
<td>47% 54%</td>
<td>1.87 2.19</td>
<td>51% 51%</td>
<td>2.06</td>
</tr>
<tr>
<td>UFDF</td>
<td>77% 82%</td>
<td>4.41 5.47</td>
<td>80% 80%</td>
<td>5.08</td>
</tr>
<tr>
<td>AS Upstream</td>
<td>55% 2%</td>
<td>2.22 1.02</td>
<td>34% 34%</td>
<td>1.52</td>
</tr>
<tr>
<td>Downstream</td>
<td>34% 48%</td>
<td>1.52 1.92</td>
<td>41% 41%</td>
<td>1.70</td>
</tr>
<tr>
<td>Total Pivotal PD</td>
<td>11% 1.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on Table 5-6, we may also note that the cycle time reductions are highest in Capture, Polishing and UFDF unit operations, but do not appear to contribute significantly to total process throughput due to a limited improvement in cycle time in upstream and AS operations, thus shifting the bottleneck to them. This therefore implies that the full benefits of HTT can only be realized if corresponding investments are made throughout the rest of the process to accommodate spikes in workload. As shown in Figure 5-4, AS resource utilization peaks earlier and at a higher level (59% vs. 41%) as a result of larger volumes of work being advanced by HTT. As acknowledged by various biopharmaceutical industry peers at the 2014 High Throughput Process Development Conference, analytics tend to become a significant bottleneck as a result of the larger burden placed on them by HTT at earlier stages and remain a challenge in today’s
industry. An ideal scenario would therefore be one where upstream, downstream and analytics coordinate their HTT investments to match each other and total process development needs [27].

Figure 5-4: Reductions in FTE utilizations at each process development phase. Each chart also displays a lower peak FTE utilization under a HTT scenario throughout a program lifetime.

In summary, although we must reject the null hypothesis due to a lower throughput increase and a lower capacity freed as a result of the combined HTT initiatives, this simulation has provided some helpful insights on the proper implementation of HTT.

<table>
<thead>
<tr>
<th>Hypothesis:</th>
<th>H2: The combined high throughput technology initiatives can free up to 30% of Pivotal PD FTE capacity and increase pivotal PD program throughput by up to 42%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result:</td>
<td>Reject null hypothesis, considering assumptions mentioned.</td>
</tr>
</tbody>
</table>

5.4.3 Hypothesis 3: Cross-Training Benefits in Pivotal DS PD

For this experiment, upstream and downstream teams were combined per program and treated as a single, larger pool of resources to draw from. Analytical teams are already shared
resources and therefore cannot benefit from any further resource pooling. This simulation run was performed under the following assumptions:

- The proposed pivotal process design improvements are fully implemented immediately.
- Lab teams (DS and AS) are only supporting program-related experimentation. They are therefore not spending any other time on report generation, technology development, meetings and administrative work.
- Staffing levels for both DS and AS will not change from Q4 2017. However, all DS scientists will be able to perform both upstream and downstream work at equal quality and efficiency.
- The standard number of full programs will be run at their designated PD sites for a span of two years (24 months). All programs will be fed-batch programs.

The simulation run resulted in a 12.5% (1.13X) improvement in throughput, which aligns with the hypothesized throughput increase of at least 10% (1.10X). As shown in Table 5-7 and Figure 5-5, there is a 10% decrease in DS FTE utilization and a 4% increase in AS FTE utilization. As a result of having a larger DS resource pool, there is an expected decrease in time spent waiting for resources to be available to perform work, but as a result, a faster turnaround of DS work, resulting in a higher workload for AS and consequently, the higher AS FTE utilization. The decrease in total FTE utilization (2%) is therefore a diluted one. This exercise therefore implies that cross-training DS scientists cannot provide the necessary throughput increase required to match the upcoming pipeline.

<table>
<thead>
<tr>
<th>Current</th>
<th>Cross-Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS FTE Utilization</td>
<td>Total FTE Utilization</td>
</tr>
<tr>
<td>Average</td>
<td>39%</td>
</tr>
<tr>
<td>Peak</td>
<td>79%</td>
</tr>
</tbody>
</table>

When the model is run with the implementation of HTT (and all scientists are equally capable of using the HTT), the benefits of cross-training are further diluted because of the lower FTE requirements coming from the use of HTT and the even higher load placed on AS. There is a cycle time reduction of 1.7% or a throughput improvement of 2% (1.02X) attributable to cross-training. Unless more lab scientists to be allocated to other types of work, thereby reducing the
available FTE resource pool, cross-training may provide little benefit to a Pivotal PD organization that is already implementing HTT.

![FTE Utilization (Current Team Setup vs. Cross-Trained Teams)](image)

**Figure 5-5:** FTE utilization before and after cross-training

In summary, we can accept the null hypothesis of at least a 10% improvement in Pivotal PD program throughput with cross-training, but only if this is in a scenario without the implementation of HTT.

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>H3: Cross-training upstream and downstream DS scientists can increase Pivotal PD program throughput by at least 10%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td><strong>Accept null hypothesis</strong>, but only in a scenario where no high throughput technology has been implemented.</td>
</tr>
</tbody>
</table>
5.5 Process Sensitivity Analysis

5.5.1 Other System Constraints and Scenario Generation

The use of high throughput technology for parallel or high-volume runs is only one factor contributing to the entire process cycle time, throughput and FTE resource utilization. Other variables include equipment failures, program team sizes, number of runs and portfolio timing. To identify possible risks and scenarios involving these variables that could undermine the benefits of HTT relative to the status quo. When running these scenarios, the standard assumptions for the simulation model apply. Additional assumptions specific to the scenario are stated in the Appendix.

For the succeeding analyses, we refer to the concept of a “tipping point” which is the boundary between two possible equilibria for a product development system: one that works positively toward the successful completion of all projects that enter the system and one that works in a vicious cycle of degrading performance or fewer projects. The tipping point is the point from which there begins a permanent decline or stagnation in performance as a result of having insufficient capacity to accommodate program demand and therefore an unsustainable level of resource utilization that places these resources at a high risk of a self-reinforcing, self-sustaining state of firefighting or “the unplanned allocation of scarce resources to solve unanticipated problems [12].” As found in Repenning’s study, once an organization has crossed its tipping point, capability rapidly declines over time, especially when limited resources must shift their focus to firefighting instead of completing actual programs. Adding any additional work (i.e. new programs) to the system only reduces the number of programs released successfully. A system is more susceptible to firefighting if it has insufficient capacity for the planned demand, since it will have less flexibility or available capacity to address any sudden issues in the process. This also makes the system more likely to cross the tipping point if perturbed with a workload spike (i.e. additional programs, changes to the portfolio).

The goal therefore of the succeeding analyses is to identify a tipping point of the proposed pivotal PD process with HTT deployed for the other variables identified. In the succeeding analyses, the tipping point is defined as the point at which the maximum number of biologics programs that the Pivotal DS and AS organization can complete in a given timeframe falls below the standard number of programs that can be completed within that timeframe. Revisiting
Equation 1-1 and Equation 2-2 which present throughput and overall R&D productivity as a function of cycle time, work-in-process and other variables, this tipping point may be expressed as the combination of variables that would result in a throughput lower than the standard. For the succeeding analyses, we examine three variables, namely equipment downtime, program team size and number of experiment runs.

5.5.2 Equipment Downtime

Machine downtime or equipment failures contribute to process waste [43]. For the context of this simulation, they are defined as the probability of a HT machine experiencing a technical breakdown that prevents further progression of the unit operation. Each type of HT equipment has its own failure or downtime rate which can be controlled through an appropriate preventive maintenance plan. In a study conducted with Novartis R&D Drug Discovery, it was found that automation decisions (similar to the case of high throughput technology) can have increase maintenance and operation costs, especially if there is a significant downtime risk foreseen [60]. The organization must also invest more resources to diagnose errors leading to equipment failures and to train operators who can use and repair the equipment at a standard level of quality.

In the base simulation, the default is set to 0% equipment failures. This means that the equipment is fully reliable and does not have breakdowns. This simulation aims to answer the question: How frequently can HT equipment break down before throughput declines below the status quo? The assumptions for the simulation design are summarized in the Appendix. The simulation model was then tested with the status quo number of programs on a range of equipment failure rates applied to all HT equipment to determine their impact on pivotal PD program throughput and total PD FTE resources in pivotal PD.

As shown in Figure 5-6, all HT equipment can sustain a maximum equipment failure rate of 44% before experiencing a decline in throughput below the status quo. This means that the equipment is only operational 56% of the time, indicating a combined mean time to failure (MTTF) and mean time to repair (MTTR) that is 44% of the equipment’s total possible operation time. At a 45% equipment downtime or failure rate, the benefits of HTT will no longer be realized. Although this failure rate is improbably high, it is important that appropriate preventive and autonomous maintenance programs are established to keep downtime low. As failure rate increases, FTE utilization also increases as a result of two factors: (1) the scientists assisting in
the troubleshooting and repair of the HTT in use and (2) the additional time required to repeat the experiment setup and execution, which may or may not result in overtime.

As also cited during the interview of Amgen PD downstream lab scientists, equipment must be provided with the correct parts to reduce the likelihood of failures. In the absence of fully trained lab staff, having an in-house technician for HTT should also be considered since delays in equipment repairs from third-party service providers have contributed to prolonged experiment periods.

**Figure 5-6**: Simulation results showing the impact of equipment downtime on pivotal PD program throughput and Total PD FTE utilization.

Equations were generated for the two lines shown in **Figure 5-6** to establish the effect of equipment failures on program throughput and FTE utilization:

\[
\text{Throughput Decrease} = -0.007559 + 0.5662162\times\text{Failures},\text{ adjusted } R^2 \text{ value of } 99.4\%.
\]

**Equation 5-3**: Equation for Relationship of Throughput and Equipment Failures

\[
\text{Total FTE Utilization} = 0.4076675 + 0.0303997\times\text{Log(Failures)},\text{ adjusted } R^2 \text{ value of } 85.2\%.
\]

**Equation 5-4**: Equation for Relationship of Total PD FTE Utilization and Equipment Failures

The detailed fits can be found in the Appendix. In summary:

| For every 1% increase in high throughput equipment failure, there is a ~0.5% decrease in throughput and a 0.1% increase in total Pivotal PD FTE utilization. | |
5.5.3 Program Team Size

The program team size refers to the number of scientists assigned to an individual program. For this simulation, we test the impact of reducing program team sizes, so that scientists can be allocated to other activities like other biologics programs, technology development, training or special research work. This also seeks to answer the question: **How lean a program team operate without compromising throughput, assuming HTT is deployed?**

The simulation model was tested for both Drug Substance (DS) and Attribute Sciences (AS) at various team sizes. For DS, it was assumed that upstream and downstream teams were still separate and that reductions in team size would apply to both upstream and downstream, never to just one team exclusively. Another critical assumption is that all scientists are able to perform experiment-related activities in a manner of equal quality and speed, and that they are all fully trained on the high throughput equipment across the unit operations. Pollard et al. [27] have identified this "activation energy" of training scientists on highly specialized and complex equipment as a significant hurdle to overcome. The other assumptions for the simulation model can be found in the Appendix. As shown in Figure 5-9, the total pivotal PD program throughput declines below the status quo at a DS team size that is 33% of the regular team size and at an AS team size that is 30% of the regular team size.

![Impact of Program Team Size on Pivotal PD Throughput](image)

**Figure 5-7:** Simulation results showing the impact of program team size on pivotal PD program throughput. Utilization is not mapped as there is an evident and proportional increase in utilization with a decrease in team size.

Equations were generated for each of the lines in Figure 5-7. DS Teams had a p-value above α which may be due to insufficient data points to establish a significant relationship. If a
relationship were to be established just based on the trend: For every 33% reduction in DS staff per program team, there is a 13% decline in Pivotal PD throughput, assuming HTT is implemented. Although HTT can free up some FTE capacity, operating teams too leanly may dilute the benefits of HTT. Although this simulation was run assuming a universal reduction in team sizes across all program teams, it is still possible that a handful of teams can operate at a smaller size with HTT. The model can be used to determine the overall impact of such a decision in the future, should capacity constraints require this.

\[
\text{Pivotal PD Throughput} = 0.5951411 + 0.3872884^{*}\text{DS Team Size}, \text{ adjusted } R^2 \text{ of 89.9%}
\]

**Equation 5-5:** Equation for Relationship of Throughput and DS Team Size

\[
\text{Pivotal PD Throughput} = 0.9741478 + 0.1817924^{*}\log(\text{AS Team Size}), \text{ adjusted } R^2 \text{ of 88%}
\]

**Equation 5-6:** Equation for Relationship of Throughput and AS Team Size

In summary:

| With high throughput technology and the new pivotal process design implemented, only up to 33% of DS program teams and up to 70% of AS teams can be reassigned to perform other, non-experimental PD work without causing the total pivotal PD throughput to decline below the pre-HTT level. |

5.5.4 Number of Runs

Rightsizing is one of the key principles behind the proposed pivotal process design which addresses a root cause behind high FTE resource utilization. Although HTT can provide some flexibility to accommodate larger runs, determining the appropriate run size increase that will not cause a decline in throughput below pre-HTT status quo will help scientists design experiments appropriately. This simulation seeks to answer the question: *How large can experiment run sizes be before throughput drops below status quo?* The simulation model was run under different run sizes relative to the rightsized version. The rightsized version refers to the standardized number of upstream and downstream runs established through a careful review of the most value-adding experiments under the LPE approach. Assumptions can be found in the Appendix. As shown in Figure 5-8, there is a noticeable decline in pivotal PD program throughput and an increase in peak utilization for both DS and AS. Assuming HTT is deployed, the maximum run size that can
be performed without compromising status quo throughput is 117% of the proposed, rightsized version under Lab Process Excellence.

Equations were also generated for the lines to better illustrate the relationships among the variables. Although run size does not appear to have a significant impact on throughput and peak FTE utilization ($\alpha > 0.05$), this may be due to the lack of sufficient data points to establish significance. As exhibited by the tapering of all lines toward the tipping point, this also implies that HTT's benefits are indeed realized under large run sizes. Assuming a relationship were to be established for run size, throughput and FTE utilization, we may say that for every 1% increase in run size (versus the rightsized version), there is an approximate 2.6% decline in total pivotal PD throughput, a 1.3% decline in peak DS FTE utilization and a 1.2% increase in peak AS FTE utilization. The decline in peak DS FTE utilization can be attributed to the fact that the benefits of HTT are further realized with larger run sizes and loads. Since majority of the HTT being explored will be used by the DS team, the benefits are more clearly illustrated in this group. This further emphasizes the need to explore opportunities to employ high throughput methods for AS to match spikes in workload coming from DS.

![Graph](image)

**Figure 5-8:** Simulation results showing the impact of run size on pivotal PD program throughput and peak FTE utilization.

Throughput = -0.88848 + 1.86437*Recip(Run Size), adjusted $R^2$ of 81.5%

**Equation 5-7:** Equation for Relationship of Throughput and Experiment Run Size

Peak DS FTE Utilization = -0.299508 + 1.0755981*Recip(Run Size), adjusted $R^2$ of 81.5%

**Equation 5-8:** Equation for Relationship of Peak DS FTE Utilization and Experiment Run Size
Peak AS FTE Utilization = 1.4610709 - 0.5736523*Recip(Run Size), adjusted R² of 81.5%

**Equation 5-9:** Equation for Relationship of Peak AS FTE Utilization and Experiment Run Size

In summary:

> Although high throughput technology can manage multiple runs at a time, the run size can only be increased to a maximum of 117% (1.17X) before causing the total pivotal PD throughput to decline below the pre-HTT level.

### 5.5.5 Portfolio Scheduling

Capacity utilization ultimately depends on the timing at which programs are started. Although there is no universal trend that can be established for the phasing of programs, **Figure 5-9** shows the large difference in FTE utilization between a properly spread out portfolio of programs and one that tries to run all programs at once. In this simulation, the current standard number of programs for a year was evenly split into two groups, with one group starting six months after the first group. As shown in the figure, total Pivotal PD FTE utilization changes by at least 5% as a result of program timing. Using life cycle management to properly spread out programs reduces the variability in program workload and therefore allows the system to be constantly prepared for unexpected disruptions (i.e. reprioritization, change of scope or process, fast-tracking programs, cancellation or failure) and consequently reallocation of resources. Naturally, differences in portfolio timing would also affect the total program throughput that can be completed in a span of two years. The effects highlight the importance of portfolio selection and management in maximizing profitability and productivity, as emphasized by past studies [17], [72].

Aside from timing and FTE utilization, other factors such as potential profit or net present value, market competition, safety, manufacturing constraints, capacity investments, firm size and risk contribute to the overall portfolio strategy of a company [67][73]. Although this simulation is capable of measuring the impact of various portfolio scenarios and several of these variables, portfolio and life cycle management are out of scope for this study and recommended for further expansion by future studies.
Key Findings and Recommendations

This second approach of using discrete event simulation to evaluate the potential benefit to be gained from high throughput technology, in addition to the lean improvements made under Lab Process Excellence, has generated several findings and recommendations that can guide Amgen in its efforts to implement the technology across its pivotal PD operations:

1. The proposed pivotal process design increases capacity in a response to a growing program pipeline, but exploring HTT is relevant due to time constraints and anticipated change management.

There is a projected throughput increase of 2.9X, well above the estimated 1.7X increase. The simulation predicts that if the full changes were realized immediately, the proposed Pivotal Process Design (LPE) would provide a sufficient increase in capacity or throughput to match the increase in program demand for the next three years. However, these changes require some time for pilot testing, adjustments and continuous training of the lab teams before its full potential can be realized. As a result, there is need to evaluate HTT options.
(2) **HTT throughput and FTE utilization benefits** are not exactly matched to the maximum capacity of the HT equipment. The throughput benefits to be gained are high but workload-dependent.

High throughput technology has the potential to deliver an additional 37% increase in throughput on top of the LPE improvements. However, as shown by running a lower number of programs, the benefits of HTT are best realized with large workloads. Therefore, a lower ROI would be realized if a company were to invest in HTT for a small program pipeline. Aside from an emphasis on HTT in process characterization, which is aligned with the findings at the 2016 HTPD Conference [27], another potential application for HTT, which has been explored for high throughput screening and PAT, is to perform more runs to generate a larger repository of historical data that can be mined for predictive modelling or reduced experimentation in the future.

(3) **HTT throughput benefits** can only be fully realized with a corresponding investment down the line.

Although cycle time reductions are large especially for downstream processes, a significant improvement in throughput will only be realized if similar cycle time reductions can be made in analytics. For example, there is a significant opportunity to invest in automation of assay analytics, with more than 50% of AS FTE touch time spent on this step. This aligns with previous studies that have emphasized the need for new technologies in analytical methods to support any process improvements arising in process development [13].

(4) **Cross-training upstream and downstream DS lab teams** is beneficial to increasing throughput, but unnecessary for HTT.

There is 1.13X improvement in throughput as a result of cross-training, but this effect is diluted with the implementation of HTT since HTT expands capacity through parallelism and high volumes. Cross-training would therefore be useful for unit operations where there are no foreseeable high throughput technologies, such as viral inactivation.

Once HTT is implemented, several factors need to be considered for successful implementation.

(5) **Equipment downtime:** The maximum possible failure rate for HT equipment is 44% before throughput begins to drop below the pre-HTT status quo.
(6) **Program team size**: Should Amgen wish to reallocate some lab scientists to other types of work (e.g. technology development, training), the current DS program teams can operate down to a size that is 67% of the current team size and AS teams up to 30% of the current size.

(7) **Run size**: Since HTT benefits are realized with large workloads, run sizes can increase up to 117% (1.2X) before a decline in throughput. Despite the benefits that can be gained from HTT, the rightsized experiments proposed under LPE are still essential to the effective implementation of the technology.

(8) **Portfolio scheduling**: The timing of programs has a significant effect on FTE utilization and naturally on the total program throughput in a span of two years. Given the many considerations and dependencies on previous and subsequent phases of drug development, portfolio scheduling for pivotal process development will require further research and modelling.

These findings pave the way for an implementation strategy and for further studies on high throughput technology in the context of other phases of drug development.
Chapter 6 Conclusions and Future Work

This chapter summarizes the key findings from the dual approaches taken by the study and assesses the combined impact of the two approaches with respect to throughput, FTE utilization and financial value. Recommendations for further work to expand and validate this research are also made.

6.1 Summary of Key Findings

6.1.1 Lean Principles through Lab Process Excellence

The first approach of Lab Process Excellence demonstrates the large throughput improvements that can be gained by adopting a lean approach to design experimental work. Unlike typical productivity studies, this thesis has approached capacity improvement through process design, mainly in the definition of standards, reinforcement of standards and use of prior knowledge through management systems and subsequent streamlining of existing process flows. The resulting improvements demonstrate the effectiveness of several principles in increasing process throughput:

- Enforcing key decision-making upfront rather than at later stages of the process
- Collaborative discussion of experiment design among key stakeholders or decision-makers, subject-matter experts and scientists
- Enforcing statement of hypotheses or experiment objectives to allocate resources appropriately and manage proposed experiments by exception rather than by meticulously reviewing all proposals
- Reducing variability across process steps, thereby increasing predictability of resources required and risks to be undertaken
- Standardizing definition of information required for handoffs between DS, AS and decision makers (i.e. management teams, resource planners)
- Building of prior knowledge through templates and leveraging this database through an established process and management system
- Aligning process definitions and standards allows identification of process improvements and opportunities for streamlining
Most of all, both the retrospective analysis and simulation have demonstrated the potential of proposed improvements to anticipate the increase in program demand for Pivotal PD.

One caveat to this approach, however, is the interdependency with the rest of the process, as summarized by Goldratt's Theory of Constraints. The total system will only be as fast as the bottleneck [74]. If a process experiences significant improvements, its increased efficiency will demand a similar level of efficiency from preceding and succeeding processes in the chain. In the example presented by Repenning & Sterman [40], the improvements did not fully succeed because the resulting efficiencies led one part of the process (e.g. manufacturing) to demand more data from the preceding, capacity-constrained process. On top of this, monitoring progress and performing further process improvements will continue to be challenging without improvements in data integrity. Although the proposed rightsizing templates are an initial effort to standardize data inputs, further integration with the electronic lab notebook and portfolio management and scheduling systems within Amgen will allow capacity planners to gain better visibility of the impact and effectiveness of these initiatives. As Gernaey et al. concluded, the storage of historical data is critical to process improvement, but extracting knowledge from this data is actually the bottleneck and still requires further research [19].

6.1.2 High Throughput Technology

The second approach of applying high throughput technology (HTT) has demonstrated the sensitivity of promising technology and automation to various system factors that may influence its effectiveness. The discrete event simulation developed shows the clear potential of HTT to increase Pivotal PD throughput in anticipation of increased PD program demand, though not in a 1:1 translation of throughput and FTE utilization. As hypothesized, HTT efficiencies are realized with an increased number of runs, making HTT ideal for use in process characterization and downstream activities where large amounts of data are collected. Additional constraints significantly influence HTT effectiveness, particularly equipment failure rates, emphasizing the need for appropriate maintenance and training plans. While there is a potential to resize program teams with the assistance of HTT, the significant "activation energy" or training required for HTT users must be considered and matched by appropriate staffing levels in the analytical lab. Cross-training is generally beneficial but need not be considered if HTT will be implemented.
This study also validates several of the findings discussed in the 2016 HTPD Conference, as summarized by Pollard et al. [27]. Investments in scientist or user training are required to fully realize the benefits of HTT, especially in the use of the equipment and analysis of the data. Similarly, sufficient support from data systems will be required following the generation of larger amounts of data, especially if the intention is to use HTT to build up prior knowledge. Recognizing the balance of the workflow and how the HTT will fit into that workflow will be important in gaining the efficiencies of HTT. Lastly, cross-functional alignment not only between DS and AS, but between PD and the rest of the drug development organizations, is needed so that they do not continue to shift the bottleneck.

6.2 Assessing Combined Impact and Viability

6.2.1 Combined Cycle Time Savings and Throughput Improvement

![Figure 6-1: Combined impact of proposed initiatives](image)

Revisiting the conceptual framework presented, the combined LPE and HTT initiatives have generated significant cycle time savings and improvements in throughput. Combining the two initiatives can potentially increase throughput by 2.75X (+175%) or reduce cycle time by 63.7%. DS FTE capacity, specifically, can potentially increase by 2.5X (+147%). These improvements therefore prepare Amgen Pivotal PD for the 2.3X (+129%) increase in its portfolio in the coming years, thus meeting the objectives originally set forth by this study.

6.2.2 Estimating the Financial Value of Improvements

The value of each month of development time saved can be estimated based on the range between the stabilized commercial value and the maximum potential of an FDA priority review
voucher, which is valued between $130-250 million. The FDA priority review voucher is the result of a program launched by Congress in 2007 to accelerate the review process for new drugs from ten months to six months. If a drug addresses a neglected disease, the FDA grants a priority review voucher for that drug as well as a bonus voucher for another drug of the company's choice [75]. The voucher grants an acceleration of four months in the FDA review process and therefore a time, competitiveness and exclusivity advantage. Based on this, every month of development time saved could be valued at up to $62.5 million for the company [75], [76]. For confidentiality, the potential time savings that Amgen can gain from LPE and HTT cannot be revealed. However, we may use an industry benchmark to illustrate a theoretical calculation.

In a simulation study on pharmaceutical portfolio management by Perez-Escobedo, et al. [73], nine programs at a biopharmaceutical firm were run simultaneously within the simulation timeframe and process development was estimated to consume 600 to 1000 days (roughly 6.7 to 11 quarters). Assuming a total cycle time reduction of 51% (40% from the revised process design and 11% from HTT), each program would save between 10.2 to 17 months. If this time saved were on the critical path, each program would save time worth between $637.5 million to $1.06 billion in value. At nine programs, this would total $5.7 billion to $9.5 billion in value for the company. This does not yet include the potential revenue that the company can gain from the additional nine programs that can be developed as a result of reduced cycle time, assuming the current throughput of nine programs were increased by 104% (2.04X) as a result of LPE and HTT, and assuming the nine additional programs are all successfully commercialized. Benchmarking on the 2016 performance of EPOGEN® [77], a 44.7% margin (taken from the publicly available company investor report) and a 10.5% discount rate as suggested by Perez-Escobedo et al [73], nine new products can potentially amount to a net present value of $49 billion.

It should be noted that these are all optimistic estimates, as increasing the number of programs in the pipeline cannot change the likelihood of attrition during clinical trials. Likewise, these are not reflective of the actual value to Amgen, but illustrate the potential value that can be generated for a company like it. It can also be noted that the proposed improvements require little to no financial investment for Amgen, therefore presenting a reasonable return on investment.
6.2.3 Viability of Proposed Improvements

It should be noted that with the learning curve and training involved for the LPE improvements and the "activation energy" that needs to be overcome for each HTT investment [27], these improvements will require some time to be realized. The portfolio timing must therefore be managed to only work within available capacity until these improvements have been fully piloted and validated.

Figure 6-2 shows a qualitative assessment of each of the initiatives' viability in terms of risk (likelihood of failing to deliver on its potential improvements, financial investment required and timing (how soon they can be implemented), where 0 is defined as the low risk, low investment and short timing, and 5 is defined as high risk, high investment and long timing. The range of scores for timing were based upon the estimated ranges of time required for implementing each initiative, which were dependent on the availability of pilot programs, the estimated completion of equipment qualification or readiness and the overall experiment lead time. The range of scores for investment were based on the estimated costs of the HTT and the value of the man-hours required to implement each initiative. The risk scores were qualitatively assessed, based on the initial results obtained from experiments conducted to date on each HTT and based on the initial feedback during and after the LPE initiatives were developed. The data table summarizing the scores can be found in the Appendix.

Figure 6-2: Assessment of the viability of each initiative where the origin is the optimal level

The evaluations given may change over time, as the HTT are developed further and as more pilot programs reveal results validating the proposed tools and processes. Based on these evaluations, the rightsizing templates and management system have the highest viability among
all LPE initiatives, while the streamlined process requires some time for adaptation. For HTT, the capture and polishing technologies downstream, which have been under development and qualification for the past year, have a stronger likelihood of implementation in the near future compared to other technologies. With downstream processes defining the bottleneck of the streamlined pivotal process design, and rightsizing experiment design as the foundation of process improvements, beginning with an immediate pilot for these initiatives will allow Amgen to begin reaping some benefits. Similarly, development must continue for both the streamlining and upstream operations due to their relatively far from ideal state.

6.3 Recommendations for Future Work

This study has presented a combination of lean principles and high throughput technology as a means to augment process development capacity in a biopharmaceutical company. The results of the study present several opportunities to conduct gain more insights on the appropriate use of both approaches and to extract more benefits, as suggested below:

6.3.1 Pilot Implementation and Immediate Actions

(1) **Further validate the proposed process design under LPE.** Due to limitations in the study duration and availability of active programs for testing, it is suggested that a pilot implementation of the proposed pivotal process design, tool and management system be conducted with at least two programs. Seek feedback from the teams involved on the effectiveness of the new process and take suggestions on further enhancements. Closely track metrics of experiment cycle time and FTE utilization using standardized data entry methods in electronic lab notebooks or, if difficult, a separate but standardized file accessible by all program teams and project managers.

(2) **Develop methods to reduce total cycle time of downstream setup and data analysis.** The results of the HTT simulation suggest that although using HTT can reduce FTE utilization and increase throughput, a significant increase in throughput is not possible without efforts to address the bottlenecks, namely in downstream material and equipment setup, and in AS assay analytics. Options to automate or further streamline these processes should be explored to effectively reduce cycle time.
(3) Continue qualification and training of all lab scientists on the use of both upstream and downstream high throughput technologies. Once the teams have been fully trained on all the HTT, identify some pilot programs for initial testing with a large volume of runs to fully reap the benefits of HTT. Identify succeeding programs that will use HTT following the guidelines established in this study, and with a forecast on throughput and FTE utilization from the simulation tool.

6.3.2 Enhancement of Tool Capabilities and Further Studies

(4) Use the simulation tool to explore the effects of other variables not captured in this study. The simulation may have provided some useful initial insights on some use cases for HTT, but it still does not capture other variables such as the overall experiment success rates based on media used, material usage, resin capacity, process yield and associated costs. Interchangeability of program team members can also be developed to add more complexity to resource planning. Modality-specific models can be developed to gain better simulation accuracy. Lastly, once more data and expertise has been developed, the model should be extended to include continuous manufacturing.

(5) Integrate the simulation tool with other platforms within Amgen. The tool provides a granular view of more realistic cycle times and FTE requirements of various unit operations, which is a perspective that is currently not available within the resource planning team’s platforms. After further validation and testing of this model, this simulation tool may be able to provide a more granular and scientific approach to estimating resource requirements for process development. Other platforms that this can be integrated with are the portfolio planning tools used by project managers and the life cycle management team, and online document repositories where an electronic document workflow can be used to support the use of rightsizing templates.

(6) Use the simulation tool to determine when capital investment will be required for additional equipment. In succeeding capital budgeting cycles, the simulation can be used to determine, based on any changes to the program pipeline and team assignments, whether investing in more units of specific HT equipment will be necessary.
(7) **Enhance the simulation tool for higher usability and more capabilities.** In this first version of the model, the cycle times are coded into the actual simulation instead of referring to an editable external array. As a result, some knowledge of ProModel may be needed to adjust the model. Further enhancements to the tool can be made to make adjustment of simulation parameters easier.

(8) **Extend the study to the other phases of drug development.** Following the concept of a shifting bottleneck, improvements to one process tend to shift the bottleneck to another process down the line.

Several of these recommendations are best supported by a robust and reliable data management system and religiously followed data standards that will ensure accessibility of prior knowledge for all lab scientists involved in PD work. Most of all, since these recommendations will entail a significant allocation of resources and continuous improvement in organizational processes, it is recommended that the senior management and all lab scientists across Amgen Process Development continue to support these efforts to ensure sustainable improvements in the overall productivity of the organization. With these supporting elements, Amgen PD can unlock the large capacity improvements that have been identified from the combined approaches of applying lean principles and high throughput technology.
Bibliography


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Appendices

Chapter 3

Section 3.1: Problem Diagnosis and Root Cause Analysis

Interview Questionnaire

a) Please give a quick overview of your process.
b) What is your group responsible from a day-to-day perspective from a process point of view?
c) What are your group's primary goals?
d) How do you know when the complete process is done?
e) What is your definition of a good product? On a scale of 1-10, how satisfied is the customer?
f) On a scale of 1 to 10, how fast is your process?
g) How do you define speed? Do you have systems in place to collect this data?
h) On a scale of 1 to 10, how efficient is your process?
i) How do you define efficiency?
j) Who are your customers, stakeholders and suppliers?
k) Based on your knowledge, what is going well?
l) What are some improvement opportunities?
m) If there were no barriers or constraints, what would you do to go faster?
n) What are the barriers or constraints in your process?
o) What do you feel are some quick wins for efficiency / speed?
Chapter 4

Section 4.3: Rightsizing Process Development Work

Rightsized Experiment Templates

*Note: Actual templates have more detailed descriptions of experiments and assays. Details have been masked for confidentiality. PC Upstream and Downstream templates are similar, with differences only in Unit Operations and Parameters assessed.*

<table>
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<tr>
<th>CPD UPSTREAM</th>
<th>Focus area</th>
<th>Include in CPD (Y/N)?</th>
<th>Objective of work if including or rationale if excluding</th>
<th>Number of bioreactor blocks</th>
<th>Start Date</th>
<th>End Date</th>
<th>Duration (wks)</th>
<th># titer samples</th>
<th># Product Quality (PQ) samples</th>
<th>PQ assays (Assay 1, Assay 2, etc.)</th>
<th>Total # PQ samples</th>
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<td>XX months will be allotted for CPD for non-biosimilars</td>
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<td>Max. 2 samples per bioreactor per block</td>
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<th>Start Date</th>
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<th>Duration (wks)</th>
<th>PQ assays (Assay 1, Assay 2, etc.)</th>
<th># PQ samples</th>
<th>Rationale / justification for PQ assays &amp; # samples chosen</th>
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### PC Upstream

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<th>DOE or one-off?</th>
<th>Unit of Measure</th>
<th>Operating range</th>
<th>Lower PC range</th>
<th>Upper PC range</th>
<th>Assessed in block #(s)</th>
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<th>End Date</th>
<th>Duration (wks)</th>
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<th>PQ assays (Assay 1, Assay 2, etc.)</th>
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Fill out info for succeeding unit ops and parameters:

Yes or program-dependent

XX months will be allotted for PC for non-biosimilars

Max 2 per experiment
Chapter 5

Section 5.3: Simulation Design

Simulation Specifications

126 Locations, 12 Entities, 25 Resources (each with multiple components)

Sample Simulation Logic

\[
\text{FedBatch\_CPDUp\_Exp N\_MaterialsPrep} \quad \text{V\_MaterialPrep} \\
\quad \text{//This will log the experiment number and program number in a tracker.}
\]

\[
y\text{tracker}[\text{program}\_\text{number}, 1] = \text{program}\_\text{number}
\]

\[
y\text{tracker}[\text{program}\_\text{number}, 2] = \text{CPD\_up\_experiments}
\]

\[
y\text{tracker}[\text{program}\_\text{number}, 3] = 1
\]

\[
1 \quad \text{FedBatch\_CPDUp\_Exp N\_EquipmentSetup} \quad \text{FIRST} \quad 1
\]

\[
\text{FedBatch\_CPDUp\_Exp N\_Arrivals} \quad \text{If site=1 Then}
\]

\[
\quad \{ \\
\quad \quad \text{Get 1 Res\{yman[\text{program}\_\text{number}, 2]\}, 1}
\quad \quad \text{aResource=Res(OwnedResource())}
\quad \quad \text{Free OwnedResource()}
\quad \}
\]

\[
\quad \text{If site=2 Then}
\]

\[
\quad \{ \\
\quad \quad \text{Get 1 Res\{yman[\text{program}\_\text{number}, 4]\}, 1}
\quad \quad \text{aResource=Res(OwnedResource())}
\quad \quad \text{Free OwnedResource()}
\quad \}
\]

\[
1 \quad \text{FedBatch\_CPDUp\_Exp N\_MaterialPrep} \quad \text{FIRST} \quad 1
\]

Simulation Screenshot
Input File Screenshot
Results removed for confidentiality.

Output Report Screenshots
Results removed for confidentiality.
Simulation Model Assumptions

(1) **PD Sites**: The simulation can only accommodate a maximum of two PD sites.

(2) **Process**: The process is largely patterned after a fed-batch production process, but can apply to both fed-batch and perfusion processes.

(3) **Process**: Cycle times are taken from time-and-motion studies, interviews of experienced scientist and a past model developed by Attribute Sciences. These cycle times are assumed to reflect actual lab performance.

(4) **Process**: Each upstream experiment will request for the same five assays, while each downstream experiment will request for the same four assays.
(5) Process: Unless otherwise stated during program input, all programs will undergo all processes defined in the proposed pivotal process design under LPE. CPD and PC are still distinguished from each other to highlight changes in resource requirements.

(6) Process: Program teams do not start the next upstream experiment until the previous experiment has entered the analytical lab phase. Downstream experiments, on the other hand, can run in parallel.

(7) Assay cadence: The implementation of assay cadence is simulated by collating then batching experimental run outputs before running their designated assays at the analytical lab.

(8) Experiment and run sizes: Unless otherwise configured, all experiments are rightsized. No ad hoc experiments are conducted.

(9) Experiment success rates: All experiments have a success rate of 100%, though this may, in reality, be lower. Allowances have been made for the possibility of an equipment failure which may also count as an experiment failure. The baseline simulation assumes 0% machine breakdowns or equipment failures. Once started, a program cannot be cancelled.

(10) Calendar: The standard work holidays for the United States are set in the annual calendar with two additional weeks for lab shutdowns.

(11) Shifts: Around 64% of an upstream scientist’s time is spent on experimentation. For downstream scientists, 50% of their time is spent on experimentation. AS spend 80% of their time on experimentation. The rest of the time available is assumed to be spent on other activities such as report generation, meetings and administrative activities. Upstream scientists can work on weekends, if the harvest of the cell culture requires it. Downstream and AS only work on weekdays. In general, FTEs work 8 hours per day, 5 days per week. Overtime is possible, but scientists will never run continuous, 24-hour work days.

(12) Workload: A program team can never work on more than one program at a time.

(13) Program Team Sizes and Available FTEs: The standard Amgen biologics program team size as of Q4 2017 is used. Available FTEs in DS and AS are based on the current resource model used at Amgen and is assumed to remain unchanged throughout the simulation period. DS and AS team leads are not considered lab hands.

(14) Team Composition: Team composition is assumed to remain the same. This means that if a team has three team members, those three members will always work with each other for succeeding programs. This assumption has been made for simplicity of modelling, but reality may require interchanging of team members.

(15) FTE Abilities: All FTEs are of equal ability and can therefore perform work at the same speed and quality. All Upstream FTEs are trained to use the HTT being explored while all Downstream FTEs are trained to use HTT deployed at any unit operation.

(16) Costs and Risks: No financial considerations or costs are considered in this model, though there is a possibility of estimating labor costs by setting a standard time.
(17) **Material availability:** All materials, utilities and other resources are readily available. There is no risk of material shortage or delays related to the procurement of these materials.

(18) **Equipment availability:** There are sufficient machines available for use for all subprocesses and unit operations. All of the machines are qualified for use.

(19) **Run period:** Since a full program is estimated to take more than one year to complete, the simulation run time is set to two calendar years, which account for holidays, shutdowns and weekends.

**Section 5.5: Process Sensitivity Analysis**

**Additional Assumptions for Equipment Failure Simulation**

- If a machine fails downstream, it is assumed to require new material which will be readily available from previously conducted material generation runs.
- Machine downtime or failure rates are applied across all available HT equipment. The simulation is capable of applying different failure rates to different types of equipment, but this will not be covered in this study.
- Machine failures are easily and immediately repairable without consuming any additional, internal FTE resources.

**Regressions for Equipment Failure, Throughput and FTE Utilization**
Additional Assumptions for Program Team Size Simulation

- No equipment failures or breakdowns occur during experimentation.
- All program team members are capable of performing their respective group's work at equal quality and speed, even with a reduction in team size. No further training is required.

Regressions for Program Team Size and Throughput
Additional Assumptions for Run Size Simulation

- Increases in run size are applied across both upstream and downstream operations, which consequently affect the AS workload.
- Additional runs may or may not be value-adding to drug development, but are included for purposes of illustrating the effect on FTE utilization and throughput.

Regressions for Run Size, Throughput and Peak FTE Utilization
Bivariate Fit of Throughput By Run Size

Transformed Fit to Reciprocal

Throughput = -0.88848 + 1.86437*Recip(Run Size)

Summary of Fit
- RSquare: 0.876357
- RSquare Adj: 0.814535
- Root Mean Square Error: 0.055985
- Mean of Response: 0.805
- Observations (or Sum Wgts): 4

Analysis of Variance
- Source: Model
- DF: 1
- Sum of Squares: 0.04443129
- Mean Square: 0.044431
- F Ratio: 14.1756

Parameter Estimates
- Term: Intercept
- Estimate: -0.88848
- Std Error: 0.45066
- t Ratio: -1.97
- Prob>|t|: 0.1874
- Term: Recip(Run Size)
- Estimate: 1.86437
- Std Error: 0.495179
- t Ratio: 3.77
- Prob>|t|: 0.0639

Bivariate Fit of Peak DS Utilization By Run Size

Transformed Fit to Reciprocal

Peak DS Utilization = -0.299508 + 1.0755981*Recip(Run Size)

Summary of Fit
- RSquare: 0.876357
- RSquare Adj: 0.814535
- Root Mean Square Error: 0.032299
- Mean of Response: 0.6775
- Observations (or Sum Wgts): 4

Analysis of Variance
- Source: Model
- DF: 1
- Sum of Squares: 0.01478852
- Mean Square: 0.014789
- F Ratio: 14.1756

Parameter Estimates
- Term: Intercept
- Estimate: -0.299508
- Std Error: 0.259996
- t Ratio: -1.15
- Prob>|t|: 0.3684
- Term: Recip(Run Size)
- Estimate: 1.0755981
- Std Error: 0.28568
- t Ratio: 3.77
- Prob>|t|: 0.0639
Chapter 6

Section 6.2 Assessing the Combined Impact and Viability

Data Table for Risk, Investment and Timing Assessment

<table>
<thead>
<tr>
<th>Lab Process Excellence (LPE)</th>
<th>Risk</th>
<th>Investment</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rightsizing Templates</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Management System</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Streamlined CPD and PC</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High Throughput Technology (HTT)</th>
<th>Risk</th>
<th>Investment</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upstream</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

| Downstream                      |      |            |        |
| Capture                         | 1    | 1          | 3      |
| Polishing 1                     | 1    | 1          | 3      |
| Polishing 2                     | 1    | 1          | 3      |
| UFDF                            | 1    | 1          | 4      |