Product Management Framework for the Development of Automation Solutions for Biologics Drug Substance Manufacturing

by

Ketan Kumar

B.S., Tufts University (2014)

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

in partial fulfillment of the requirements for the degrees of

Master of Science in Chemical Engineering

and

Master of Business Administration

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

May 2020

Author .....

Department of Chemical Engineering and the MIT Sloan School of Management

May 1, 2020

Certified by .....

Richard D. Braatz

Edwin R. Gilliland Professor, Department of Chemical Engineering

Thesis Supervisor

Certified by .....

Retsef Levi

J. Spencer Standish (1945) Professor of Operations Management

Thesis Supervisor

Accepted by .....

Maura Herson

Director, MBA Program

MIT Sloan School of Management

Accepted by .....

Patrick Doyle

Robert T. Haslam (1911) Professor

Department of Chemical Engineering

Product Management Framework for the Development of Automation Solutions for Biologics Drug Substance Manufacturing

by

Ketan Kumar

Submitted to the Department of Chemical Engineering and the MIT Sloan School of Management
on May 1, 2020, in partial fulfillment of the
requirements for the degrees of
Master of Science in Chemical Engineering
and
Master of Business Administration

Abstract

This thesis presents a product management framework for the development of innovative manufacturing automation solutions, and the application of this framework to the development of automation for a continuous biomanufacturing platform at Amgen. A recently formed team at Amgen – Next Gen Automation (Drug Substance) (NGA(DS)) – is working to develop innovative automation solutions that support Amgen's strategic initiatives. Being an innovation team, NGA(DS) faces uncertainty regarding what aspects of the existing process are best suited to be improved using automation and what the best automation solutions are to achieve these results. The framework presented in this thesis provides NGA(DS) a methodology to develop useful solutions in the presence of this uncertainty. Supporting automation development for the continuous biomanufacturing platform is one of the work streams of NGA(DS), and was used as a case study for the development of the product management framework.

Several prominent innovation and product management frameworks were leveraged in the development of the framework for this project, including *Lean Startup* and *Disciplined Entrepreneurship*. As recommended by the sources studied, this project modelled innovation as a collaborative and iterative process of testing hypotheses regarding the value of the product being developed. Specific tools and concepts were applied from the source frameworks, as relevant to the teams's needs. The framework developed in this project consisted of two phases – Opportunity Analysis and Solution Development – with multiple data collection and analysis activities in each phase. Results from the activities were validated through reviews by the NGA(DS) team leadership and other relevant Subject Matter Experts within Amgen. The framework developed in this project is intended to guide future decision making for

product development activities by NGA(DS).

Thesis Supervisor: Richard D. Braatz
Title: Edwin R. Gilliland Professor, Department of Chemical Engineering

Thesis Supervisor: Retsef Levi
Title: J. Spencer Standish (1945) Professor of Operations Management

Acknowledgments

I would like to thank Amgen for sponsoring this project. Working with the Next Gen Automation team has been an amazing opportunity. I have learned a tremendous amount working with my supervisors, Jeremy Conner and Mark Quinlan, and the rest of the NGA team. I am grateful to everyone at Amgen who took time to meet with me and to help with my project. I would like to especially thank Dollie Grajczak for making this internship opportunity possible, and for consistently making my life easier before, during, and after the internship.

I would like to thank my advisors, Retsef Levi and Richard Braatz, for providing invaluable advice for executing the project and writing the thesis.

Leaders for Global Operations (LGO) has been an incredibly exciting and supportive community over the past two years. I would like to thank the staff – Patty, Thomas, Ted, Anna, Josh, and others – for their support. Thank you to all the alumni who have provided invaluable inspiration and advice (this project and beyond). Thank you to the entire Class of 2020 for being incredible friends. A special shout-out to my roommates during the project (Ellie Azolaty and Ellen Coleman), Team 6, and the Amgen intern class of 2020.

Finally, I would like to thank my family – Mom, Dad, Tejas, and Manisha – for their constant love and support.

THIS PAGE INTENTIONALLY LEFT BLANK

Contents

List of Figures

THIS PAGE INTENTIONALLY LEFT BLANK

List of Tables

THIS PAGE INTENTIONALLY LEFT BLANK

Chapter 1

Introduction

1.1 Executive Summary

This thesis presents a product management framework for the development of innovative manufacturing automation solutions, and the application of this framework to the development of automation for a continuous biomanufacturing platform at Amgen. Biomanufacturing capability is a strategic priority for Amgen and automation is integral to Amgen's manufacturing processes. A recently formed team at Amgen, Next Gen Automation (Drug Substance) (NGA(DS)), is working to develop innovative automation solutions that support Amgen's strategic initiatives. Being an innovation team, NGA(DS) faces uncertainty regarding what aspects of the existing process are best suited to be improved using automation and what the best automation solutions are to achieve these results. Supporting automation development for a continuous biomanufacturing platform, referred to in this thesis as Platform A, is one of the work streams of NGA(DS). This work stream was used as a case study for the development of the product management framework.

Section 1.2 of this thesis provides a literature review of the three fields relevant to this project: biomanufacturing automation, continuous biomanufacturing, and product management. Literature about biomanufacturing automation and continuous bioprocessing provided information regarding the general state of the art, benefits, and challenges of these technologies. Literature in the field of product management

provided ideas for how a product management framework could be designed for the NGA(DS) team. These ideas included both general principles and specific managerial tools.

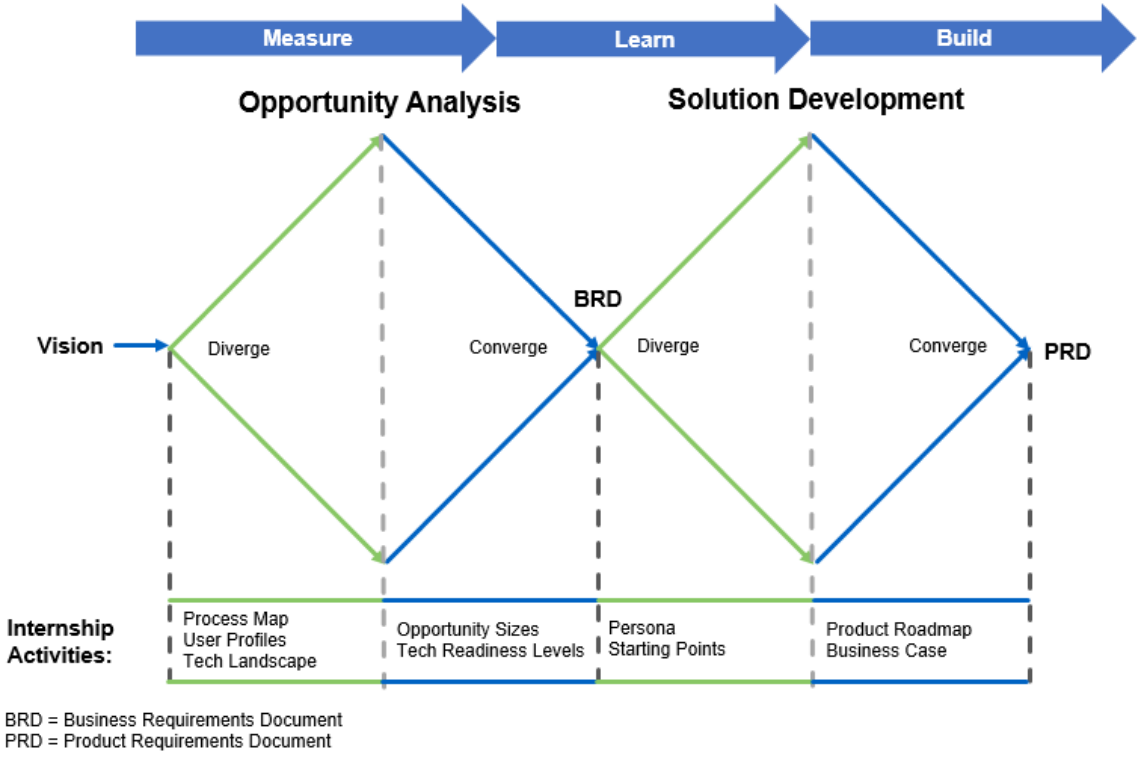

Figure 1-1: Product management framework for NGA(DS)

Section 1.3 presents the overall approach for the project and how a framework was developed for NGA(DS) based on the product management sources covered in the literature review. Based on the recommendations of theses sources, this project emphasized collaboration, iterative development, and hypothesis testing. The framework developed in the project is presented in Figure 1-1. The input to the framework is a broad vision for the product(s) being pursued – in this case, automation solutions to reduce the cost per gram for Platform A. The framework consists of two phases of analyses – Opportunity Analysis followed by Solution Development. This ordered structure of the framework is intended to keep the product development process focused on addressing the most important business opportunities, rather than developing any specific technological solution.

Chapter 2 provides background regarding the vision of the NGA(DS) team for

Platform A. The vision is analyzed in terms of how it supports Amgen's overall strategy. Given that NGA(DS) team acts as an internal supplier of automation, first the overall supply chain from automation suppliers to Amgen's customers (i.e. patients) is considered. Then the general strategic benefits and costs of insourcing automation (e.g., from NGA(DS)) as opposed to outsourcing are considered. The location of NGA(DS) within the supply chain as an internal supplier of automation is considered. The team's customers and partners are identified. Finally, background information is provided regarding the development of Platform A as a strategic initiative, and the involvement of NGA(DS) in this initiative. The reduction of cost per gram for Platform A is identified as a strategic goal for NGA(DS).

Chapter 3 presents the methods and results for the Opportunity Analysis phase. This phase began with searching for all opportunities pertaining to the vision for the product. In this project, the search was done through three activities: (i) mapping the Platform A process, (ii) generating user profiles for potential internal customers of NGA(DS), and (iii) analyzing the technology development landscape for other development teams within Amgen. From these three activities, various opportunities were documented that improved different kinds of performance metrics at different parts of the process. The performance metrics included labor time, yield, throughput, raw material utilization, footprint, and deviation rate. To prioritize these opportunities, they were all assessed in terms of their potential benefit and development risk. Relative potential benefit was compared by calculating opportunity sizes. The opportunity size metric was adapted from the Total Addressable Market concept [1] to internal products and was defined as the maximum cost savings possible from fully exploiting an opportunity. Development risk was judged by adapting the criteria of Technology Readiness Levels. Finally, an overall criteria was presented to the team leadership that allowed them to prioritize projects based on the team's risk-benefit tradeoff and development capacity.

Chapter 4 presents the methods and results for the Solution Development phase. Several solutions were being developed by the NGA(DS) team at the time of the project, of which one – automated sampling – was chosen to be analyzed in this

phase. The Solution Development phase started with the documentation of information regarding the opportunity to be addressed by automated sampling in a Business Requirement Document (BRD), based on the analysis in the Opportunity Analysis phase. Three activities were performed to help generate ideas for possible solutions for this opportunity: (i) mapping the process of sample collection and analysis, (ii) generating personas for the scientists intended to be the lead users, and (iii) evaluating existing solutions for the opportunity. Based on the information collected, a roadmap of features was generated to guide the development of successive versions of the solution. The roadmap was designed as a series of Minimum Viable Products (MVPs) to sequentially test hypotheses regarding the value of the long-term solution being built. Two additional activities were recommended to the NGA(DS) team to be completed as part of the solution development phase, but could not be completed within the time frame of the project: (i) calculation of the long-term Net Present Value (NPV) for the product and (ii) documentation of the output from the Solution Development phase in a Product Requirements Document (PRD).

Chapter 5 recapitulates the results of this project, recommends ways to use the framework developed, and identifies areas of future growth for the framework.

1.2 Literature Review

1.2.1 Continuous Manufacturing

Continuous processing of biologics is a technology being developed widely in the biomanufacturing industry and studied in academia. Konstantinov and Cooney [2] define a continuous unit operation and a continuous process as:

"A unit operation is continuous if it is capable of processing a continuous flow input for prolonged periods of time. A continuous unit operation has minimal internal hold volume."

"A process is continuous if it is composed of integrated (physically connected) continuous unit operations with zero or minimal hold volume in between."

In a drug substance biomanufacturing process, these definitions have different implications for the upstream process, consisting of cell culture and harvest, and the downstream process, consisting of various purification steps.

For the upstream process, the difference in batch and continuous processing is primarily in the operation of the harvest step. In a batch upstream process, product is accumulated in the reactor during the cell culture and harvested at the end. In a continuous upstream process, product is continuously harvested from the reactor during cell culture, after an initial expansion of the cells. Perfusion, i.e. the continuous addition of fresh media to and removal of waste products from the bioreactor, is necessary for continuous harvest, but optional for batch cultures.

For the downstream process, batch operation involves processing an entire lot through one purification unit operation before starting the next unit operation. Continuous operation, on the other hand, implies continuously feeding the outflow from one unit operation to the next and minimizing the hold volume in between. Some units, such as tangential flow filtration, can be operated truly continuously i.e. can process a continuous flow input for prolonged periods of time, with hold volume required only for variations in flow rate. Other units, such as bind-and-elute chromatography and UF/DF, have a cyclical operation and require product to be held internally within each cycle. For these units, hold volumes can still be minimized by using shorter cycles.

The potential benefits of continuous processing for biomanufacturing operations have been documented in literature [2, 3, 4] and are summarized below. The magnitude of these benefits may vary among manufacturers and process designs, and there may also be trade-offs for these benefits such as increased labor or increased raw material costs. The potential benefits are:

1. **Increased plant throughput**: Before protein can be harvested from the production bioreactor, cells undergo expansion through incrementally larger stages of cultures and finally need to grow in the production bioreactor. This initial expansion phase can be considered as "setup time". In a continuous bioreactor, each setup would be used for a longer time and to produce more protein

than a single batch operated for a relatively shorter time period. Hence. the throughput of a reactor of a given volume can be increased.

2. **Pull scheduling**: In a batch process, product is manufactured in increments of predefined batch sizes. However, in a continuous process the amount manufactured can be modulated by changing the duration of the run. Hence continuous processes can be used to more closely match the pull from commercial demand. In an Economic Order Quantity model, a shorter setup time would also allow smaller batches and less inventory to achieve the same service levels.

3. **Reduced capital expenditure from smaller footprint**: Smaller hold volumes within and between unit operations can allow continuous processes to occupy a significantly smaller physical footprint than batch processes, which reduces the capital expense required to add manufacturing capacity.

4. **At-scale process development**: While a new drug is being developed and tested, there is also a concurrent lengthy and expensive process development effort to be able to manufacture the drug at a commercial scale. Due to the high cost of operating manufacturing scale equipment, much of the process is designed using small-scale laboratory equipment and then the process parameters are scaled up to manufacturing scale. Although these scale-up calculations have been extensively studied by academics and professionals in the area of Chemical Engineering, the calculations can be complex and not always fully reliable. The predictive power of these scale-up models can be limited by differences in geometry and configuration of large-scale manufacturing equipment versus laboratory-scale development equipment.

   Given the smaller footprint of continuous manufacturing processes, it is hypothesized that relatively small laboratories may be able to house the manufacturing-scale process, and hence develop the process "at scale". Larger capacity may then be achieved by "scaling out" (i.e., adding additional lines of the identical process) rather than scaling up, or by just running the process for a longer time period.

Konstantinov and Cooney identify various challenges for the development of upstream and downstream continuous processes. Achieving higher and sustained bioreactor productivity through media design, cell line development, and optimization of bioreactor conditions is a major challenge for cell culture. Optimization and standardization of equipment design is a major challenge for downstream unit. Supervisory process control and automation needs to be developed to synchronize the operation between continuous unit operations. Process Analytical Technology (PAT) and single-use technologies are also identified as having synergies with the development of continuous processing [2]. Supervisory control, PAT, and single-use technology are discussed further in section 1.2.2.

1.2.2 Biomanufacturing Automation

An article by the consulting firm, McKinsey & Company, on automation in manufacturing recommends that even though manufacturers may "view automation primarily as labor-savings lever," the benefits of automation often extend beyond this to reduce costs in other ways including by "increasing throughput and productivity, eliminating variation and improving quality, improving agility and flexibility, and improving safety and ergonomics" [5]. Reviews of innovation in biopharmaceutical manufacturing automation reference a similar range of benefits [6, 7, 8].

The major technology drivers of automation innovation identified in these reviews are (i) Process Analytical Technology (PAT), (ii) multivariate modelling, (iii) continuous processing, and (iv) new designs for unit operations [6, 7, 8]. Biomanufacturing automation may also be affected by disruptive innovation from the development of the Internet of Things (IoT). All of these technology drivers are reviewed below.

PAT is defined by the FDA as "a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality" [9]. A review by Jiang et al. [7] identifies a range of new and emerging sensor technologies that measure various critical quality attributes in the manufacturing process. These measurements may be used to improve the monitor-

ing or control of the process for better quality outcomes. The review also identifies technologies in development that can automatically move sample material from the process to standalone analyzer units.

Multivariate models of the process can improve monitoring and control of the process as well. The reviews by Jiang et al. [7] and Hong et al. [8] discuss the construction of multivariate models from first-principles, process data, or a combination of the two. These models can allow setting and monitoring parameters for the process to achieve better quality. Models that can predict critical quality attributes from existing data may allow the removal of tests required to directly measure these attributes. Models may also help in developing advanced process control loops which can optimize process performance and product quality in real time.

Continuous processing, being a major focus of this project, has been discussed in Section 1.2.1 in terms of benefits and challenges. Many of the process or equipment changes required for continuous processing will require automation updates to build or maintain functionality. Additionally, Konstantinov and Cooney [2] identify that the integration of multiple continuous unit operations requires a supervisory control layer which provides "oversight functions" such as "coordination of flow rate, event-based control, and exception handling." The supervisory control layer may also be used for a plant-wide implementation of real-time process optimization using model-based feedback control [8]. This concept has been simulated for a small-molecule pharmaceutical plant by Mesbah et al. [10], but is more challenging to apply to a biomanufacturing plant due to greater complexity.

New designs for unit operations, which may be driven by a very wide range of process innovations, frequently require changes in automation design. Some of the current and potential future process innovations can be considered to illustrate the range of changes that may be seen. A major recent trend in biopharmaceutical manufacturing has been the shift from stainless steel-based reusable equipment to plastic based single-use equipment. Automation systems have needed to be re-engineered for single-use unit operations because these units have different processes, actuators (pumps and valves) and sensors than their reusable equivalents [11, 12]. Hong et al.

[8] suggest that the development of novel bioseperation techniques may provide cost benefits for downstream processing. These novel techniques include aqueous two-phase extraction, precipitation, and crystallization. Crowell et al. [13] have demonstrated the performance of a small-scale biologics manufacturing platform that uses *P. pastoris* yeast cells, which may be cheaper to use as expression host instead of the industry standard Chinese Hamster Ovary (CHO) cells. Further development of the platform may allow the technology to be adopted for commercial biologics manufacturing as well.

The Internet of Things (IoT) has some fundamental similarities with industrial control systems. A comparison between the websites of a prominent IoT vendor (Amazon Web Services) and a prominent industrial control system vendor (Emerson) reveals that both technologies consist of similar components including sensors, actuators, controllers, computers, and communication. However, the actual hardware, software, and communication protocols used in IoT and industrial controls systems are often very different [14, 15]. IoT is often marketed for consumer applications and uses technology stacks consisting of open software and communication protocols. IoT, having entered at a low-end market with a cheaper product, may pose a risk of disruption to industrial control systems if the capabilities of IoT can grow to be sufficient for industrial automation [16].

1.2.3 Product Management

In developing a product management framework for the innovation team NGA(DS), this project applied existing ideas about entrepreneurship and innovation management described in *Beyond the Idea* by Govindrajan and Trimble (2013), *Lean Startup* by Eric Reis (2011), *Disciplined Entrepreneurship* by Bill Aulet (2013), *Double Diamond* framework by the UK Design Council, and anecdotal information from product managers at leading technology companies. These sources emphasize similar principles for product innovation such as collaboration, iterative development, and hypothesis testing, but provide different managerial tools based on their target audience.

Though entrepreneurship typically refers to founding or managing a startup com-

pany, *Lean Startup* and *Beyond the Idea* suggest that internal innovation teams within large companies face similar managerial requirements as startups – both seek to create innovative solutions, face uncertainty regarding the value of their potential products, and have relatively more flexibility than the core operations of a large company. Due to such similarities, it is appropriate for an innovation team such as NGA(DS) to shape its managerial practices based on entrepreneurship literature.

The sources reviewed in this section provide theory and recommendations developed within formal or informal networks of design, innovation, or product professionals. The usefulness of these frameworks is best judged by their degree of adoption, as indicated by citations or internet engagement, or adoption at companies with a successful track record of developing innovative digital products. Besides a small number of case studies provided in the texts of the sources, raw data are generally not available to independently validate if certain frameworks yield greater results. This lack of data is likely because companies would generally keep information regarding their innovation and product development practices confidential, given the competitive nature of these activities.

Beyond the Idea by Govindrajan and Trimble (2013)

Beyond the Idea deals with the question of "how to execute innovation in any organization". This book is written based on 10 years of research by Govindrajan and Trimble, consisting of case studies of innovation initiatives at a number of (mostly large) companies. *Beyond the Idea* and previous related books by Govindrajan and Trimble – *The Other Side of Innovation* and *Ten Rules for Strategic Innovators* – have a combined total of close to 600 citations, per Google Scholar [17].

Beyond the Idea describes three models of innovation within companies:

1. **Model S - Small**: This refers to small, ongoing continuous improvement innovation that all employees can participate in their slack time. In the terminology of Lean Production, this model may be considered similar to the concept of Kaizen [18].

2. **Model R - Repeatable**: In this model, innovation is executed using a staged/gated process which can be mapped and repeated to generate iterative generations of a product. The process is treated as a "factory for innovation." This model can be optimized for efficiency but is limited in its flexibility.

3. **Model C - Custom**: This model is for all innovation that is too big for model S and that requires more flexibility than Model R can offer.

Most of the rest of the book offers recommendations for how to build a team and create a plan for Model C innovation. The book defines the term *Performance Engine* (PE) as the core operations of a company that are optimized for stable and efficient creation of value. Model C innovation, with its mandate for change and flexibility, is expected to have some tensions with the PE, even though the results are intended to eventually improve the PE. Model C requires collaboration between a dedicated team outside of the PE and shared staff within the PE itself. Govindrajan and Trimble recommend building the dedicated team "as though you are building a new company from the ground up". The dedicated team should have a structure and process that break from the PE: they should be optimized for learning, as opposed to generating stable profits. In this context, learning specifically refers to an ability to predict how the PE can be improved, based on disciplined, scientific testing of hypotheses. The book provides many finer recommendations regarding how the dedicated team, the shared staff, and their collaboration should be managed [19].

Lean Startup by Eric Reis (2011)

The lean startup framework was developed by Eric Reis by combining principles from Steve Blank's Customer Development methodology and the lean manufacturing methodology derived from the Toyota Production System [20]. Reis developed lean startup at first based on his own experience as an entrepreneur and then in collaboration with the community that developed around his writing. According to Google Scholar, the original book by Reis, a follow up Harvard Business Review (HBR) article by Steve Blank, and a related Harvard Business School case have been cited a

combined number of close to 6500 times [17]. The term "lean startup" was also popular on Google's web search, as indicated by Google trends. Worldwide and in the US, this term surpassed the terms "lean production" and "Toyota production system", and was about half as popular as "lean manufacturing" [21]. Lean startup emphasizes five principles:

1. **Entrepreneurs are everywhere**: Reis defines a startup as "an institution designed to create new products and services under conditions of extreme uncertainty." These startups can be independent companies or teams within larger companies or organizations.

2. **Entrepreneurship is management**: Reis observes two likely failure modes for startups. First, managers may try to use traditional management techniques, developed for stability and predictability, for the uncertain work of innovation. Alternatively, seeing the failure of this strategy, the managers may decide that innovation cannot be managed and resort to a "Just Do It" approach. Lean startup claims to offer a third way, by creating a management technique that takes the uncertainty into account.

3. **Validated learning**: Lean thinking starts with the identification of *value* in a process, and for lean startup it is validated learning. In this framework, the startup is primarily a process of testing hypotheses regarding what value their potential product provides and how it is expected to grow.

4. **Build-Measure-Learn**: This principle breaks down the three broad steps in the cycle that produces validated learning. As part of this principle, the lean startup framework emphasizes the need for Minimum Viable Products (MVPs), which are intermediate constructs that can provide early and inexpensive validation of the startup's long-term vision.

5. **Innovation accounting**: Reis suggests that in monitoring the progress of their startup, entrepreneurs should use metrics that can directly prove or disprove

their value and growth hypotheses. Traditional business metrics may not be granular enough or may lag product changes too much to be actionable.

Disciplined Entrepreneurship by Bill Aulet (2013)

The *Disciplined Entrepreneurship* framework was developed by Bill Aulet at the Massachusetts Institute of Technology based on his experience as an entrepreneur and the workshops he leads with other entrepreneurs [22]. The framework was developed to bring together ideas from many different relevant sources (including *Lean Startup* by Eric Reis) for innovation-driven entrepreneurs. Aulet found these sources to contain concepts complementary to each other, and the book presents 24 steps that a startup must take to add structure and discipline to the chaotic entrepreneurship process. The steps are presented as an ordered, linear process, but the author acknowledges that knowledge gained later in the process may require updating the earlier steps. The book considers startups more narrowly than the *Lean Startup*, as those that are their own companies. Appendix A considers the applicability of each step of the 24-step process to internal innovation teams within large companies such as Amgen and specifically to NGA(DS).

Double Diamond framework by the UK Design Council

Design Council is an organization based in the United Kingdom that provides consultation, collaboration, and training in the field of design for various public and private organizations. The Double Diamond is a methodology "at the heart of the [Design Council's] framework for innovation" [23]. The framework, as represented in Figure 1-2, recommends subsequent divergent and convergent thinking to understand the problem and provide a solution. The four phases of the framework involve: (i) **discovering** the various needs of the end users, (ii) **defining** the problem statement that will be addressed, (iii) **developing** various ideas for solutions, and (iv) **delivering** a solution that best addresses the problem identified. The framework also identifies four design principles that guide the whole process: (i) "put people first," (ii) "communicate visually and inclusively," (iii) "collaborate and co-create," and (iv)

"iterate, iterate, iterate."

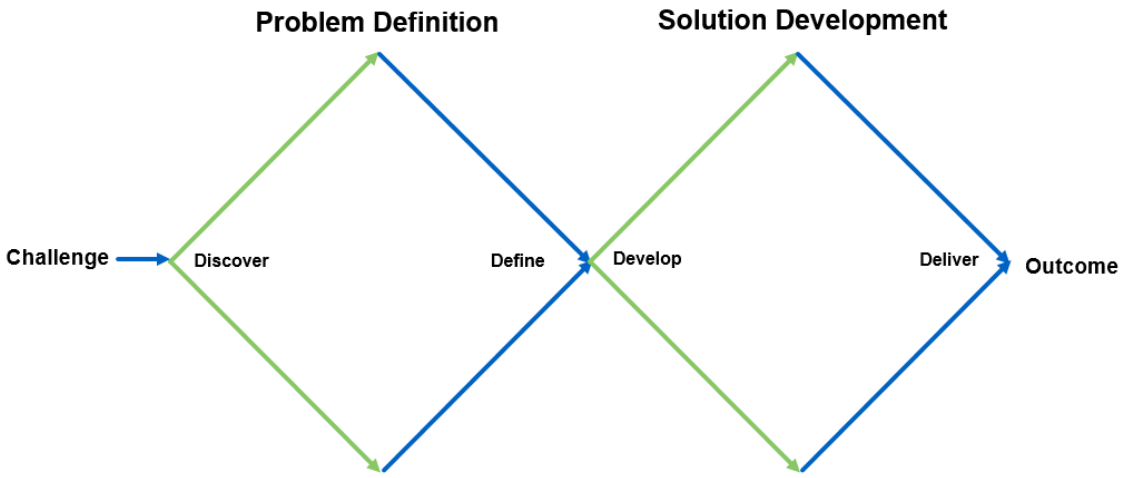

Figure 1-2: Design Council Double Diamond framework

Anecdotal information from product managers

Two additional sources were used, which helped to adapt common product management frameworks to an "internal product" development setting: an interview with an internal Product Manager at a major technology company and a LinkedIn article "An Introduction to Internal Product Management" by David E. Weekly, who is the Product Management lead for Google's datacenter software team.

In the interview with the internal Product Manager, it was suggested that the role of Product Manager for internal products is, in some ways, similar to that for externally marketed products – both serve as the voice of the customer to the engineering team, help to define and prioritize product features, and communicate about the product. Some of the differences between the two roles are that: (i) internal customers are more accessible and hence can be easier to talk to, and (ii) the internal product manager would likely take on more work to drive adoption of their products, since there is no support of formal sales and marketing teams as there is for external products.

The article by David E. Weekly has the tagline "aka 'Building Great First Party Tools' ". Weekly provides the general workflow that he used in his role as an internal

Product Manager. He worked with his end users, or their representative, to document their needs in a Business Requirements Document (BRD). This document includes information about current processes, problems faced, and the impact desired, but does not specify the solution. Weekly emphasizes not taking the users' requests at face value but following up with questions to understand the root cause. Once drafted, the BRD is circulated amongst various stakeholder groups to validate. Based on the BRD, Weekly would develop solutions which were captured in a Product Requirements Document (PRD). These solutions were verified by the user, before being implemented by the engineering team. Weekly recommends being open to changes based on feedback at any time during the development of the documents or the build of the actual solution. After the build, Weekly would help with testing the solution before release; and measuring its performance and impact after release [24].

1.3 Approach

As discussed in Sections 1.2.1 and 1.2.2, there is a wide variety of ways in which automation can help improve continuous biomanufacturing processes. In this situation, NGA(DS) faces uncertainty regarding what aspects of Platform A are best suited to be improved using automation and what the best automation solutions are to achieve these results. This uncertainty stems from a variety of factors such as Amgen's cost structure, supply chain decisions, process design decisions by other groups, and the technology available. All of these factors can change rapidly, especially for a process that is not currently deployed and still under development. Fully resolving any one source of uncertainty can be complex and expensive, since it may require extensive analysis and/or testing.

However, the requirement to build impactful products in the presence of uncertainty is not unique to NGA(DS). Innovation teams and startups generally face a similar situation and the frameworks reviewed in Section 1.2.3 provide managerial tools to maximize the chances of success in this situation. In general, these tools are designed to focus the team's work on maximizing validated learning about the

value of the product being developed. The tools emphasize collaboration, iterative development, and hypothesis testing.

The product management framework developed for the NGA(DS) team in this project applied relevant principles and tools from all of the sources reviewed in Section 1.2.3. At a high level, the development of automation solutions for Platform A would be defined as a Model C innovation, per *Beyond the Idea*, with NGA(DS) being a dedicated team. Both *Beyond the Idea* and *Lean Startup* would suggest that the organizational processes of NGA(DS) need not conform entirely with Amgen's existing processes and should be constructed fit for purpose. Given that the purpose being addressed here is to design new solutions, the Double Diamond framework was used to model the high level structure of these processes. As shown in Figure 1-3, this structure is also consistent with the Measure-Learn-Build cycle suggested by *Lean Startup*.

The framework developed in the project starts with a vision for the product(s), (presented in Chapter 2) and then consists of two phases of activities – Opportunity Analysis (Chapter 3) and Solution Development (Chapter 4). Opportunity Analysis involves searching for all opportunities relevant to the vision of the product and then prioritizing them. Solution Development involves generating ideas for the solution and then creating a roadmap that allows testing of key hypotheses regarding the value of the product. This ordered structure of the framework is intended to keep the product development process focused on addressing the most important business opportunities, rather than developing any specific technological solution.

Activities done within each phase of the framework were adapted from *Disciplined Entrepreneurship*, *Lean Startup*, and the anecdotal information from internal product managers. The rationalization for each activity is included in the respective activity's methods section in Chapters 3 and 4. *Disciplined Entrepreneurship*, which provides a detailed and specific list of activities, was applied systematically in the project. Details regarding the application of *Disciplined Entrepreneurship* are tabulated in Appendix A. Other source frameworks do not mandate a fixed set of activities and hence activities recommended by these frameworks were used as needed for decision

making. Additional types of activities that this framework could be expanded to include in the future are briefly considered in Chapter 5.

Despite the commonalities between startups and internal innovation teams, NGA(DS) is of course different, in some ways, from a true startup company. We found two specific differences that our framework needed to address:

1. **The NGA team's strategy must support Amgen's overall strategy**: As opposed to startup companies, which can be expected to set a strategy to optimize their own growth and sustainability, NGA(DS) must strive to support the larger strategy of Amgen. Due to this, the analysis of the vision for NGA(DS) solutions in Chapter 2 is based entirely on a consideration of Amgen's overall strategy and how it is supported by automation.

2. **The NGA team primarily addresses cost, not revenue**: Product typically implies a solution that may be sold. Hence product development/management often focuses on maximizing revenue. However, given the position that NGA currently occupies (discussed in Chapter 2), their efforts focus primarily or reducing cost of operations, rather than generating additional revenue. This difference was factored into the methodology for the financial analyses presented in Chapters 3 and 4.

The above requirements do not contradict the core principles of the sources cited, but only require modifications to the specific analyses performed.

The analysis presented in this thesis was performed in close collaboration with other members of the NGA(DS) team.

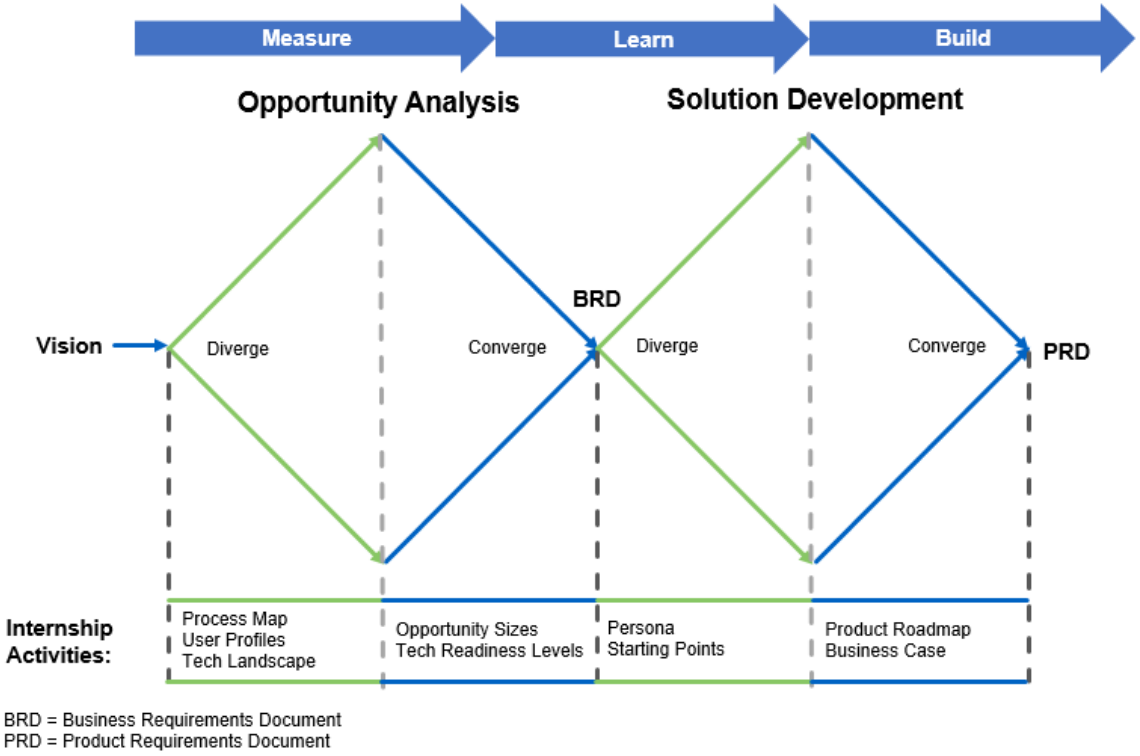

Figure 1-3: Product Management Framework for NGA(DS)

Chapter 2

Understanding the Vision – Background and Strategic Considerations

Key Takeaways:

1. Amgen sources automation for biomanufacturing from both internal and external suppliers. This strategy allows Amgen to benefit from the different advantages of both kinds of suppliers.

2. NGA(DS) serves as an internal supplier of automation. It is differentiated from other internal automation teams based on its capability to develop novel automation products.

3. The development of Platform A is a major strategic initiative, which involves many teams within Amgen, including NGA(DS). A major opportunity for NGA(DS) in this development program is to help reduce the cost per gram for the platform.

The motivation for this project stems from the intersection of two strategic initiatives driven by Amgen's commitment to advancing biomanufacturing. The first is the advancement of manufacturing automation and the second is the development of

a continuous biomanufacturing platform (referred to in this thesis as Platform A). This chapter analyzes how these two initiatives support Amgen's overall strategy. This analysis provides insights regarding the vision of NGA(DS) for Platform A, such as who the customers and partners of NGA(DS) are, what differentiates NGA(DS) from other internal teams and external automation vendors, and how NGA(DS) can prioritize various opportunities to improve Platform A.

Biomanufacturing capability is a strategic priority for Amgen. Most of Amgen's commercial portfolio consists of biologics (biological therapeutics): 16 out of a total of 21 products, as well as 6 of the 7 highest selling products are biologics [25] [26]. Amgen's strategy, as detailed on its website, consists of 7 pillars, with one being "Next-Generation Biomanufacturing" [27]. Amgen's 2018 annual report identifies their manufacturing capability as a "competitive advantage." Amgen's supply of biologics is primarily provided by its internal manufacturing network, with third-party contract manufacturing providing supplemental capacity [27]. An article on the Amgen Science website indicates that advances in biomanufacturing improve Amgen's competitive position by (i) reducing costs, (ii) improving product differentiation based on quality and reliability of supply, and (iii) supporting a "Biology first" modality-independent research and development strategy [28].

2.1 Next Gen Automation (Drug Substance)

Amgen's mission is "To Serve Patients" [29]. All of Amgen's work, including the development of automation by the NGA(DS) team, must be aligned with this mission. Hence, in order to explain the role of NGA(DS) within Amgen, this section provides context regarding the supply chain that delivers value from biomanufacturing automation and equipment suppliers to the patients. Amgen's vertical integration strategy in this supply chain is considered in order to understand the benefits and costs of insourcing vs. outsourcing automation. Finally, the location of NGA(DS) within the supply chain and the relationships of NGA(DS) to other teams are considered.

2.1.1 Structure of the Automation Supply Chain

The flow of the biomanufacturing equipment and automation supply chain is broadly depicted in Figure 2-1. The tiers of the supply chain are:

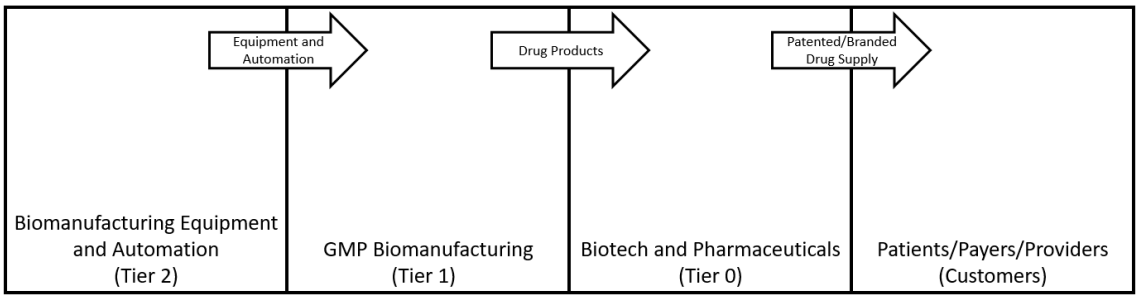

Figure 2-1: Supply chain from biomanufacturing automation and equipment suppliers to patients

1. **Customers – Patients through Payers and Providers**: Amgen maintains a singular focus on serving patients through its mission, values, and culture. Insurance payers and healthcare providers can also be considered customers, are critical partners in ensuring that patients are appropriately served by Amgen's products, and are mentioned significantly in the company's Annual Reports [26].

2. **Tier 0 – Biotech and Pharmaceuticals**: Companies in the biotech and pharmaceuticals industry generally have the strategy of serving products strongly differentiated by their patents and brands. The industry is marked by heavy spending in research and development, in order to gain marketing exclusivity through patents, and commercial (marketing and sales) operations, in order to create a brand with healthcare providers and patients. 27% and 40% of Amgen's total operating expenses in 2018 were for "research and development" and "selling, general, and administrative" respectively [26]. Competitors of Amgen in this industry include Pfizer, Merck, and Johnson & Johnson [30]. A related industry of off-patent biosimilars, which Amgen also participates in, would be expected to equally emphasize the commercial operations, but require less investment in research and development.

3. **Tier 1 – GMP Biomanufacturing**: Tier 1 consists of Good Manufacturing Practices (GMP) biomanufacturing companies, which are separate from tier 0 companies because the latter generally have the option of outsourcing the manufacturing of their patented drugs. While Amgen's strategy emphasizes its own manufacturing capability, other tier 0 competitors such as AstraZeneca have relied more heavily on their external supply network, especially for chemical (as opposed to biological) manufacturing [31]. External suppliers are generally referred to as Contract Manufacturing Organizations (CMOs) in this context, and include WuXi Biologics, Fujifilm Diosynth Biotechnologies, and Boehringer Ingelheim BioXcellence.

   There are multiple stages of manufacturing within tier 1 (e.g., Drug Substance, Drug Product, and Finished Drug Product). They are grouped together here because the stakeholders at each stage are expected to have similar considerations for manufacturing automation.

4. **Tier 2 – Biomanufacturing Equipment and Automation**: This tier can be considered to produce the "tooling" for tier 1. Subcategories of tooling include manufacturing equipment for various stages, process development laboratory equipment, and analytical equipment. Each subcategory has various suppliers. Suppliers may also provide solutions at different levels of integration – from individual sensors and actuators, to full unit operations, to plant-wide systems. Equipment and automation are considered together due to being closely linked and depending on each other for functionality. On the other hand, equipment and automation can be provided by the same or different vendors for a single system. Some examples of major suppliers for Drug Substance manufacturing systems are Pall Life Sciences (Danaher), Sartorius Stedim, and Repligen. Amgen's vertical integration strategy into this tier is discussed in the next section.

2.1.2 Amgen's Backward Integration Strategy

This section examines Amgen's vertical integration into tier 2 through a team such as NGA(DS), and the potential benefits and costs associated with such an integration strategy. As discussed earlier, Amgen is mostly, but not entirely, vertically integrated into tier 1 – that strategy is not analyzed here. Amgen's position in the supply chain is shown in Figure 2-2.

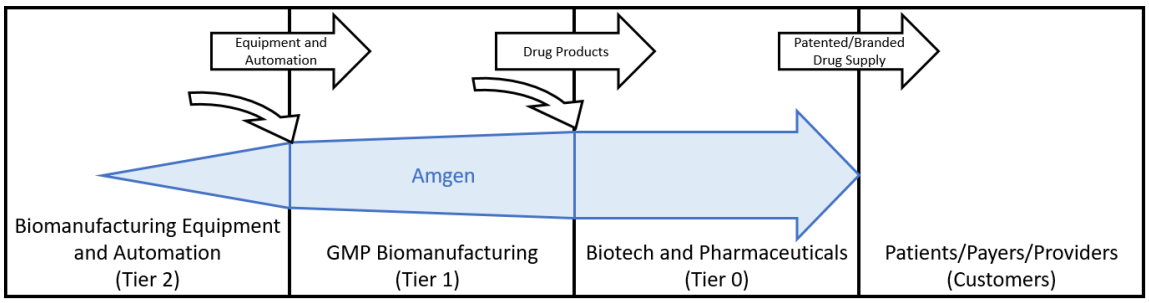

Figure 2-2: Amgen's position in the biomanufacturing automation and equipment supply chain

In *Competitive Strategy*, Porter defines tapered integration as "partial integration backward or forward" and quasi-integration as "the establishment of a relationship between vertically related businesses that is somewhere between long-term contracts and full ownership" [32]. Amgen already participates in tapered integration and quasi-integration in tier 2 through various existing internal automation development teams and has the opportunity to further formalize and strengthen this strategic position through the establishment of the NGA(DS) team. An example of tapered integration, in this context, would be developing some automation software in-house, while sourcing others from vendors. An example of quasi-integration would be collaboratively developing an automation solution with an external vendor, the IP for which is subsequently shared by Amgen and the vendor.

Competitive Strategy provides a generic list of benefits from vertical integration. The benefits that may apply to vertical integration into tier 2 are:

1. **Buttressing tier 1 integration**: Tier 2 integration can help ensure the success of the tier 1 integration strategy. The innovation provided by internal

automation and equipment development can help a company's internal manufacturing maintain its differentiation and/or lower cost compared to contract manufacturers, which ensures that the benefits of tier 1 integration continue to be captured.

2. **Economies of integration**: Internally developing automation and equipment can allow a company to more quickly address its needs when a market solution is not immediately available. The solutions would be custom-made and fit to conform within a desired manufacturing platform, thus enabling quicker integration. Needs can be communicated earlier and more freely with the development group, without risk to intellectual property. A stable relationship between users and developers may allow greater commitment to more ambitious projects.

   All of these factors together can provide a tier 2 integrated company with cost saving. These cost savings can then be fed back into bolstering the strategy of differentiation using research & development and commercial operations.

   These benefits are addressed well with tapered integration or quasi-integration, because internal development teams can choose to work only on solutions which would provide such economies.

3. **Differentiation and revenue generation using process patents**: In addition to product patents regarding the nature and use of their products, biotech companies may also claim process patents around the manufacturing of the products. Internal automation and equipment innovation groups can help in developing these patents. These process patents can allow a company to further differentiate its products, or collect royalties by licensing the patent [33].

Besides the benefits, Porter also provides the costs of integration. The relevant costs, including how a team like NGA(DS) may keep them low, are as follows:

1. **Cost of overcoming entry barriers**: Several entry barriers apply to automation and equipment development. A tier 1 integrated company can keep its tier 2 barriers low (in some cases lower than for external players) in three ways.

(a) Capital is required for lab equipment and software development platforms. A tier 1 company's Process Development group may already have these resources and internal teams can, as much as possible, try to work within the slack capacity of existing assets.

(b) Products from external vendors are differentiated based on the vendor's experience and loyalty of its customers. Internal teams cannot provide the same differentiation, but can instead differentiate themselves based on flexibility, accessibility, and quick response rate.

(c) Customers within a tier 1 company who rely heavily on a single external vendor for their automation and equipment may incur switching costs to start using the internal vendor. These costs may be in the form of configuration, external systems integration, or retraining. Internal teams can lower these switching costs by being highly flexible and providing products similar to what the customers already use.

2. **Reduced flexibility to change partners**: There can be a risk of internal developers exploiting captive customer relationships to take on projects that are more appropriate to be sourced externally. This risk is lower with tapered integration than with full integration. The mandate of internal teams in tier 2 should be not only to develop solutions internally, but also to advise on and partner in sourcing external products.

   Given the nature of digital solutions, automation teams will always be building on top of externally sourced platforms or products, whether open source or proprietary. The design task, in this case, is to consider what combination of externally sourced products along with internal customizations and integrations fulfills the requirements while keeping overall costs low. A methodology for this task is developed in Chapter 4.

3. **Dulled incentives**: If given captive customers, an internal team may have weaker incentives than external vendors, whose survival may depend on selling products. To mitigate this scenario, internal customers should be allowed to

seek external vendors freely when vendors may provide better value than internal teams. Internal teams could also be encouraged to compete with each other based on value provided to the company, for instance, by comparing performance in reducing a cost metric.

4. **Differing managerial requirements**: As explored in Section 1.2, the work of developing automation and equipment solutions differs significantly from operating these to manufacture drugs. The same organizational structures, controls, incentives cannot be used for both tasks. Teams operating in tier 2 should model themselves on others working on similar tasks, not necessarily on other teams within their company. This thesis provides a framework for that recommendation.

2.1.3 Position of NGA(DS) in the Supply Chain

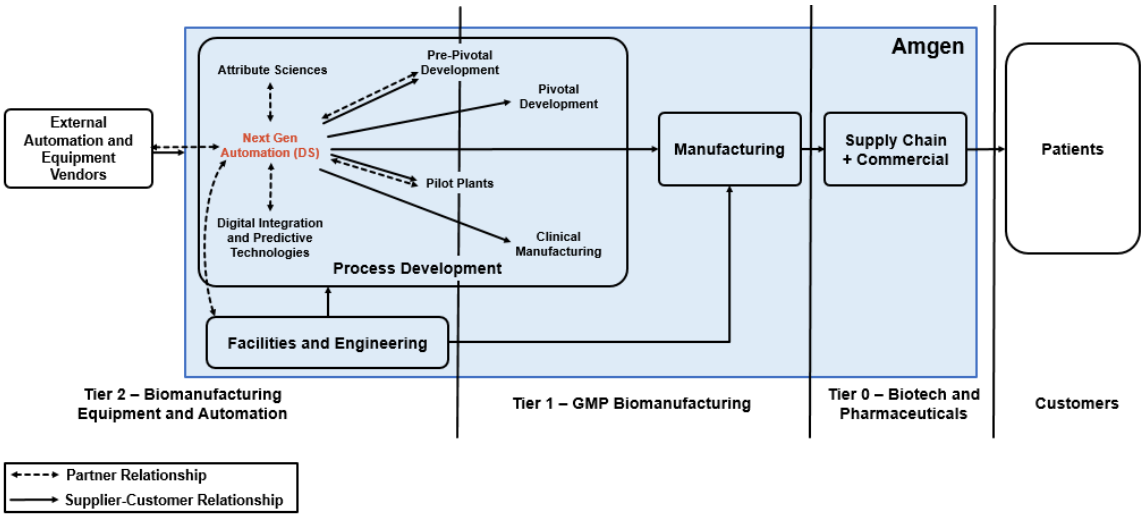

Figure 2-3: The position of the NGA(DS) team in the automation and equipment supply chain. Solid lines show a supplier-customer relationship and dashed lines show a partner relationship

Figure 2-3 provides more detail than Figure 2-2, to show the position and network of the NGA(DS) team. The NGA(DS) team is primarily a product team working on delivering innovative automation products to its customers shown in the figure: process development labs, pilot plants, clinical manufacturing plants, and commercial

manufacturing plants. In developing its products, NGA(DS) partners with several internal groups and external vendors (shown with dashed arrows). While, NGA(DS) collaborates closely with both its customers and partners, the expectations are different from each. The customers are primarily expected to share their needs, use the products, and provide feedback. The partners, on the other hand, are expected to provide technical resources during the development of NGA(DS) products. These resources may be in the form of engineering time, use of equipment, experimental data, or existing code base.

In the literature review, it was discussed that automation can reduce overall operations costs in many different ways, such as by improving quality, cycle time, throughput, yield, labor efficiency, and safety. These are all possibilities for NGA(DS) products as well. In prioritizing its work, NGA(DS) is guided by Amgen's overall existing strategic initiatives (such as the development of Platform A). The team is informed about such initiatives through its customers in tier 1 and tier 0 groups. On the other hand, the team can use their internal and external partners, and the team's own research to stay current regarding the state of the art within automation technology. Based on this information, NGA(DS) expects to form hypotheses regarding how automation may further Amgen's strategic initiatives (Chapter 3) and then build solutions to test these hypotheses (Chapter 4).

The ability to independently form and test hypotheses differentiates the role of NGA(DS) as an innovation team within Amgen. This role is different from other service-based automation teams at Amgen, which provide engineering development for solutions that are generally well specified and support units deployed in production environments.

2.2 Development of Platform A

In a review of biopharmaceutical manufacturing control, Hong et al. [8] identify that manufacturing processes for biologics generally consist of similar sequences of unit operations and shared critical quality attributes. Due to this similarity, Amgen has

pursued a strategy of developing process platforms that can be used to manufacture multiple products, as opposed to developing the process for each product from scratch. Baldwin and Woodard [34] define platforms as "modularizations of complex systems in which certain components (the platform itself) remain stable, while others (the complements) are encouraged to vary in cross-section or over time." The design of Amgen's process platforms comply with this definition. The modules are components of equipment, automation, and raw materials. The platforms, defined based on strong design principles, are expected to contain some modules that stay stable over time and for different products. This stability allows faster development of processes for new products and lower costs of inventory due to fewer SKUs. Other modules may vary over time, to accommodate technological evolution, or by product, to allow product specifications to be met.

At the time of the project, the development of Platform A was a large initiative at Amgen, involving many of NGA(DS)'s customers and partners. Continuous processing was a central design principle in the development of Platform A. Amgen had already incorporated continuous processing technology in parts of previous process platforms, but was hoping to develop the technology much further in Platform A. The groups leading the development of the platform were the Process Development (PD) group – for technology development – and the Operations Strategic Planning & Risk (OSPR) team within the Supply Chain group – for business case development. One iteration of the platform had already been implemented in clinical manufacturing, but the technology of the platform was being developed further.

Leaders in PD and managers in OSPR had indicated that a major strategic focus for Platform was to reduce its Cost Per Gram (CPG), which is the cost of manufacturing per gram of product in the final DS lots. This cost model was being maintained by OSPR. The model included costs of raw materials, labor (direct and indirect), and depreciation. The cost model did not include any costs downstream of the DS lots or any other allocations. Information regarding the costs had been sourced from relevant engineering and operations groups within Amgen. Further details regarding the costing methodology are considered in Chapter 3, as relevant.

As discussed in Section 2.1.3, the differentiating capability of NGA(DS) is to develop innovative products to support strategic initiatives. This capability positioned NGA(DS) well to support the development of Platform A. Before this project started, NGA(DS) had already been involved in developing solutions for Platform A and saw many additional opportunities for the platform. While prioritizing these opportunities, the NGA(DS) team also set its own primary goal as the reduction of CPG, in order to stay aligned with the broader strategy for the platform.

Chapter 3 details how qualitative and quantitative data was gathered regarding the various opportunities, and then how the opportunities were compared based on their CPG benefit and development risk.

THIS PAGE INTENTIONALLY LEFT BLANK

Chapter 3

Opportunity Analysis

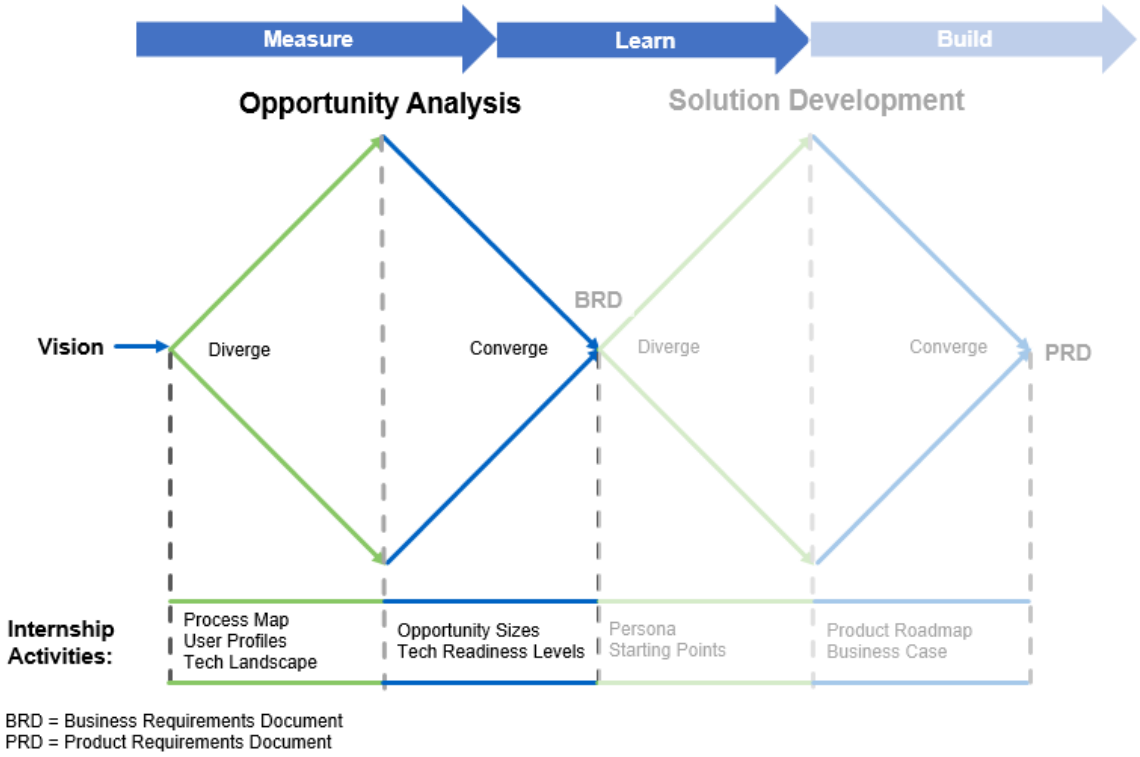

Figure 3-1: Framework for the Opportunity Analysis phase

Key Takeaways:

1. Diverge – Identifying Opportunities
   (a) Within the scope of Platform A, NGA(DS) serves multiple internal customer teams and partners with other development teams. The user profiles and technology development landscape map were used to better understand these teams, and their relationship to NGA(DS).
   (b) NGA(DS) has developed ideas that may improve various cost metrics for different unit operations. These unit operations and metrics (including labor time, equipment utilization, yield, and deviation rate) were compiled in a Process Map.
   (c) Based on these three tools, a list of opportunities was compiled, with each opportunity expressed as a hypothesis that automation may improve a specific metric for certain unit operations.
2. Converge – Prioritizing Opportunities
   (a) The metrics from the process map were combined with a cost model to calculate Opportunity Sizes. The Opportunity Size metric was adapted from the Total Addressable Market concept to internal products and was defined as the maximum cost savings possible from fully exploiting an opportunity.
   (b) Development risk was judged by adapting the criteria of Technology Readiness Levels.
   (c) An overall criteria was developed to prioritize projects based on benefit (Opportunity Size), risk (Technology Readiness Levels), and development capacity.

This chapter provides the methods and results for the the Opportunity Analysis

phase of the project. This phase was further divided into "Diverge" and "Converge" sub-phases. As part of the Diverge sub-phase, the first step was to explore all the opportunities that NGA(DS) could address as part of its vision for developing Platform A. By generating user profiles, a process map, and a technology landscape map, information was gathered on the current state of NGA(DS)'s customers and Platform A. Using this information, hypotheses were formulated regarding the opportunities available to the NGA(DS) team. These opportunities were subsequently evaluated in the Converge sub-phase in terms of their opportunity sizes and technology readiness levels.

The analysis presented in this chapter was performed in close collaboration with other members of the NGA(DS) team.

3.1 Diverge – Identifying Opportunities

3.1.1 User Profiles

Method

User profiles were generated in order to gain a qualitative understanding of the customers of NGA(DS). The set of potential customers had already been identified by the NGA(DS) team before this project. Interviews were conducted as part of this project with leaders within the customer groups to understand their requirements.

The user profiles were based on the Value Proposition Canvas method by Alexander Osterwaler [35]. The method recommends considering three aspects of the customer's needs: customer jobs (i.e., what the customer wants to or needs to do), gains (i.e., what helps or can help the customer do their jobs), and pains (i.e., what hinders or can hinder the customer in doing their job). This method was used because it provides multiple ways to question a customer regarding their needs. Questions used in interviews with the customers were:

1. **Customer Jobs**:
    (a) Could you walk me through the operations of this plant/lab?

(b) Could you briefly explain the role of your group?

(c) Who are your group's customers?

2. **Gains**:

   (a) What are currently the biggest priorities for your group/this project?

   (b) What is the next step for this project?

3. **Pains**:

   (a) What are the biggest challenges your group/this project is facing right now?

   (b) Follow-up questions regarding unsolicited remarks such as "we are struggling with this right now" or "that [operation]/[task] doesn't usually work too well."

Jobs, pains, and gains are not mutually exclusive, but asking about all of them helps to elicit more information from the customer.

Results and Discussion

Appendix B provides the response data collected in the interviews with the DS Pre-Pivotal Development, DS Pivotal Development, and the DS Pilot Plants groups. The appendix also includes my interpretation of each response in terms of its implication for NGA(DS). Since the NGA(DS) team primarily works within the DS space (rather than Drug Product (DP) or Finished Product (FP)), the customer groups are referred to simply as Pre-Pivotal, Pivotal, and Pilot Plants groups.

Additional potential customers of the NGA(DS) group include the clinical and commercial DS manufacturing plants. The user profiles for these groups have not yet been generated, but it is recommended that the NGA(DS) team will generate the user profile for each customer before the team develops a solution for the customer.

The data presented in Appendix B support five conclusions:

1. Early versions of NGA(DS) solutions should be developed for the Pre-Pivotal or Pilot Plant groups. The Pre-Pivotal group generates process definitions that are transferred to the the Pilot and Clinical production facilities and eventually to Pivotal Development group for commercial process development. The Pre-Pivotal group can, if it is appropriate, include the use of NGA(DS) solutions within process definitions before transferring them. The Pilot Plants, on the other hand, can also transfer technology to the clinical and commercial plants, especially if it does not significantly affect process definitions. NGA(DS) solutions are unlikely to be implemented in the clinical or commercial plants without first being tested in a Process Development group.

2. All of the interviewed groups support the development of Amgen's pipeline molecules towards commercialization. Any solutions introduced by NGA(DS) should not disrupt this work and, if possible, should seek to improve it. In the words of *Beyond the Idea*, commercialization of molecules is Amgen's Performance Engine, while NGA(DS) products are Model C change initiatives.

3. The Process Development labs and pilot plants are fairly large and expensive operations in themselves, which can be optimized using automation. However, the scale of their costs is still smaller than those of the clinical and commercial manufacturing network. Hence, improvements to Process Development operations can be an indirect benefit of NGA(DS) products, but are not expected to be the primary goal.

4. Safety is a primary concern for all groups interviewed. NGA(DS) solutions should be built with utmost consideration for safety during install and use.

5. The customers interviewed already partner with other Amgen teams in developing process and automation technology. These partners include Attribute Science, Digital Integration and Predictive Technologies, and Development Supply Chain Facilities & Engineering Automation. NGA(DS) should continue to partner with these groups as well.

3.1.2 Process Mapping

Methods

The process map was generated to show the flow of the Platform A process, from one unit operation to the next. The process map also shows metrics that reflect the performance of the unit operations. The metrics calculated and their data sources were the following:

1. **Total Direct Labor Time (hours/run) and Setup/Breakdown Labor Time (hours/run)**: Total Direct Labor Time includes both operating labor time and setup/breakdown labor time.

   Data regarding the labor time required to setup, operate, and breakdown each unit operation were collected via interviews with lead operators of a clinical manufacturing plant who had run the Platform A process in the past. Direct labor time only includes time when operators are expected to be physically present at the unit, and not when the equipment is operating without in-person supervision.

2. **Total Equipment Utilization Time (hours/run), Processing Equipment Utilization Time (hours/run), Capacity Utilized of Scheduled (%), and Capacity Utilized of Total (%)**: Total Equipment Utilization Time was defined as the setup, processing, and breakdown time required for each unit operation for a run. Processing Equipment Utilization Time included only the processing time, and not the setup and breakdown time. Data for the equipment utilization times were collected via the interviews with the lead operators of the clinical manufacturing plant.

   Capacity utilization was calculated based on equipment utilization time, assumed as being constant throughput over time.

   Capacity Utilized of Scheduled was defined as the Total Equipment Utilization Time divided by the total time for which the unit was scheduled for a Platform A run. For instance, if a unit has a Total Equipment Utilization Time of 24

hours/run and is scheduled for two days for a Platform A run, then its Capacity Utilized of Scheduled is $\frac{24 \text{ hours}}{2 \text{ days} \times 24 \text{ hours}} = 50\%$. Capacity Utilized of Scheduled estimates true capacity utilization if the unit is scheduled for a Platform A run every day. An example schedule for a Platform A run was obtained from a manager in the clinical manufacturing plant.

Capacity Utilized of Total was defined as Process Equipment Utilization Time divided by the total duration of a Platform A run. For instance, if a unit operation has a Processing Equipment Utilization Time of 24 hours/run, and a Platform A run takes 10 days (not actual data), then the Capacity Utilized of Total is $\frac{24 \text{ hours}}{10 \text{ days} \times 24 \text{ hours}} = 10\%$. Capacity Utilized of Total estimates capacity utilization if the unit was operated continuously throughout the duration of a Platform A run. Not all units in Platform A are setup for continuous use, but this metric was calculated to demonstrate how much smaller the capacity of a unit could be if operated continuously.

3. **Yield (%), Cumulative Yield (%), and Throughput (g/day)**: Yield was recorded for harvest and each unit operation downstream of it. The harvest yield is the percentage of product in the bioreactor that is harvested. The yield of each downstream purification unit is the percentage of product that is recovered from the unit out of the product that goes into the unit.

   Cumulative Yield at a unit is the yield from the bioreactor to the output of that unit. The Cumulative Yield is obtained by multiplying all the unit yields between the bioreactor and the output of the unit.

   The throughput of each unit is the grams of product obtained in the output of the unit normalized by the number of harvest days in a Platform A run.

   The throughput data for harvest and yield data for all units were received for three Platform A runs in the clinical manufacturing plant from a Process Development engineer supporting the plant. The rest of the figures were calculated using this data.

4. **Output Bag Size (L)**: The output bag size is the size of the bag used to hold the output material from a unit operation, before the material is fed into the subsequent unit operation. This metric was recorded as a measure of equipment footprint.

   Data for the bag sizes were collected via the interviews with the lead operators of the clinical manufacturing plant.

5. **Distribution of Deviations in Platform B**: The relative occurrence of deviations between various process areas (some process areas include multiple unit operations) was calculated for a more mature process platform – Platform B. A deviation, simply put, is an incident that deviates from normal qualified operations and that must be recorded in Amgen's quality management system. Platform B was used as a proxy for Platform A because they both comprise of similar unit operations and there is much more data for the older Platform B. Deviation data was collected from Amgen's quality management system for three years of Platform B runs in Plant A.

The metrics were recorded in a table shown (but masked) in Figure 3-3. Some of the metrics were color coded based on their value to generate a "heat map" of potential opportunities. Relatively well performing units/areas were colored green, while relatively low performing units/areas were colored red. The logic used for the color coding is shown in Figure 3-2.

Results and Discussion

As shown in Figure 3-3, the Platform A process generally follows a typical drug substance biomanufacturing process flow [36]. Design details that differentiate Platform A are not included here to protect proprietary technology. In addition to the main process flow (from seed train to final filter), the raw material preparation (buffer and media) and sampling operations were also considered.

The process map was discussed within the NGA team to understand the performance of the Platform A. Several observations were made that allowed a deeper

	Low High	Rationale
Labor Time (hours/run)		Higher labor time implies higher labor costs
Equipment Utilization Time (hours/run)	No scale	Equipment Utilization Time cannot be meaningfully compared for different unit operations.
Capacity Utilized (%)	0% 100% >100%	Underutilization (<100%) of capacity can indicate excessive capital investment. Overutilization (>100%) here would imply greater utilization time than the unit is scheduled for. Chronic overutilization would lead to schedule delays.
Yield (%)	0% 100%	Lower yield implies product loss and hence greater cost per gram of product at the end.
Cumulative Yield (%)	No scale	Downstream steps in the process will always have lower cumulative yield.
Throughput (g/day)	No scale	Downstream steps in the process will always have lower throughput, as defined here.
Output Bag Size		Larger bag size implies a larger footprint and hence potentially greater capital costs.
Distribution of Deviations (%)		High relative number of deviations imply lack of reliability in the operation of the unit, leading to greater indirect labor costs and costs of quality incidents.

Figure 3-2: Color coding for process map metrics heat map

understanding of the process. Two observations which helped inform the next steps for my project were:

1. Certain units have relatively high labor requirements. We hypothesized that lowering the labor requirements for these units using automation may be an opportunity for NGA(DS).

2. Certain units that are currently not operated continuously have a very low Capacity Utilized of Total. We hypothesized that, if NGA(DS) could automate these units to operate fully continuously, their footprint could be reduced leading to lower capital costs.

These hypotheses were included in the analysis of the Converge sub-phase.

3.1.3 Internal Technology Development Landscape Mapping

Methods

The final activity performed to identify potential opportunities was the internal technology development landscape mapping. In this activity, current and previous tech-

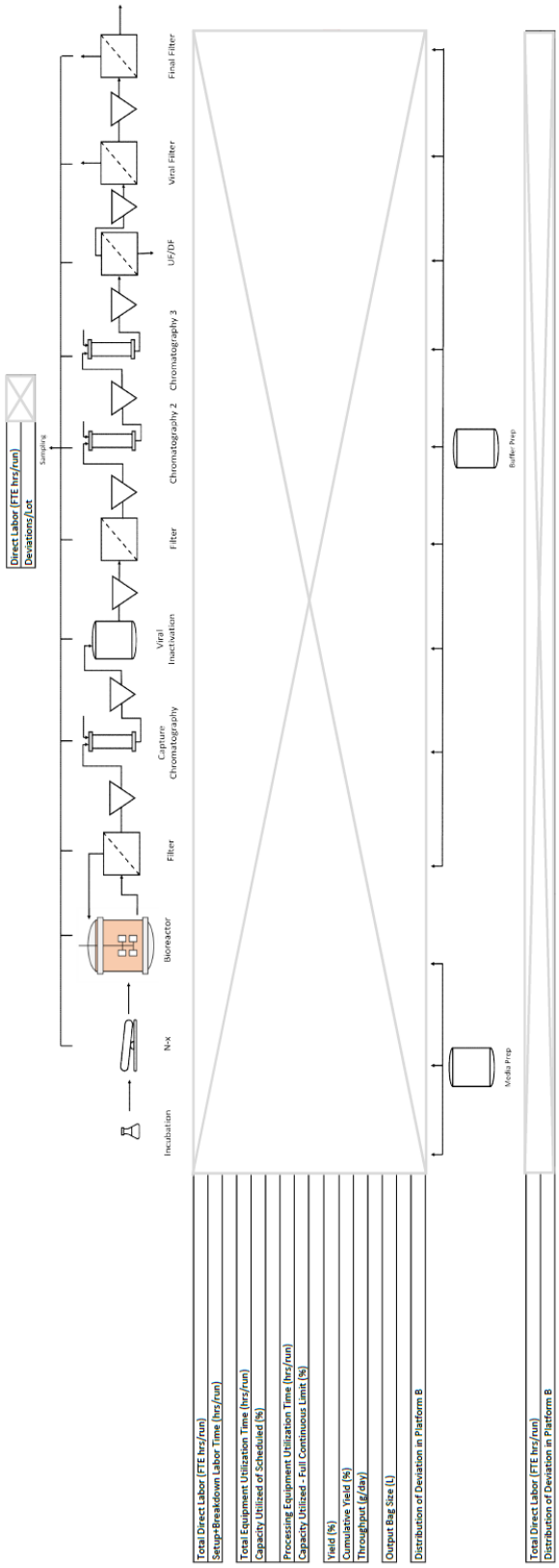

Figure 3-3: Process map for Platform A (data masked)

nology development projects at Amgen relevant to Platform A were listed. The list was compiled from multiple sources: project trackers maintained by other teams, presentations that NGA(DS) had received, and ideas or projects that had been mentioned to NGA(DS) in meetings. For each project, the objective was to identify the opportunity that could have motivated the project and then judged each opportunity to have one of four statuses:

1. **Not a significant opportunity (anymore)**: This status may be because the opportunity had been successfully addressed or because the project had found the opportunity to not be significant.

2. **Owned by [group name]**: This status was to indicate that the opportunity was actively owned by another group and did not require additional collaboration with NGA(DS).

3. **Current NGA(DS) product**: This status was to indicate that NGA(DS) was currently developing a product to address this opportunity.

4. **Potential opportunity for NGA(DS) (collaboration with [group name])**: This status was to indicate the opportunity could be taken up by NGA(DS), either independently or in collaboration with another group.

The process of identifying opportunities and their statuses was performed internally within NGA(DS). This process was possible because of the significant experience and expertise the team had regarding Amgen's technology development history in this space. Where an opportunity or status was not clear, questions were recorded that could be taken up with the project owner.

Results and Discussion

Opportunities associated with 18 recent or current projects were identified and analyzed. Out of these, three were found to be not significant, seven were found to be owned by other groups, one had a current NGA(DS) product, five were found to be potential opportunities for NGA(DS), and the remaining two could not be classified

for lack of sufficient information. The potential opportunities identified for NGA(DS) were included in the analysis in Section 3.1.4

3.1.4 Defining Opportunity Hypotheses

Based on the above three activities, hypotheses were formulated for opportunities that NGA(DS) could address. These hypotheses are presented in Table 3.1 along with the activities that helped to arrive at each hypothesis. The opportunities are also named in bold for easy referencing.

While the NGA(DS) group was aware of the opportunities listed in the table in general terms before this project, the preliminary data collected in the activities allowed more specific phrasing of the hypotheses. The activities also provided greater confidence that the opportunity space had been searched exhaustively and no important opportunities had been missed.

Each opportunity is phrased in terms of reduction in CPG since that was considered the primary objective for this project, as explained in Section 2.2. The opportunity hypotheses were deliberately phrased only to consider the upside of cost saving and not the downside of additional costs required to address the opportunity. This was done so that underlying opportunities could be identified without having to consider which specific solutions were currently available or could be developed. Such formulation of opportunity hypotheses also supported the calculation of Opportunity Sizes, as discussed in Section 3.2.1.

3.2 Converge – Prioritizing Opportunities

Once the set of potential opportunities for NGA(DS) were identified, the next step was the Converge sub-phase whose objective was to prioritize the opportunities. The prioritization was based on (i) the opportunity sizes, which were used to rank the relative benefits from each opportunity, and (ii) technology readiness levels, which were used to rank the relative risk and development time for each opportunity.

	Opportunity Hypothesis Identified	Informed By Activities
1	**Direct Labor**: Additional automation may be developed for unit operations x, y, and z to reduce their direct labor requirements, leading to a lower cost of direct labor per gram. Note: This would be considered a separate opportunity for each of the units x, y, and z, since the solutions required for each unit operation would be different. They are grouped together here for brevity and because the methodology to calculate the Opportunity Size for each is the same.	User Profile, Process Map, Tech. Dev. Landscape Map
2	**Indirect Labor**: Additional automation may be developed to improve the reliability of process area x, leading to a lower number of deviations. Hence less indirect labor time would be required to process those deviations, lowering cost of indirect labor per gram.	Process Map, Tech. Dev. Landscape Map
3	**Yield Improvement**: The addition of automated equipment to unit operation x may increase its yield and hence reduce the fixed costs per gram for a run.	Process Map
4	**Fully Continuous Operation**: Providing automated fully continuous operation for units x, y, and z would allow a reduction of footprint by using smaller equipment and hold vessels. This would reduce the cost of depreciation per gram.	Process Map, Tech. Dev. Landscape Map
5	**Fouling Reduction**: Automation or equipment design changes that reduce fouling of the harvest filter would allow running the bioreactor at higher cell densities, leading to higher throughput at the bottleneck, and hence a reduced fixed cost per gram.	Tech. Dev. Landscape Map
6	**Dynamic Loading**: While loading the chromatography column in unit operation x, variation in the titer of the incoming material can lead to under-loading, causing under-utilization of a column, or breakthrough, causing loss of product. The former causes a higher raw material cost per gram, and the latter causes higher fixed cost per gram. Automated loading of the column based on real-time titer measurements can reduce these costs.	User Profile, Tech. Dev. Landscape Map

Table 3.1: Opportunities identified for NGA(DS) relating to the development of Platform A

3.2.1 Opportunity Size

Methods

The concept of opportunity size adapts the commonly used concept of Total Addressable Market (TAM) to internal products. A Credit Suisse report defines TAM as "the revenue a company could realize if it had 100 percent share of a market" and mentions that "The ability to calibrate the total addressable market (TAM) is a major part of anticipating value creation. Assessing value creation requires understanding how much a company can invest and the returns those investments will earn" [1].

In comparing various opportunities, a team like NGA(DS) can also benefit from estimates of value creation and returns on investment. The value and returns come not in the form of revenue, but rather costs savings as compared to the current state. Hence, opportunity size is defined as the maximum possible cost savings that could be achieved if a given opportunity was completely addressed. An opportunity size is the segment of the current cost structure that can be attributed to a specific opportunity statement. In this way, the opportunity cost can also be understood as the TAM of an internal market. If, for instance, if the General Managers of Amgen's manufacturing plants were considered to be the internal market, the most that they would be willing to pay to have a new automation solution is presumably how much they are spending on solving the same problem currently.

Similar to TAM, the opportunity size does not (i) account for any additional costs incurred to develop, install, or operate the solution, or (ii) provide an estimate of how much of the opportunity size that any given solution could realistically capture. Although an accounting of these two factors would eventually be needed to judge the true value of a product, the opportunity size by itself is also a useful metric for teams like NGA(DS) for several reasons:

1. **Opportunity sizes can help set priorities**: The opportunity size provides an upper limit for the returns that Amgen can achieve by investing in an innovation opportunity. Hence opportunity sizes can help in the initial comparison of potential benefits from different kinds of opportunities (e.g., increasing yield vs.

reducing labor). Considered along with risk (explored in Section 3.2.2), this relative estimate of benefit can help a team focus its efforts. There may be a risk-benefit tradeoff between opportunities, but if two opportunities have the same level of risk, a team would be expected to pursue the opportunity with the larger opportunity size.

Based on the experience in this project, the process of quantifying opportunity sizes also necessitates a deeper qualitative understanding of the customer and their processes. The opportunity size number builds on the hypothesis for how the customer's situation would improve if a solution was provided to them. This assessment requires a holistic understanding of all the constraints that the customer faces.

2. **Opportunity sizes can be calculated quickly**: Given that NGA(DS) works on innovative products, the best (or maybe any) solution to a given opportunity is not defined at the beginning. In this case, predicting the cost or performance of a solution is a guessing game, at best. On the other hand, opportunity sizes can be calculated fairly quickly because they are calculated based on current costs. For this project, estimates for opportunity sizes were able to be generated within a few weeks or a month, while fully developing and costing solutions would be a matter of many months, if not years.

3. **Opportunity size serves as a benchmark**: As a team iteratively builds a solution, the team will likely find ways to optimize its cost and performance. In this process, the opportunity size serves as a benchmark. Realizable goals for performance can be set as a percentage of the total opportunity size, and the cost of the solution should be less than these realizable savings in order to create value.

   The opportunity size is a stable benchmark if, as mentioned in the previous point, its calculation is with a full understanding of the customer's needs and constraints. The opportunity size does not depend on *how* the engineering team evolves the solution. Factors that affect the calculation of the opportunity size

are usually game changers and likely require the engineering team to step away from the solution and re-examine their assumptions regarding what is needed.

For this project, opportunity sizes were calculated in terms of reduction in cost per gram (CPG). This metric was used in order to stay aligned with Amgen's larger Platform A strategy (explored in Section 2.2). TAM is usually measured in dollars per year, and opportunity sizes can be measured in the same way. CPG reduction can be converted to annual savings by multiplying CPG reduction by the expected grams of product produced using Platform A in a year. Annual savings would be required to calculate Net Present Values (NPVs) and compare opportunities across different platforms. However, since this project only considered opportunities within Platform A, the CPG reduction values could be used.

The cost models for calculating opportunity sizes were built in three steps:

1. Build initial model based on the NGA(DS) teams internal understanding of the opportunity.

2. Present model to Subject Matter Experts (SMEs) familiar with Platform A to get feedback regarding methodology, assumptions, and data. Update the models based on the feedback.

3. Present updated models to SMEs for final approvals. Ask SMEs to provide a rating to each model (along with any comments): generally agree, agree with reservations, or generally disagree.

The final step was performed primarily for the purpose of this thesis. In the NGA(DS) team's context, it would be appropriate to simply keep iterating step 2 and evolve the models as additional feedback is received.

Four SMEs assisted with steps 2 and 3 – one each from the Pre-Pivotal DS Development, Pivotal DS Development, DS Technology & Engineering, and Operations Strategic Planning & Risk groups.

Results and Discussion

Appendix C presents the full methodology, assumptions, and data sources of the six models developed by the end of step 2. During step 2, the feedback for four (out of six) models included only minor adjustments, while the feedback for the other two challenged the underlying assumptions of the model. Appendix C notes that the latter two opportunities (#5 and #6) are "not currently viable". and provide the reasoning for this assessment.

Table 3.2 shows the results of step 3, i.e., the final reviews from the four SMEs. The reviews were used to validate the methodology, assumptions, and data sources for the opportunity size models. Two conclusions were drawn from the reviews:

1. The models for opportunities 1, 2, 3, 4, and 6 were accepted with ratings of Generally Agree or Agree with Reservations from all reviewers. Comments provided can inform minor changes to the model or how its results are interpreted, but do not substantively change the underlying assumptions.

2. The model for opportunity 5 received a Generally Disagree rating from SME 4, who questioned the underlying assumption that higher cell densities would be constrained by the efficient tangential flow of cells through the filter. In this case, further data would need to be sought in order to decide whether this opportunity is viable.

The models for opportunities 1, 3, and 4 were able to be used to generate values for opportunity sizes. The model for opportunity 2 was validated but the data required for the model could not be retrieved within the time frame of the internship. Values were not calculated for opportunities 5 and 6 because, as mentioned, they were found to be "not currently viable" by the end of step 3. The values obtained from the models cannot be shared in this thesis in order to protect proprietary technology. Figure 3-4 is an illustrative graph to show how the final opportunity size values would be presented.

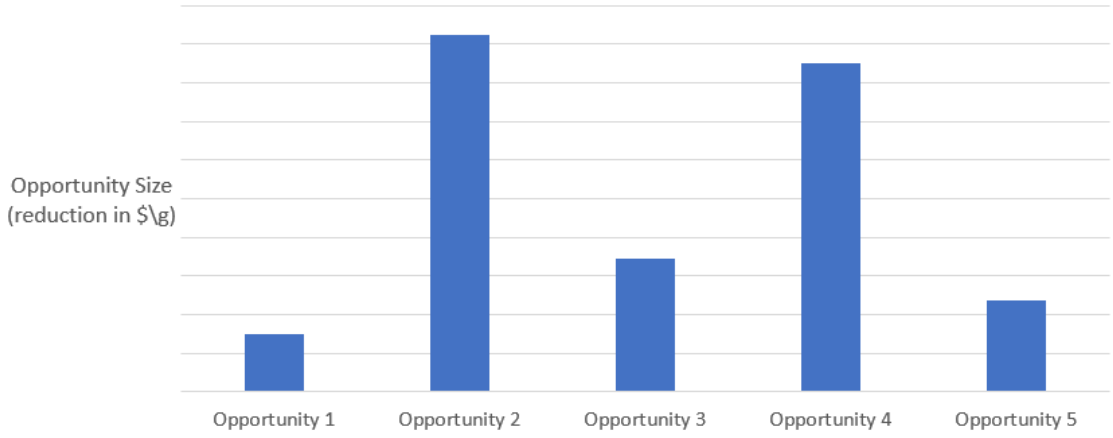

Figure 3-4: Illustrative results for opportunity size calculation (does not reflect real data)

	Opportunity Name	SME 1 Review	SME 2 Review	SME 3 Review	SME 4 Review	Comments
1	Direct Labor	Generally Agree	Generally Agree	Generally Agree	Generally Agree	SME 1: “Someone with a finance background may point out that the incremental reduction in labor time may not lead to reduction of direct labor costs because the overall labor structure for the plant would not be changed significantly."
2	Indirect Labor	Generally Agree	Generally Agree	Generally Agree	Generally Agree	SME 3: “An assessment should be made regarding how well the distribution of deviations in Platform B would perform as a proxy for that in Platform A? Would it over- or under-estimate the relative number of deviations for each unit. This could be judged based on if the unit is used relatively more, less, or the same in Platform A than Platform B.”

3	Yield Improvement	Generally Agree	Generally Agree	Generally Agree	Agree w/ Reservations	SME 4: "[Some of the] buffer raw materials and buffer prep labor [which are considered fixed costs in the model] should be considered variable with respect to the yield of the unit." SME 4: "Product remaining in [a hold volume] of the unit at the end of a cycle is drained and not recovered. Hence it should be subtracted from the maximum yield."
4	Fully Continuous Operations	Generally Agree	Generally Agree	Agree w/ Reservations	Agree w/ Reservations	SME 3: "An effort to reduce footprint should consider the entire process, including the solution preparation and hold. Solution preparation and hold can take up significant footprint and cannot be easily reduced for a facility with a given throughput. That footprint is also not addressed by this opportunity, which focuses only on the continuous operation of the main process equipment." SME 4: "Decreasing the footprint by half is not a realistic outcome and hence does not need to be considered."

5	Fouling Reduction	Generally Agree	Generally Agree	Generally Agree	Generally Disagree	SME 3: "The result is based on an implicit constraint of having a fixed filtration area, and this should be mentioned." SME 4: "Higher cell densities could be achieved, so this opportunity should be considered viable."
6	Dynamic Loading	Generally Agree	Generally Agree	Generally Agree	Generally Agree	None

Table 3.2: SME reviews for opportunity size calculations

3.2.2 Technology Readiness Levels

Methods

While estimating the opportunity sizes as the relative benefit, we also developed a quick and rough way to compare relative risks of pursuing different opportunities. For this purpose, we adapted the concept of Technology Readiness Levels (TRLs) which is used by NASA [37] and the Department of Defence [38]. The definitions of levels provided by the Department of Defense were interpreted into criteria that may be used in an Amgen technology development context. These definitions are presented in Table 3.3. (Note that these stages of technology development do not reflect the processes or stages used by Amgen to develop the manufacturing processes of their pipeline molecules.)

In an internal discussion within the NGA(DS) team, we identified the most promising solutions currently available for each of the opportunities listed in Table 3.1. The TRL of an opportunity was defined as the highest TRL of any of its available solutions.

Results and Discussion

The TRLs of opportunities were considered together with the opportunity sizes using a graph similar to that shown in Figure 3-5. The graph shows the TRL on the X-axis and the opportunity size of the Y-axis. In internal discussions with NGA managers, Four zones were proposed on such a graph to prioritize NGA(DS) opportunities:

1. **Support partners with exploration**: NGA(DS) likely will not engage in early scientific exploration by itself, but will rather rely on other groups inside and outside Amgen for such insights.

2. **Opportunities for NGA(DS) development**: An opportunity can be taken on by NGA(DS) if there is at least an idea formulated for an equipment or automation solution to address the opportunity. Ideas with higher TRLs have been validated and carry less risk. As discussed earlier, if there is a need to

choose between two opportunities with the same TRL, the team would be expected to choose the opportunity with a bigger opportunity size.

3. **Lower Priority Opportunities**: These are generally opportunities with smaller opportunity sizes. The exact shape and position of the boundary between zones 2 and 3 is affected by a team's operating decisions.

   The shape of the boundary is affected by the team's risk-reward tradeoff expectations. A sharper downward slope would indicate a more conservative approach – in this case higher TRLs would be preferred over higher opportunity sizes. On the other hand a flatter boundary would indicate a riskier approach.

   The lateral position of the boundary is affected by the resources available within the NGA(DS) team. With fewer resources, the boundary would move up until the number of projects in zone 2 matched the engineering capacity available. On the other hand, with more resources a bigger portfolio of solutions could be developed.

4. **Support GMP Automation with implementation**: Once solutions are well developed and have been vetted in laboratory and/or pilot plant settings, NGA(DS) would be able to hand the solutions over to other automation groups within Amgen which are able to build, qualify, and support automation for GMP manufacturing settings.

TRL	DoD Description	Thesis Author's Interpretation for Amgen Process Development
1	Basic principles observed and reported	Basic biology, chemistry, materials, and controls research
2	Technology concept and/or application formulated	Applications of basic research to develop process ideas
3	Analytical and experimental critical function and/or characteristic proof of concept	Proof of concept of new process ideas
4	Component and/or breadboard validation in a laboratory environment	Testing of process ideas under ideal conditions or with ideal materials
5	Component and/or breadboard validation in a relevant environment	Testing of process ideas with actual conditions and actual materials
6	System/subsystem model or prototype demonstration in a relevant environment	Small scale qualification in Pre-Pivotal/Pivotal
7	System prototype demonstration in an operational environment	Engineering runs in Pilot Plants or GMP Plants
8	Actual system completed and qualified through test and demonstration	IOQ at GMP Plants
9	Actual system proven through successful mission operations	GMP runs at GMP plants

Table 3.3: Department of Defense descriptions for Technology Readiness Levels and the thesis author's interpretations for Amgen Process Development

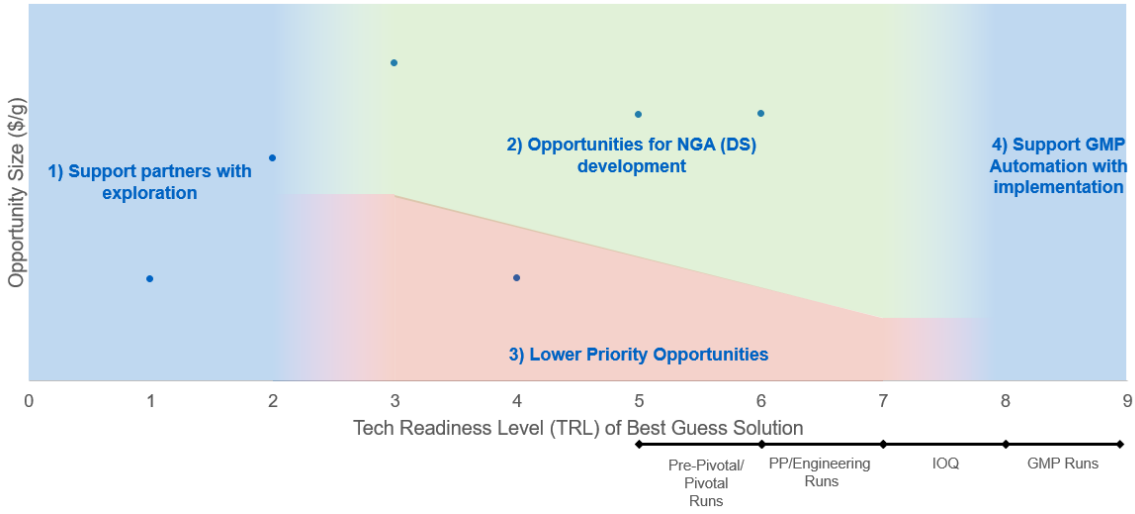

Figure 3-5: Illustration of opportunity prioritization for NGA(DS) using TRLs and opportunity sizes. (does not reflect real data)

THIS PAGE INTENTIONALLY LEFT BLANK

Chapter 4

Solution Development Case Study

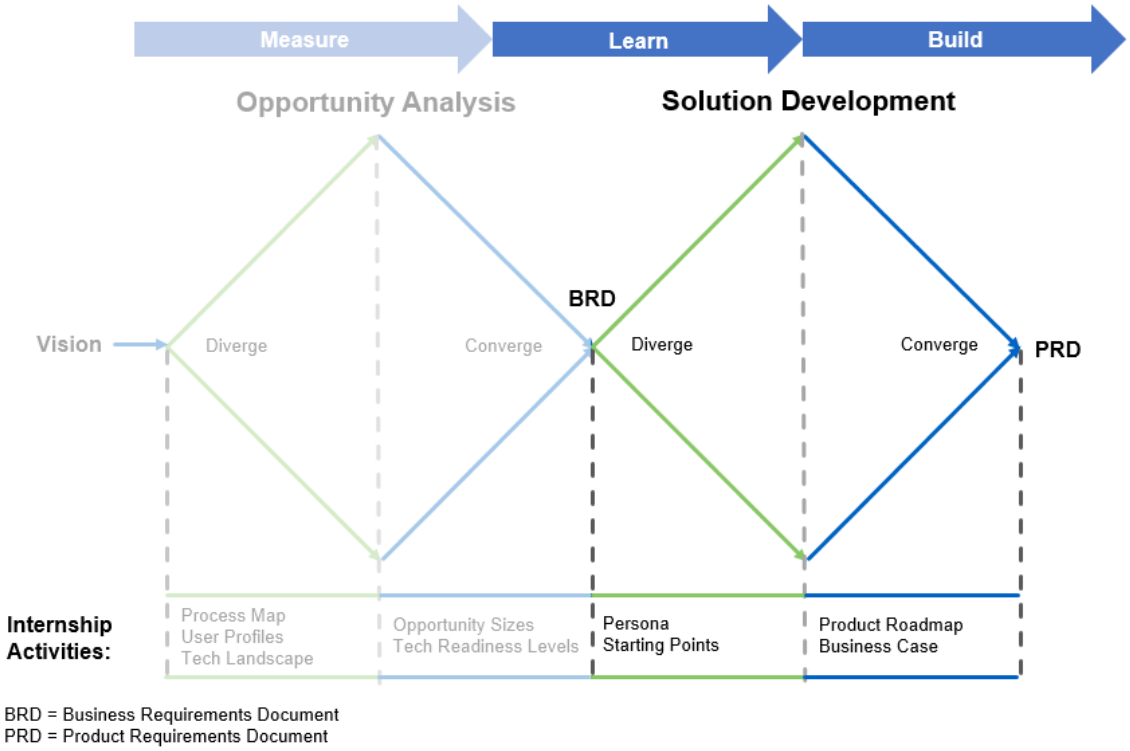

Figure 4-1: Framework for the Solution Development phase

Key Takeaways:

1. Diverge – Ideating
   (a) Several solutions were being developed by the NGA(DS) team at the time of the project, of which one – automated sampling – was chosen to be analyzed in this project.
   (b) Information regarding the users and the process were recorded in a level of detail that would allow various solutions to be proposed for the automated sampling opportunity. A process map and a persona were used as tools to record and communicate this information.
   (c) Existing solutions that could be used as starting points for development were evaluated against a list of priorities for the customers of the automated sampling end product.
2. Converge – Roadmapping
   (a) A roadmap of features was generated to guide the development of the automated sampling product. The roadmap was designed to test hypotheses regarding the value of the solution, through a series of Minimum Viable Products (MVPs).
   (b) A business case was developed to analyze the viability of the first Minimum Viable Product.
   (c) The calculation of a long-term Net Present Value (NPV) for the automated sampling product solution was recommended to NGA(DS) but not completed within the time frame of the project.

This chapter provides the methods and results for the Solution Development phase of the project. At the time of the project, the NGA(DS) team had multiple solutions in development. One of these solutions, an automated sampling system, was used as a case study for the methodology developed in this chapter. Automated sampling

addresses opportunities #1 and #2 from the Opportunity Analysis phase.

The solution development phase began with documenting our understanding of the opportunity in the Business Requirements Document (BRD). The activities were then divided into two sub-phases: Diverge and Converge. As part of the Diverge sub-phase, a persona was established for the lead user, a current state process map was documented, and existing solutions were evaluated as starting points. In the Converge sub-phase, we documented an initial roadmap of features for the product and performed a full cost analysis of the MVP. This chapter also discusses how a Net Present Value (NPV) analysis of this solution should be performed, although that analysis was not completed within the duration of the project. The outcome of the Converge Solution Development phase is recommended to be documented in a PRD (Product Requirements Document), which can then guide the build of the product.

The analysis presented in this chapter was performed in close collaboration with other members of the NGA(DS) team.

4.1 Motivation – Business Requirements Document

Methods

Consistent with the recommendations of the article by the Google product manager discussed in Section 1.2, the solution development process was started with a full documentation of the opportunity that we were attempting to address. The purpose of this document is to align the NGA(DS) team, its customers, partners, and leaders in how they understand the opportunity. This alignment is a two-way process that allows stakeholders to understand NGA(DS)'s plans but also to provide feedback. The document can be revised based on this feedback. The document is intended to be short (2 to 4 pages) with relatively simple and non-technical language, so that it could be easily circulated to a wide audience.

The BRD was intended to document

1. A brief **vision** statement that summarizes the need for a solution.

2. Detailed statement of **motivation** for why a solution should be pursued, including who the solution is meant for, what solutions already exist, and why a new solution is being pursued now.

3. A **use scenario** which briefly outlines how the solution would be used.

4. The **opportunity sizes** for the opportunities addressed by the solution, as calculated in Section 3.2.1.

5. **Adoption barriers, risks, and dependencies** a solution might face.

While the BRD includes details that are relevant to developing a solution, it is still only a definition of the opportunity, not the solution itself. The BRD is written to be specific about the current state and opportunity, but as general as possible regarding the solution.

Results and Discussion

The draft of the Business Requirement Document as developed by the end of the project is included as Appendix D. The draft was reviewed with the broader NGA group, the DS Pre-Pivotal Development group, and the Pilot Plant group. It is expected to be reviewed with other customers and stakeholders as product development continues.

4.2 Diverge – Ideating

4.2.1 Persona

Methods

Software designer and programmer Alan Cooper is credited with originating the use of personas for product development. In his article, "The Origin of Personas", he writes, "At the next group meeting, I presented my designs from the points of view of [personas] Chuck, Cynthia, and Rob instead of from my own. The results were

dramatic. ... the programmers could clearly see the sense in my designs because they could identify with these hypothetical archetypes. ... engineers began to talk about 'what Cynthia would do' or 'whether Chuck could understand' some dialog box" [39].

Personas are abstract representations of the target customers that a development team can relate to. Personas are meant to allow developers to take the user's perspective when making design decisions for the solution. This purpose is different than for user profiles, which help with decision making on a much broader level, i.e., regarding what opportunities are pursued. Because of this difference in purpose, User Profiles and Personas are also written differently. User profiles include general facts and data about a group of users, while personas include specific details about a single hypothetical person. "Generating a Persona" is step 5 of the Disciplined Entrepreneurship framework [22].

Results and Discussion

For reasons discussed in the User Profiles section (Section 3.1.1), the lead customer group of the automated sampling solution was chosen to be the DS Pre-Pivotal scientists. Furthermore, as mentioned in the BRD, the bioreactor was chosen as the lead use case because of the relatively higher frequency of sampling required. A persona was developed for the **DS Cell Culture Pre-Pivotal Scientist** based on interviews with four scientists in this role and a walk-through of their lab. The data for the personas were collected jointly with other members of the NGA(DS) team.

For simplicity, the persona is presented just as a list of traits, without any further categorization or organization. Personas often use a made up name, but is not used here to avoid confusion – in a setting where personas are not widely used and the user base is very small (<10–20 individuals), a name may suggest that the persona refers to a real person.

The persona traits should not be attributed to any particular interviewee since the persona is based on the thesis author's interpretation.

1. The scientist is deeply familiar with the cell culture process and has many years of experience running experiments in this area.

2. The scientist takes ownership of their experiments and is invested in the success of the experiments. The scientist needs to take care of the cell culture and keep the cells alive. Many things can kill cell cultures, e.g., a contamination or a malfunctioning sensor.

3. The scientist works long hours, including frequently in the evening and on weekends. On some of the weekend days, the scientist comes to the lab only to collect samples and analyze them.

4. In making decisions about a run, the scientist uses all the process data that they have (critically including sample analysis), along with their experience from past runs. Quick and easy access to relevant data can help them during run time. For example, if the online pH sensor does not agree with the offline pH measurement, the scientist may consider the trends of both values within the run, the expected pH range in such a run, previous experience with accuracy of the online and offline instruments etc. Based on this, the scientist will form a hypothesis and act on that. This process is different from a manufacturing run, where all procedures are pre-determined.

5. At the end of the run, the scientist needs to document the results of the experiment in GLP validated databases. Here again, the scientist needs data, but the priorities are different – completeness, reliability, and integrity instead of speed and easy access.

6. The scientist is used to regularly evaluating and adopting new technologies. The scientist would be open to a new automated sampling system if it helps, but probably not if it creates more work than is saved.

4.2.2 Process Map

Methods

The process map, in this case, documented the flow of material and data for sampling. As compared to the process map in Section 3.1.2, the process map here zooms into the

process of collecting and processing samples. The process map was only documented for the bioreactor samples, since that was the lead use case. This step was primarily executed by another member of the NGA(DS) team. The map was documented as a table containing information on:

1. The **analytical instrument** for which the sample was collected
2. **Preparation** required before introducing sample into analytical instrument
3. **Frequency and timing** of sample
4. **Duration of processing** the sample, from the time that the sample is drawn from the bioreactor until the analytical results are retrieved
5. **Types of measurement data** retrieved from the instrument (e.g., cell counts, metabolites)
6. **Data storage systems** for the measurement data
7. **Reasons for collecting the data** (e.g., re-calibrating sensors, monitoring cell health, adjusting setpoints)

Results and Discussion

The process map cannot be shared here to protect confidential information. The process map was used in the Converge sub-phase to generate ideas for how the sampling workflows may be re-engineered when using an automated sampling system.

4.2.3 Existing Solutions

Methods

As discussed in Section 2.1.2, all automation solutions build on existing platforms, whether proprietary or open-source. Hence, before developing a solution, the NGA(DS) team must evaluate all the existing solutions that they can build on top of. Different starting points may offer different capabilities. All existing solutions are expected to

require at least some development before they can be used within Amgen's processes, but the amount of development required may vary from minimal integration and customization, to full custom software development. The TRLs discussed in Section 3.2.2 can serve as a good scale to judge the relative amount of development required from each starting point.

In addition to identifying existing solutions, we evaluated how these solutions were expected to perform against an initial list of general requirements for the final solution.

Analyzing existing solutions relates to step 11 of the Discipline Entrepreneurship framework ("Chart Your Competitive Position")[22]. While externally marketed products must compete against existing solutions, an internal product team can choose to use and build on top of the existing solutions. The analysis, however, is similar in both cases.

Results and Discussion

As mentioned in the BRD, three starting points were identified for the automated sampling opportunity: (i) automated sampling system 1 by vendor A, (ii) automated sampling system 2 by vendor B, and (iii) a Raman probe by vendor C. Automated sampling systems 1 and 2 are both complex systems that are able to draw liquid samples from vessels, dilute samples, store samples, and send samples to analytical instruments. Both systems provide physical and digital integrations with many analytical instruments which are used in biomanufacturing. The third option, the Raman probe, provides very different functionality, but addresses the same essential opportunity that is documented in the BRD. The probe provides *in situ* measurements of the chemical composition of the bioreactor contents using Raman spectroscopy. In this way the Raman probe can, presumably, provide much of the same data that are currently measured by offline analytical instruments.

All three existing solutions would require additional integration by NGA(DS), before the solutions could address the opportunity documented in the BRD. The existing solutions would need to be integrated into the lab's/plant's process control

system and into Amgen's databases.

We compared the existing solutions based on their potential to fulfill the seven general requirements:

1. Ability to **provide all the measurements** that are currently collected, as documented in the sampling process map. For the automated sampling systems 1 and 2, this assessment implied being able to integrate with the analytical instruments that could provide such measurements. At minimum, the final solution should account for all the measurements required in some way, but ideally the measurements collected would be as or more precise and accurate as those measurements currently being collected by Amgen.

2. The solution should provide **safe and clean** handling of the sample, and not affect the sterility of the process.

3. The existing solution should have been **vetted by process development teams** within Amgen for the above two points before NGA(DS) develops integrations with Amgen systems.

4. If all measurements are not currently available, the vendor should be **willing to co-develop future integrations** with additional analytical instruments per Amgen's requirements.

5. The vendor should provide adequate **support with installation and commissioning**.

6. The final solution should provide **data integrity and easy management of measurement data**.

7. The solution should physically **fit within the limited space available** in the labs and plants.

The assessment of specific solutions to specific requirements is not provided here to protect confidential information. Overall it was decided that existing solution (i) – automated sampling system 1 by company A – was the most appropriate to use for

initial development. Other existing solutions were not abandoned but rather kept in active consideration for future versions of the NGA(DS) automated sampling product.

4.3 Converge – Roadmapping

Based on the information collected in the Diverge sub-phase, the objective of the Converge sub-phase was to define an initial plan for the solution.

4.3.1 Roadmap and Features

Methods

In this step, the roadmap of the product was defined as a prioritized list of features. As recommended by all sources in the Literature Review (Section 1.2), the priorities were set to allow the sequential validation of key hypotheses regarding how the solution creates value. The roadmap was split into three "versions" of the product: v1 (Minimum Viable Product), vNext, and vLongTerm. Special attention was paid to defining the Minimum Viable Product (MVP). Lean Startup describes the MVP as "that version of the product that enables a full turn of the Build-Measure-Learn loop with minimum amount of effort and least amount of development time" [20]. The MVP provides value by validating or invalidating a key hypothesis. vNext and vLongTerm are documented to keep the MVP connected to the long-term goals of the product, but we would expect these versions to evolve based on the learning from the MVP. Lean Startup intends the entire development process to actually be a series of MVPs.

For each version, a set of features were listed by a simple brainstorming exercise within the NGA(DS) team. In this exercise, three members of the team developed a list of all the features that had been thought of within the team, or been requested by customers in interviews. Each feature was then sorted into the three versions based on the following questions: is this feature needed to test the MVP hypothesis? If not, is this feature needed to test the vNext hypothesis? If the feature was not needed for

either but fulfilled an unmet need, we included the feature in vLongTerm.

Results and Discussion

v1 (MVP)

Hypothesis: An automated sampling solution can be built for the Pre-Pivotal Development lab such that the scientists would avoid manual sampling at least on weekends. This solution would provide net time savings for the scientists.

Features:

1. Integration with analytical instruments A and B to provide measurements C, D, and E
2. Ability to draw cell-free samples using technology F
3. Integration with a fraction collection to hold samples for offline testing
4. Dilutions of up to a 1:x ratio.
5. Flow line cleaning to avoid cross-contamination
6. Scheduler for planned samples
7. Integration with DCS to display sample results and trends.
8. Safety assessment for the entire system and each feature

vNext

Hypothesis: An automated sampling solution can be built for clinical or commercial manufacturing plants that would provide a net cost decrease. The cost savings would be expected primarily from lower direct labor requirements and greater reliability.

Features:

1. Integration with manufacturing platform analyzers for all required measurements

2. Ability to trigger sampling commands from the DCS
3. DCS alarms based on sample results
4. Dilutions of up to a 1:y ratio
5. Reduced cycle time for each sample
6. Re-calibration of sensors based on offline results
7. Ability to draw cell-free samples using technology F
8. Integration with a fraction collection to hold samples for offline testing
9. Vendor commitment for parts supply

vLongTerm

Hypothesis: An automated sampling solution can be used to further optimize the performance of the manufacturing plant and build new capabilities.

Features:

1. PAT and feedback loops based on sample results
2. Maintenance management and performance analytics for measurement instruments
3. Custom sample scheduler interface for logic, time, or process condition based sample plans
4. Potential integration with offline or online Raman probe

4.3.2 MVP Cost Analysis

Methods

A cost analysis was done to estimate the value of the MVP to its customers. This cost analysis was not conducted with an expectation of a positive value, or to help

decide whether the product should be pursued. As discussed, the major value of the MVP to Amgen as a whole is in validating or invalidating hypotheses. The purpose of the cost analysis was primarily to understand how various design decisions and user behaviors drive cost and benefit.

Results and Discussion

The cost model for the MVP compared the benefit of saving the scientists' time against the cost of the MVP solution. The model was built to calculate an annual net cost or benefit. Time value of money was not considered and capital costs were simply amortized in a straight line. An NPV approach was avoided for simplicity.

The net time savings were calculated as the time for manual sampling that could be avoided with the MVP minus the additional setup and operation time required for the MVP. These time savings included commute time for when scientists may be able to avoid coming to the lab only to take samples. We calculated the time savings on an annual basis based on how many runs could be supported by one unit of the MVP. We multiplied the time savings by a nominal hourly cost of labor to get the monetary savings. As discussed later, the cost of labor is highly variable and hence was subjected to sensitivity analysis.

In order to determine the cost of the MVP, two Bill of Materials (BOMs) were generated and costed – one for the assembly of a unit of the MVP, and one for operating the MVP for a single run. The BOMs were costed based on vendor quotes and past invoices. From the assembly BOM, two levels of costs were calculated – the cost of the full assembly BOM and the cost of the first build. The latter did not include the cost of equipment that Amgen already owned and that could be used to assemble the first MVP unit. The cost of assembly was amortized over the expected useful life of the vendor equipment in a straight line. The operation BOM provided a per-run cost, which was then multiplied by the expected number of runs the MVP could support, to get the annual cost.

Multiple scenarios were tested in the model by altering assumptions regarding design constraints, current costs, and product performance. In all likely scenarios,

the MVP was found to have net negative, or close to net neutral financial value. As mentioned, this did not affect the decision for whether the product was pursued. Another output of the model was the amount of time saved for scientists, which was found to be significant. This was valuable in a setting where scientists already had many demands on their time – an automated sampling system could help even if it slightly increased the cost of the labs.

Key performance parameters for the product that emerged from the model were (i) the number of days in a week the scientists could use the MVP to avoid manual sampling (e.g., all days or only weekends), (ii) the number of reactors a single MVP unit could support within a single run, and (iii) the number of runs an MVP unit could support in a year. The value of these parameters were not yet known, so the model was tested with target and realistic values for each parameter. As mentioned earlier, another uncertain input to the model was the hourly cost of labor. Measuring its value is complicated by the fact that sampling is done primarily by salaried employees who do not work at a fixed hourly wage. Additionally, the salary data were not available and are expected to be highly variable given that scientists of different experience levels all collect and analyze their own samples. In this case, our scenarios were tested with the range of salaries that could realistically be expected in this context, converted to an hourly wage for a standard forty-hour week.

It could be argued that the financial benefit from time savings that we have calculated is not actually realizable since a single MVP unit may not save enough time to actually reduce the number of scientists in a lab. In discussions within NGA(DS), it was decided to include the benefit despite this argument. This decision was based on the assumption that accounting for benefits in such a way incentivizes improving process efficiency over the long run. Even if one version of one solution is not enough for a step decrease in the cost, sustained innovation would provide savings eventually.

4.3.3 Future Work: Long-Term NPV

It is recommended that the NGA(DS) team perform a long-term NPV analysis for their automated sampling product. As opposed to MVP cost analysis, which was

concerned with costs in the lab context in which the MVP would be deployed, the long-term NPV analysis would focus on the original opportunities for which this product was pursued: increased reliability and decreased direct labor requirements for clinical and commercial manufacturing plants. The NPV analysis could be carried out on a per manufacturing line basis and would include similar cash flows as the MVP business case: benefit of sampling time saved, ongoing costs of operating the new solution, and capital expenses for assembling the product units. While the opportunity size calculations in the Chapter 3 were limited to Platform A, this solution may be applicable to other platforms, and the NPV calculation could be done for all platforms with the same methodology.

4.4 Future Work: Product Requirements Document

It is recommended that once the long-term NPV is calculated and all the analysis of the Solution Development phase has been internally vetted, the NGA(DS) team should create a Product Requirements Document. This document would repeat the definition of the opportunity from the BRD, and add the information about the planned product. Specifically it should add the roadmap, features, and the long-term NPV (if already positive). Additional outcomes of the Solution Development phase, including personas, process maps, existing solution analysis, and MVP cost analysis could be included as appendices for readers who may wish to dive deeper into these details. As with the BRD, the PRD would be a tool to align the expectations of stakeholder and to seek feedback from them. The PRD should also be kept short and easily readable.

THIS PAGE INTENTIONALLY LEFT BLANK

Chapter 5

Conclusion

During the course of this project, a product management framework was developed for the NGA(DS) team. The framework was built up by applying relevant principles and tools from existing prominent frameworks to the NGA(DS) team's vision of providing automation solutions for a continuous manufacturing process platform at Amgen. The framework generated in this project helped the NGA(DS) team to (i) search for opportunities in the current process, (ii) prioritize the opportunities identified, (iii) develop multiple solution ideas for a single opportunity, and (iv) set a roadmap focused on testing hypotheses regarding the opportunity and solution. A single iteration of the framework methodology was completed within the time frame of the project (discounting two activities that are detailed in this thesis but not completed during the project). All results from the application of the framework methodology were validated by reviews within the NGA(DS) team and some were validated by reviews with other SMEs within Amgen as well.

This framework is expected to guide decision making for the NGA(DS) team in the future, for making several types of decisions:

1. Once the Minimum Viable Product (MVP) has been released for the automated sampling solution, the Solution Development phase can be repeated to decide whether the NGA(DS) team should persist with the existing roadmap or pivot their plans based on new learnings.

2. If multiple opportunities are being pursued for Platform A, the Solution Development phase can be executed for the additional opportunities.

3. If additional opportunities are discovered for Platform A or if there are major changes in the current process, the Converge sub-phase of the Opportunity Analysis phase can be repeated to re-prioritize opportunities.

4. The framework, including both phases, can be executed for other NGA(DS) work streams, which include development of automation for other processes and process platforms.

The framework itself is also expected to evolve over time. The specific methodology and communication format for each activity may be different for each manager using the framework, but the goals of each activity and the broader principles of the framework are expected to be more stable. The framework can be expected to grow to support additional activities of the NGA(DS) team. The areas of growth can be hypothesized based on activities recommended by the source frameworks that were not implemented in this project. For instance, the anecdotal information from product managers indicated that product managers often also support engineering workflow management, for instance using Agile [40], and technical documentation for the solutions [24]. *Disciplined Entrepreneurship* and *Double Diamond* recommend user experience development activities such as wireframing and storyboarding [22, 23]. *Disciplined Entrepreneurship* and *Lean Startup* emphasize management of customer acquisition and growth focused activities [22, 20]. These or other tools can be added to the framework as needed to support product development within NGA(DS).

Appendix A

Application of Disciplined Entrepreneurship Framework to Amgen Next Gen Automation

Table A.1 applies Bill Aulet's Disciplined Entrepreneurship (DE) framework to teams building internal products to improve operations. The table considers which steps are applicable to such a setting and, where applicable, how the steps were executed in my project. Of the 24 steps, 22 were found to be fully or partially applicable to internal product team such as NGA(DS), while two were found to be generally not applicable (steps 16 and 19). Adapting the framework to use in my project required three broad modifications:

1. Analyzing **internal customers and internal "markets"** is somewhat different than customers in an actual market. Many of the steps are affected by this difference, but the modifications required are fairly straightforward and are explained in the table.

2. The **volume of units** that NGA(DS) would expect to install for any one of its products is smaller than most stand-alone companies would install. A finished NGA(DS) product would only have a few units total – for instance, one in each lab or plant within Amgen. This difference in volume from Aulet's intended

audience affects the steps focusing on customer acquisition. While companies selling high-volume products would need to have a repeatable sales and marketing operation cycle, NGA(DS) would likely manage each unit install as an individual project.

The above is not necessarily the case for all internal products. For instance, if a big company like Amgen intended to roll out a high-volume internal solution, such as a smartphone application for each employee to use, then the customer acquisition should be performed as Aulet recommends. For such high-volume internal products, a repeatable process would likely be needed to "acquire" employees as users.

3. The framework developed in this project **combines DE with other frameworks** discussed in Chapter 1. These frameworks generally tend to converge two similar principles but provide different perspectives. As mentioned in the table, all the applicable steps in DE were performed in my project or are recommended for the future. These steps were not necessarily performed in the order that the DE framework identifies.

	Step	Interpretation for internal teams	Project execution/results
1	Market Segmentation	This step is applicable to internal product teams but the set of potential customers is likely already defined fairly narrowly for a team by the company's organizational structure. For internally focuses team, this step should include analyzing relevant internal and external supply chains for the company.	Analysis presented in Chapter 2

2	Select a Beachhead Market	The criteria provided to select the beachhead market applies well to internal markets. The only caveat is for criterion 2 – internal teams do not have formal sales forces. However, teams should still consider which customers would be willing to even start talking about potentially accepting and using their solutions.	For this project, the NGA(DS) team had already arrived at Platform A as a beachhead market. This decision was outside the scope of the project but was made using similar considerations as prescribed by DE.
3	Build an End User Profile	This step is fully applicable to internal product teams. Value stream/process maps can also be useful in capturing information relevant to this step in manufacturing/operations settings.	End user profiles and the process map for Platform A are documented in Chapter 3.
4	Calculate the Total Addressable Market (TAM) Size for the Beachhead Market	This project adapted the concept of TAM to internal solutions as Opportunity Size. The methodology for this adaptation is discussed in Section 3.2.1.	Opportunity sizes for various potential opportunities were calculated (methodology documented in Section 3.2.1). Each opportunity can be considered a subsegment of the beachhead market.
5	Profile the Persona for the Beachhead Market	This step is fully applicable to internal product teams. In an internal setting, the persona would be expected to focus on the professional, rather than personal, life of the customer.	A persona was created for the automated sampling solution case study and is presented in Chapter 4.

6	Full Life Cycle Use Case	The use case for the use of a product is fully applicable to internal products. As defined by DE, a full life cycle use case also includes the process of acquiring customers and delivering the product to them. These processes should be included in the use case for high volume products, but not for low volume products. For the latter, these processes can be executed as individual projects with the specific needs for each installation accounted for in real time.	A use case for the use of the product was prepared for the automated sampling case study and is presented in Chapter 4.
7	High-Level Product Specification	This step is fully applicable to internal product teams.	For the automated sampling case study, a product road-map was prepared as the high-level specification and is presented in Chapter 4. Visual tools to communicate the specification, as suggested by DE, are recommended but were not completed within the timeframe of the project.
8	Quantify the Value Proposition	This step is fully applicable to internal product teams.	A business cases for the MVP was developed in the Solution Development phase. A long term NPV calculation was recommended as part of the project framework but was not completed within the timeframe of the project. The methodologies for both activities are presented in Chapter 4.

9	Identify Your Next 10 Customers	The motivation of this step, i.e. not losing focus on the long-term vision of a product while building the MVP, is applicable to internal products. In the case of low volume products, there may not be 10 customers even in the long term. In that case, the step can be framed as identifying all the potential long term users and stakeholders.	Within the time frame of the project 5 additional potential users of the long-term product, beyond the user presented in the initial persona, were interviewed. Additional interviews are recommended and will likely occur as the development progresses. The results of the interviews are not presented in this thesis..
10	Define Your Core	Internal teams should find core capabilities that differentiate them from both other internal teams and external vendors.	This analysis is presented in Chapter 2.

11	Chart Your Competitive Position	This step may be applicable to internal teams, with a few caveats: 1. An internal innovation team does not have to compete with existing solutions, and has the option of using them instead. Hence for internal teams, this step can be framed as finding the best starting point instead of evaluating competitors. A decision to build an internal product from scratch where a product already exists in the market should be justified in terms of the overall cost and benefit of both options. 2. For a high volume market, it can be appropriate to judge competitors using two major customer priorities, as the book suggests. For a low volume market, it is possible to more reliably gather a larger set of requirements from customers and it can be informative to judge competitor products against all of these requirements. The relative importance of each requirement can be also judged. We can record this information in a matrix format, as shown in Chapter 4.	The performance of various starting points available for the automated sampling solution was judged against a set of a general requirements. This analysis is presented in Chapter 4.

12	Determine the Customer's Decision-Making Unit	This step is fully applicable to internal products.	This step was completed for the automated sampling product by analyzing the formal and informal networks within the company. The analysis is not presented in the thesis to protect company information, and because the methodology is expected to be different for each company and team.
13	Map the Process to Acquire a Paying Customer	This step is fully applicable to internal product teams. Only minor details may be different for internal products e.g. there may not be a formal marketing group involved. For low volume products, each acquisition may need to customized and run as a project rather than relying on a predetermined process.	The NGA(DS) team was developing the customer acquisition plan for the automated sampling solution during the project, but the development of the plan was not included in the scope of the thesis. Since this was a low volume product, the plan was being developed specifically for the MVP solution and not to be generalized for future versions and customers.
14	Calculate the Total Addressable Market Size for Follow-on Markets	This step is fully applicable to internal products. Follow-on markets may be for other steps in the same process or similar steps in an other process.	The initial set of opportunities analyzed in Chapter 3 may be considered follow-on markets. It is also recommended to calculate the opportunity size for adopting the automated sampling solution to other process platforms besides Platform A, but this calculation was not performed during this project.
15	Design a Business Model	Teams building internal products do not need to design a business model but rather need to examine how their work fits into their company's business model.	Amgen's business model and the roles of NGA(DS) within Amgen is analyzed in Chapter 2.

16	Set Your Pricing Framework	This step is not applicable to internal product teams, unless they are funded using an internal transfer pricing arrangement.	Transfer pricing was not considered as part of this project.
17	Calculate the Lifetime Value of an Acquired Customer	With a product that is both developed and used internally, the lifetime value is equivalent to the Net Present Value (NPV) of the product to the company. The NPV should be calculated.	It is recommended to calculate the NPV, but the full costing of the automated sampling case study solution could not be completed to perform the NPV calculation within the time frame of the project.
18	Map the Sales Process to Acquire Customers	Internal product teams, especially smaller teams like NGA(DS), are unlikely to have a full-fledged sales force. The teams can establish rough numbers for the percentage of overhead time that team managers, products managers, and engineers spend on communicating with the internal customers.	This step was not included in the scope of the project. Once the team's processes are stabilized, it is recommended that NGA(DS) calculate rough numbers for the amount of overhead required for various team members for external communication.
19	Calculate the Cost of Customer Acquisition	This step is likely not applicable if there is no dedicated customer acquisition staff or if the product is low volume. For high volume products, if adoption requires significant internal "selling", CoCA would be an important metric to track.	This step was not performed for this project.
20	Identify Key Assumptions	This step is fully applicable to internal products.	Key assumptions are identified in the calculation of the opportunity size (Chapter 3) and as risks in the BRD (Chapter 3).
21	Test Key Assumptions	This step is fully applicable to internal products. The documentation used to capture agreements with internal customers may vary based on the customary processes within a company.	The BRD (Chapter 3) and PRD (Chapter 4) for the automated sampling solution are recommended to be used to validate assumption with stakeholders and to jointly agree on plans for pilot implementations.

22	Define the Minimum Viable Business Product	This step is fully applicable to internal products.	A MVBP for automated sampling was designed and is presented in the solution roadmap (Chapter 4).
23	Show that "The Dogs Will Eat the Dog Food"	This step is fully applicable to internal products.	The MVBP designed in step 22 was being developed, but was not completed within the project timeline.
24	Develop a Product Plan	This step is fully applicable to internal product teams.	A product road-map for automated sampling was developed to include vNext and vLongTerm versions, and is presented in Chapter 4. This road-map is expected to evolve based on learnings from building and testing the MVBP.

Table A.1: 24 Steps of the Disciplined Entrepreneurship framework adapted to internal product teams and NGA(DS)

THIS PAGE INTENTIONALLY LEFT BLANK

Appendix B

User Profiles

The following tables provide the user profiles for the DS Pre-Pivotal Development, DS Pivotal Development, and the DS Pilot Plants groups. Since the NGA(DS) team primarily works within the DS space (rather than Drug Product (DP) or Finished Product (FP)), the user groups are referred to simply as Pre-Pivotal, Pivotal, and Pilot Plants groups. The methodology for gathering data for these user profiles is explained in Section 3.1.1.

Only data points that were found to be relevant to this project are included here. Full user profiles contain additional data collected in interviews, which may be relevant to NGA(DS)'s other work-streams or for ideation.

Table B.1: User profile for DS Pre-Pivotal Development group

Jobs To Be Done		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	The Pre-Pivotal group develops the process for early pipeline aka pre-pivotal molecules.	This is the primary job of Pre-Pivotal group. Any NGA(DS) product introductions should cause minimal disruption to this job, and if possible, should help to improve the performance of the job.
2	The Pre-Pivotal group has to transfer process definitions to the Pilot and Clinical Production Facilities Pivotal Development group and eventually to Pivotal Development group for commercial process development.	NGA(DS) products intended for clinical and commercial manufacturing plants should first be provided to the Pre-Pivotal groups, so that the products can be incorporated into the process definitions.
3	The Pre-Pivotal group advises the engineering and manufacturing groups regarding equipment and automation technology. The pre-pivotal group is building its own automation capabilities to support this function.	This functions aligns well with the role of NGA(DS). The pre-pivotal group can be expected to be a strong partner for NGA(DS).
4	For their experiments, the Pre-Pivotal group operates x # of bioreactors using a, b, and c equipment/automation platforms, and y # of downstream lines using d, e, and f equipment/automation platforms.	The Pre-Pivotal labs are a fairly large operation in themselves, which can be optimized using automation. The can be an indirect result of NGA(DS) products. It will not be the primary objective for the products, since the scale of clinical and commercial manufacturing costs is larger.
5	The Pre-Pivotal group intends to develop Platform A, with a major current goal being reduction of CPG.	NGA(DS) will be collaborating with the Pre-Pivotal group to achieve this.
6	The Pre-Pivotal group must maintain safe working conditions for everyone working in the labs.	NGA(DS) products should be safe to use and install. The NGA(DS) team can achieve this by a combination of organizational processes that verify that the products are safe to use, and software-based automated fault detection which can detect and prevent unsafe equipment conditions in real-time.

Gains		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	Individuals with cross-functional process and automation engineering expertise have been able to develop useful automation in the group's labs.	NGA(DS) should maintain a deep familiarity with process engineering concerns, in addition to their automation engineering expertise.
2	The Pre-Pivotal group has collaborated with *Attribute Sciences* and *Digital Integration and Predictive Technologies* groups to develop new process and automation technologies.	The NGA(DS) team should also continue to partner with the *Attribute Sciences* and *Digital Integration and Predictive Technologies* during the development of NGA(DS)'s products.
3	Early experiments with automated sampling systems have shown promising results and the group is hoping to develop this technology further.	NGA(DS) has take on automated sampling as an opportunity. This opportunity is considered in this thesis for the solution development case study in Chapter 4.
4	The group is evaluating dynamic loading technology for chromatography columns (i.e., automated loading based on real-time titer measurements).	This opportunity is evaluated for NGA(DS) in Chapter 3.
5	The Pre-Pivotal group has developed automation internally with low capital costs by using open source tools a, b, and c.	NGA(DS) may consider using these open source tools for development in the future. However, this opportunity is not considered within the scope of this thesis.
Pains		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	Issues with communications within automation systems have interrupted Pre-Pivotal experiments in the past.	NGA(DS) should consider communication issues as a risk for the products they develop, and mitigate the risk as far as possible. This risk is included in the BRD and PRD in Chapter 4.

2	Process technology transfers can be especially complex and costly when the process uses new technology previously not implemented by the receiving group.	While developing new solutions with the Pre-Pivotal group, the NGA(DS) team should keep the intended eventual target users of the solution informed. The target user's requirements should be considered and the technology should be demonstrated to them early, in preparation of the technology transfer.

Table B.2: User profile for DS Pivotal Development group

Jobs To Be Done		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	The Pivotal group develops the process for late pipeline aka pivotal molecules.	This is the primary job of Pre-Pivotal group. Any NGA(DS) product introductions should cause minimal disruption to this job, and if possible, should help to improve the performance of the job.
2	The Pivotal group receives process definitions from the Pre-Pivotal Development group and eventually, after further development, transfers them to the clinical and commercial manufacturing plants.	NGA(DS) products intended for clinical and commercial manufacturing plants should also be provided to the Pivotal group, so that the products can be stay incorporated into the process definitions.
3	For their experiments, the Pivotal group operates x # of bioreactors using a, b, and c equipment/automation platforms, and y # of downstream lines using d, e, and f equipment/automation platforms.	The Pivotal labs are a fairly large operation in themselves, which can be optimized using automation. The can be an indirect result of NGA(DS) products. It will not be the primary objective for the products, since the scale of clinical and commercial manufacturing costs is larger.
4	The Pivotal group intends to develop Platform A, with a major current goal being reduction of CPG.	NGA(DS) will be collaborating with the Pivotal group to achieve this.
5	Amgen has a culture of safety, where safety in the labs and workspaces is high priority.	NGA(DS) products should be safe to use and install. The NGA(DS) team can achieve this by a combination of organizational processes that verify that the products are safe to use, and software-based automated fault detection which can detect and prevent unsafe equipment conditions in real-time.
Gains		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	A custom automation system developed internally in the Pre-Pivotal group has been recently transferred to the Pivotal group and has been operated successfully.	NGA(DS) can model the process to transfer their own products from the Pre-Pivotal to Pivotal group, based on the process followed for this system.

2	The Pivotal group mostly uses the same equipment and has the same scale of processes as the Pre-Pivotal group. This simplified technology transfers.	NGA(DS) products provided to the Pre-Pivotal group may not require major changes before the products can be provided to the Pivotal group as well.
Pains		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	Issues with communications within automation systems have interrupted Pivotal experiments in the past.	NGA(DS) should consider communication issues as a risk for the products they develop, and mitigate the risk as far as possible. This risk is included in the BRD and PRD in Chapter 4.
2	Process technology transfers can be especially complex and costly when the process uses new technology previously not implemented by the receiving group.	While developing new solutions with the Pivotal group, the NGA(DS) team should keep the intended eventual target users of the solution informed. The target user's requirements should be considered and the technology should be demonstrated to them early, in preparation of the technology transfer.
3	In performing JTBD #4 (i.e., reduction of CPG for Platform A), the Pivotal group has found that certain segments of process cost structure, e.g., depreciation, cannot be optimized based on process improvements that the Pivotal group can make at this point.	NGA(DS) also may not be able to optimize these segments of the process cost structure, as discussed in Section 3.2.1

Table B.3: User profile for DS Pilot Plant groups

Jobs To Be Done		
	User Profile	Author Interpretation of Implication for NGA(DS)
1	The Pilot Plants run processes on commercial manufacturing scale equipment. The primary purpose of this is to provide experimental data to support the Pivotal, Pre-Pivotal, and Commercial Process Development groups. The secondary purpose is to produce material for lab studies (not for human use).	This is the primary job of Pilot Plant groups. Any NGA(DS) product introductions should cause minimal disruption to this job, and if possible, should help to improve the performance of the job.
2	The Pilot Plants, in collaboration with DSC F&E Automation, develop and test new equipment and automation which is then implemented in clinical and commercial manufacturing plants.	This functions aligns well with the role of NGA(DS). The Pilot Plants and DSC F&E Automation can be expected to be partners for NGA(DS).
3	The Pilot Plants own and operate a wide variety of process equipment that reflects the capabilities of the clinical and commercial manufacturing network.	NGA(DS) products could be staged in the Pilot Plants for development and testing before they are introduced in clinical and commercial manufacturing plants.
4	The Pilot Plants run x upstream batches and y downstream runs per year.	The Pilot Plants are a fairly large operation in themselves, which can be optimized using automation. The can be an indirect result of NGA(DS) products. It will not be the primary objective for the products, since the scale of clinical and commercial manufacturing costs is larger.
Gains		
1	The Pilot Plant has been able to run unit operations x and y in a "lights out" manner, i.e., with no operator at the unit operation and only remote monitoring.	The Pilot Plants can help NGA(DS) develop automation that can operate equipment in a lights out manner. Such automation can help improve quality and lower labor costs, but needs to be highly reliable.

2	The Pilot Plant process runs tend to be more variable than clinical and commercial runs, since they are experiments. Pilot Plant operators tend to be highly familiar with the automation of their equipment, so that they can operate it flexibly.	Pilot Plant operators can serve as "power users" of NGA(DS) products, providing informed ideas and feedback.
Pains		
1	Pilot Plant runs are expensive costing $ x per run.	Optimization of operations through automation would benefit overall cost per run, as referenced in JTBD #4.
2	Issues with communications within automation systems have interrupted Pilot Plant runs in the past.	NGA(DS) should consider communication issues as a risk for the products they develop, and mitigate the risk as far as possible. This risk is included in the BRD and PRD in Chapters 3 and 4.

Appendix C

Opportunity Size Models

This appendix provides the methodology, assumptions, and data sources for the models used to calculate opportunity sizes.

C.1 Direct Labor

C.1.1 Opportunity Hypothesis

Additional automation may be developed for unit operations x, y, and z to reduce their direct labor requirements, leading to a lower cost of direct labor per gram.

Note: The opportunity would be considered separate for each of the units x, y, and z, since the solutions required for each unit operation would be different. These are grouped together here for brevity and because the methodology to calculate the Opportunity Size for each is the same.

C.1.2 Status

This opportunity is currently considered viable.

C.1.3 Methodology, Assumptions, and Data Sources

The total cost per gram was broadly segmented into costs of raw material, depreciation, indirect labor, and direct labor, which is consistent with the OSPR cost model

(Section 2.2):

$$\text{cost per gram} = \$\ \text{RM/g} + \$\ \text{depreciation/g} + \$\ \text{indirect labor/g} + \$\ \text{direct labor/g}$$

Only direct labor costs are considered to be affected in this opportunity. The maximum reduction in the direct labor cost per gram would be the cost of direct labor required for the single unit x, y, or z. The total direct labor cost per gram is known from the OSPR model, and is allocated to a specific unit operation based on the total direct labor time required for that unit operation (including setup, operation, and breakdown), as recorded in the process map:

$$\begin{aligned}\max(\Delta(\text{cost per gram})) &= \$\ \text{direct labor/g for unit x/y/z} \\ &= \text{total }\$\ \text{direct labor/g} \times \frac{(\text{unit operation floor time})_{\text{current}}}{\text{total floor time}}\end{aligned}$$

C.2 Indirect Labor

C.2.1 Opportunity Hypothesis

Additional automation may be developed to improve the reliability of process area x, leading to a lower number of deviations. Hence less indirect labor time would be required to process those deviations, lowering cost of indirect labor per gram.

C.2.2 Status

This opportunity is currently considered viable.

C.2.3 Methodology, Assumptions, and Data Sources

The total cost per gram was broadly segmented into into costs of raw material, depreciation, indirect labor, and direct labor, which is consistent with the OSPR cost

model (Section 2.2):

$$\text{cost per gram} = \$\ \text{RM/g} + \$\ \text{depreciation/g} + \$\ \text{indirect labor/g} + \$\ \text{direct labor/g}$$

Only indirect labor costs are considered to be affected in this opportunity.

The maximum reduction in the indirect labor cost per gram would be the cost of indirect labor required to process deviations from process area x:

$$\begin{aligned}\max(\Delta(\text{cost per gram})) &= \$\ \text{indirect labor/g for area x deviations} \\ &= \text{total } \$\ \text{indirect labor/g} \cdot \frac{\text{Mfg FTEs for devs} + \text{Quality FTEs for devs}}{\text{Total Indirect FTEs}} \\ &\quad \cdot \%\ \text{devs for sampling}\end{aligned}$$

The total indirect labor cost per gram is known from the OSPR model, and is first segmented by the time of indirect labor that is spent processing deviations. This information would be collected via interviews with manufacturing and quality staff who process deviations. Then the cost of processing all deviations is segmented into specific areas based on the distribution of deviations in Platform B, as recorded in the process map.

An assumption for this model is that the relative distribution of deviations amongst process areas is the same for Platform A as Platform B.

Note: This opportunity considers only the indirect labor associated with processing deviations and not any potential effects of the deviation incident itself.

C.3 Yield Improvement

C.3.1 Opportunity Hypothesis

The addition of automated equipment within unit operation x may increase its yield and hence reduce the fixed costs per gram for a run.

C.3.2 Status

This opportunity is currently considered viable.

C.3.3 Methodology, Assumptions, and Data Sources

This model is based on the assumption that if yield is improved, the duration of each run will be kept constant and additional product will be produced. In the opinion of the SMEs that I consulted, this situation was more likely to happen than the possibility of the run being shortened to generate the same amount of product.

The cost per gram is given by

$$\begin{aligned}\text{cost per gram} &= \text{variable cost per gram} \\ &\quad + \frac{\text{fixed cost per run}}{\text{g output from unit x} \cdot \text{downstream yield}} \\ \max(\Delta(\text{cost per gram})) &= \frac{\text{fixed cost per run}}{\text{downstream yield}} \left(\frac{1}{(\text{g output from unit x})_{\text{max yield}}} \right. \\ &\quad \left. - \frac{1}{(\text{g output from unit x})_{\text{current}}} \right)\end{aligned}$$

Certain costs within the total cost per gram are variable with respect to the yield of unit operation x, and others are fixed. As the total grams of product from a run increases, the fixed cost per gram decreases (variable costs are not affected). The total product from the run is the grams outputted from unit x multiplied by the yield downstream of unit x. The model makes seven assumptions:

1. All costs (raw material, labor, and depreciation) upstream of the change are fixed.

2. All depreciation and indirect labor costs are fixed.

3. Within downstream labor, the costs of buffer prep, sampling, and setup times are fixed while that of operating time is variable.

4. Within downstream raw materials, the costs of bags, flow path, filter, and misc costs are fixed while those of media, buffer, and columns are variable.

5. Yield downstream of unit x is assumed to be constant.

6. Maximum yield is 100%.

The overall raw material, labor, and depreciation costs were available from the OSPR cost model. Direct labor hours and unit yields were used from the process map. The raw material cost breakdown was based on a costed Bill of Materials received from an engineer in Process Development.

C.4 Fully Continuous Operation

C.4.1 Opportunity Hypothesis

Providing automated fully continuous operation for units x, y, and z would allow a reduction of footprint by using smaller equipment and hold vessels, which would reduce the cost of depreciation per gram.

C.4.2 Status

This opportunity is currently considered viable.

C.4.3 Methodology, Assumptions, and Data Sources

The total cost per gram was broadly segmented into costs of raw material, depreciation, indirect labor, and direct labor, which is consistent with the OSPR cost model (Section 2.2):

$$\text{cost per gram} = \$\ \text{RM/g} + \$\ \text{depreciation/g} + \$\ \text{indirect labor/g} + \$\ \text{direct labor/g}$$

Only depreciation costs are considered in this opportunity.

We found that the OSPR cost allocation methodology allocates plant depreciation equally to all process lines running within a plant. Since the Platform A line is currently strategically planned to be introduced into an existing plant, a smaller footprint does not reduce the depreciation allocation much for Platform A itself.

We could expect a step change in the opportunity size if the footprint of the whole process is halved, because in that case, a whole additional line could be fit into the same space within the plant:

$$\max(\Delta(\text{cost per gram})) = \Delta(\$ \text{ depreciation/g})$$
$$= \begin{cases} \frac{(\$ \text{ depreciation/g})_{\text{current}}}{2} & \text{if footprint halved} \\ \text{estimated small} & \text{if footprint reduction any less than half} \end{cases}$$

The overall depreciation cost per gram was available from the OSPR cost model.

C.5 Fouling Reduction

C.5.1 Opportunity Hypothesis

Automation or equipment design changes that reduce fouling of the harvest filter would allow running the bioreactor at higher cell densities, leading to higher throughput at the bottleneck, and hence a reduced fixed cost per gram.

C.5.2 Status

This opportunity is currently considered not viable.

C.5.3 Methodology, Assumptions, and Data Sources

An SME that we interviewed advised that higher cell densities are not likely to be pursued even with lower fouling due to the constraint on cell densities that can be handled by the filter's tangential flow. Hence throughput from the reactor will not be affected.

Throughput through the harvest filter is currently maintained by using a high perfusion rate. Being able to reduce this perfusion rate, and hence the cost of media, represents a separate opportunity that may be analyzed.

C.6 Dynamic Loading

C.6.1 Opportunity Hypothesis

While loading the chromatography column in unit operation x, variation in the titer of the incoming material can lead to (a) under-loading, causing under-utilization of a column, or (b) breakthrough, causing loss of product. The former causes a higher raw material cost per gram, and the latter causes higher fixed cost per gram. Automated loading of the column based on real-time titer measurements can reduce these costs.

C.6.2 Status

This opportunity is currently considered not viable.

C.6.3 Methodology, Assumptions, and Data Sources

In the current process, the column in unit operation x is not loaded directly with the inflow from the upstream unit operation. Rather, the inflow is pooled over time and the titer of each pool is determined before the pool is loaded, which allows low variation in titer at the time of loading. Hence this opportunity, as currently formulated, does not provide any value. Automated loading of columns based on real-time titer can, however, allow continuous operation of the column. For the size of that opportunity, model C.4 can be used.

THIS PAGE INTENTIONALLY LEFT BLANK

Appendix D

Automated Sampling Business Requirements Document

Authors: NGA(DS)

Reviewers: NGA, Pre-Pivotal DS Development

D.1 Vision

For Amgen's DS manufacturing sites and development labs which currently face high operator time requirements and potential for deviations from manual sampling workflows, this product is an on-line or at-line measurement system that provides sample collection (if necessary), analytical tests, data management, and feedback process control. This product allows Amgen to develop a more reliable and efficient supply of therapies to our patients.

D.2 Motivation

D.2.1 Intended User

The intended users of automated sampling systems are:

1. DS Pre-pivotal group for development and as lead users

2. Pilot Plant for development and as lead users

3. Plant A or Plant B as lead users for GMP clinical and commercial manufacturing

4. Plant C, Plant D, and Plant E as eventual users for GMP commercial manufacturing

The technology may be applied to both Stainless Steel and Single Use facilities. Bioreactors present a promising lead use case due to frequent sampling, but all unit operations may be evaluated for applicability.

D.2.2 Unmet Needs & Jobs to be Done

1. Plants are required to spend a lot of manual labor on the sampling workflow, including cleaning, pulling samples, dilutions, and paperwork.

2. Development lab staff may be required to come in around the clock or on weekends only to collect samples.

3. Plants face deviations/NCs caused by human errors during manual sampling and data entry.

4. Plants face high lead time for results from manual sampling and testing workflows. This prevents developing IPC feedback loops to the control systems based on sample results.

5. Plants are required to prevent contamination of the process and the samples during sampling.

6. Plants are required to maintain data integrity of all data related to samples.

7. Plants use off-line testing of samples to manually re-calibrate pH and DO sensors.

8. Manual sampling leads to variability on an operator to operator basis in analyses such as dissolved gas composition.

D.2.3 Existing Solutions

1. All plants in the network currently use manual sampling.

2. Automated sampling system 1 by company A is being evaluated in the Pilot Plant.

3. Automated sampling system 2 by company B is being evaluated in the Pre-Pivotal Labs.

4. Raman spectrscopy technology is being evaluated by Amgen as a replacement for offline analytical tests.

D.2.4 Why Now?

1. Automated sampling system 1 by company A is a new technology and its evaluation by the Pre-Pivotal and AS groups indicated that its use may be viable for GMP environments.

2. Automated sampling system 2 by company B is being tested with offline samples in the Pilot Plant.

3. There is an Amgen initiative to reduce COGS, which automated sampling can have an impact on.

4. Raman technology is being developed rapidly leading to greater accuracy, lower costs, and ease of use.

D.3 Use Scenarios

1. Automated sampling system and analytical instrument assembly is set up by operators at the beginning of a process run.

2. Time and day and/or trigger condition of samples to be collected are inputted to the autosampler or analytical equipment.

3. Process begins, and the samples are automatically pulled from the bioreactor and sent to offline analyzers, if needed.

4. Any dilutions that are necessary for analyzing will be performed automatically.

5. Samples are automatically tagged with appropriate meta data which is stored in a GMP database.

6. Analyzer results are sent real-time from the database to the DCS for adjustment to appropriate set points for the IPC feedback loops, and for re-calibration for sensors.

7. After each sampling, automatic cleaning occurs to avoid cross-contamination of samples, if necessary.

8. At the end of the process, automated sampling system and analytical instruments are disassembled by operators.

D.4 Opportunity Size

Direct labor required for sampling in Platform A is expected to cost \$X/g. Indirect labor required to process deviations in sampling in Platform A is expected to cost \$Y/g.

D.5 Adoptions Barriers

1. Plants face switching costs in re-engineering their sampling work-flows, which will come in the form of re-writing SOPs, operator training, and potential for deviations in the early days of operation of the automated system.

2. Installation of automated sampling would require qualification of the new database and its integration with existing data systems.

3. The manufacturing and quality network may be concerned about having different sampling processes at different plants/suites/equipment in the network. This increases variability and causes them to be "off-platform" while some units have automated sampling, and others have manual.

4. For scheduling samples, GMP plants will require stability, while a Pilot Plant will require flexibility.

5. Implementing in GMP plant will require vendor commitment to supplying single-use material.

6. Manufacturing will need to develop a waste management protocol for samples, cleaning solution, and purge.

7. The equipment and single use material may need to undergo cleaning validation.

D.6 Other Risks/Dependencies

	Project or Technical	Risk	Mitigants
1	Technical	Connectivity issues with system may cause missed samples or broken feedback loops	Engineer system to also allow manual sampling as backup. Using reliable communication protocols (i.e. not OPC DA).
2	Technical	Disabled sampling system may disable the process	Engineer system to also allow manual sampling as backup. Having redundant sampling system.
3	Technical	Cleaning between samples doesn't meet cleaning requirements	No internal mitigant – strict requirement for vendor system.
4	Project	Not getting appropriate run/test time in the pilot plant	Early engagement of partners and customers and advanced planning of engineering and testing/qualification runs.
5	Project	Operator or resource help/commitment is low	Early engagement of partners and customers and advanced planning of engineering and testing/qualification runs
6	Project	Requirements changing during product development	Early development will be agile and in close collaboration with customers. Requirements will be locked in before beginning final development of system for delivery to GMP plant.
7	Project	Communication among five different departments	Clear definition of roles and responsibilities. Regular steering team meetings and updates with representation from all teams.
8	Project	Inexperienced operators with new system	Developing training material along with final design documents.
9	Technical	Transferability to manufacturing – more restrictions, higher QA requirements.	Engage with QA representative before locking in requirements for final development.

Table D.1: Risks and dependencies for automated sampling

Bibliography

[1] Michael J. Mauboussin and Dan Callahan. Total Addressable Market - methods to estimate a company's potential sales. *Credit Suisse*, 2015.

[2] Konstantin B. Konstantinov and Charles L. Cooney. White paper on continuous bioprocessing May 20-21, 2014 Continuous Manufacturing Symposium. *Journal of Pharmaceutical Sciences*, 104(3):813–820, 2015.

[3] Alois Jungbauer. Continuous downstream processing of biopharmaceuticals. *Trends in Biotechnology*, 31(8):479–492, 2013.

[4] Daniel J. Karst, Fabian Steinebach, Miroslav Soos, and Massimo Morbidelli. Process performance and product quality in an integrated continuous antibody production process. *Biotechnology and Bioengineering*, 114(2):298–307, 2017.

[5] Michael Chui, Katy George, James Manyika, and Mehdi Miremadi. *Human + Machine: A New Era of Automation in Manufacturing*. McKinsey & Company, September 2017. `https://www.mckinsey.com/business-functions/operations/our-insights/human-plus-machine-a-new-era-of-automation-in-manufacturing`. Accessed: 2020-03-28.

[6] Mo Jiang and Richard Braatz. Integrated control of continuous (bio)pharmaceutical manufacturing. *American Pharmaceutical Review*, 19(6):110–115, 2016.

[7] Mo Jiang, Kristen A. Severson, John Christropher Love, Helena Madden, Partick Swann, Li Zang, and Richard D. Braatz. Opportunities and challenges of real-time release testing in biopharmaceutical manufacturing. *Biotechnology and Bioengineering*, 114(11):2445–2456, 2017.

[8] Moo S. Hong, Kristen A. Severson, Mo Jiang, Amos E. Lu, John Christropher Love, and Richard D. Braatz. Challenges and opportunities in biopharmaceutical manufacturing control. *Computers and Chemical Engineering*, 110:106–114, 2018.

[9] FDA. *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*. Food and Drug Administration, Rockville, Maryland, 2004.

[10] Ali Mesbah, Joel A. Paulson, Richard Lakerveld, and Richard D. Braatz. Model predictive control of an integrated continuous pharmaceutical manufacturing pilot plant. *Organic Process Research and Development*, 21(6):844–854, 2017.

[11] Flemming Jørgensen and Peter Lambert. Accurate biopharmaceutical dispensing: peristaltic or piston pumps? *Innovations in Pharmaceutical Technology*, (26):78–80, 2008.

[12] Kevin J. R. Clark and Jim Furey. Suitability of selected single-use process monitoring and control technology. *BioProcess International*, 6:16–20, June 2006.

[13] Laura E. Crowell, Amos E. Lu, Kerry R. Love, Alan Stockdale, Steven M. Timmick, Di Wu, Yu Annie Wang, William Doherty, Alexandra Bonnyman, Nicholas Vecchiarello, Chaz Goodwine, Lisa Bradbury, Joseph R. Brady, John J. Clark, Noelle A. Colant, Aleksandar Cvetkovic, Neil C. Dalvie, Diana Liu, Yanjun Liu, Craig A. Mascarenhas, Catherine B. Matthews, Nicholas J. Mozdzierz, Kartik A. Shah, Shiaw Lin Wu, William S. Hancock, Richard D. Braatz, Steven M. Cramer, and J. Christopher Love. On-demand manufacturing of clinical-quality biopharmaceuticals. *Nature Biotechnology*, 36(10):988–995, 2018.

[14] Amazon Web Services. AWS IoT guide. `https://docs.aws.amazon.com/iot/latest/developerguide/`. Accessed: 2020-03-28.

[15] Emerson. emerson.com. `https://www.emerson.com/en-us`. Accessed: 2020-03-27.

[16] Clayton M. Christensen, Michael Raynor, and Rory McDonald. What is disruptive innovation? *Harvard Business Review*, pages 44–53, December 2015.

[17] Google. Google scholar. `https://scholar.google.com/`. Accessed: 2020-02-20.

[18] James P. Womack and Daniel T. Jones. *Lean Thinking*. Free Press, New York, NY, 2010.

[19] Vijay Govindraja and Chris Trimble. *Beyond the Idea – How to Execute Innovation in Any Organization*. St. Martin's Press, New York, NY, 2013.

[20] Eric Ries. *The Lean Startup*. Penguin Random House LLC, New York, NY, 2011.

[21] Google. Google trends. `https://trends.google.com/`. Accessed: 2020-02-20.

[22] Bill Aulet. *Disciplined Entrepreneurship: 24 Steps to a Successful Startup*. John Wiley & Sons, Inc., Hoboken, New Jersey, 2013.

[23] Design Council. *What is the framework for innovation? Design Council's evolved Double Diamond*. London, UK, 2004. `https://www.designcouncil.org.uk/news-opinion/what-framework-innovation-design-councils-evolved-double-diamond`. Accessed: 2020-01-20.

[24] David E. Weekly. An introduction to internal product management aka "building great first party tools". *LinkedIn*, April 2018.

[25] *Amgen – Product.* Amgen, Thousand Oaks, California. `https://www.amgen.com/products/`. Accessed: 2020-01-25.

[26] *Amgen 2018 Annual Report.* Amgen, Thousand Oaks, California, 2018.

[27] *Amgen – Our Strategy.* Amgen, Thousand Oaks, California. `https://www.theamgendifference.com/our-strategy.html`. Accessed: 2020-01-25.

[28] *Amgen Science – The Next Generation of Biotech Manufacturing.* Amgen, Thousand Oaks, California. `https://www.amgenscience.com/features/the-next-generation-of-biotech-manufacturing/`. Accessed: 2020-01-25.

[29] *Amgen Mission and Values.* Amgen, Thousand Oaks, California. `https://www.amgen.com/about/mission-and-values/`. Accessed: 2020-01-19.

[30] Dan Sptizer. US industry (NAICS) report - brand name pharmaceutical manufacturing in the US. Technical Report 32541A, IBIS World, New York, NY, 2020.

[31] *AstraZeneca Annual Report and Form 20-F Information 2018.* AstraZeneca, Gaithesburg, Maryland, 2018.

[32] Michael E Porter. *Competitive Strategy: Techniques for Analyzing Industries and Competitors.* The Free Press, New York, NY, June 2008.

[33] Louis S. Sorell and Rochelle K. Seide. Patenting biotechnology process inventions. *Nature Biotechnology*, 14(2):158–159, 1996.

[34] Carliss Y. Baldwin and C. Jason Woodard. The architecture of platforms: A unified view. In Annabelle Gawer, editor, *Platforms, Markets and Innovation*, pages 19–44. Edward Elgar Publishing, Cheltenham, UK, 2009.

[35] Alexander Oserwalder. Think about jobs, pains, and gains. *The Wall Street Journal*, December 2012.

[36] John Conner, Don Wuchterl, Maria Lopez, Bill Mishall, Prusti Rabi, Dave Boclair, Jay Peterson, and Chris Allen. The biomanufacturing of biotechnology products. In Craig Shimasaki, editor, *Biotechnology Entrepreneurship*, chapter 26, pages 351–385. Academic Press, Oxford, UK, 2014.

[37] John C. Mankins. *Technology Readiness Levels – A White Paper.* NASA Office of Space Access and Technology, April 1995.

[38] Department of Defense. Technology readiness levels in the department of defense, 2010. `https://api.army.mil/e2/c/downloads/404585.pdf`. Accessed: 2020-03-14.

[39] Alan Cooper. The origin of personas. *Cooper Professional Education*, May 2008. https://www.cooper.com/journal/2008/05/the_origin_of_personas/. Accessed: 2020-02-23.

[40] Atlassian. What is agile? https://www.atlassian.com/agile. Accessed:2020-03-28.