Enhancing Workflows in Biologics Drug Substance Process Development Through Automation

by

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Abstract

In the face of increasing competition, increasing pipeline complexity, and increasing resource requirements for bringing new drugs to market, streamlining process development is an important means of controlling costs and achieving competitive advantage in the biopharmaceutical industry. One potential means of achieving such improvements in process development is through the implementation of high throughput technologies, equipment (and associated methods and software) used to generate and process large amounts of data in little time. It is important, however, that implementation of these solutions is optimized across the entire process development organization rather than applications be deployed piecemeal within specific functions.

This thesis develops a framework for identifying promising opportunities for use of high throughput technologies and quantifying the value that can be derived from their implementation. Though the framework is more broadly applicable than just to research and development organizations, the thesis is focused on its application to biologics process development within Amgen. It is used to assess the value of implementing a specific high throughput platform, Sartorius ambr® 250 systems, in upstream biologics process development.

Through mapping and analyzing the workflows of Amgen's Biologics Drug Substance Technologies (Biologics DST) group, the implementation of this system was identified as a promising opportunity for employing high throughput technologies. In particular, a net present value (NPV) analysis was performed to show that investment in ambr 250 systems is likely to yield a positive NPV. However, the expected NPV depends strongly on both the expected useful lifetime of the systems and their capacity utilization. In addition, high throughput technologies provide substantial upside potential not captured in the NPV. Specifically, for the ambr 250 this includes cutting 6.5 weeks off development time for projects where process development is on the critical path. Using ambr 250 for Process Characterization (PC) on such programs could increase highly valuable weeks of sales.

A framework was also developed for assessing how three models of staffing support for high throughput technologies affect the value that can be derived from their implementation. This framework was applied to the use of ambr 250 systems at Amgen to determine how to

realize the maximum possible value from investment in this equipment. The assessment found that a dedicated team model is most likely to successfully facilitate the high capacity utilization and maximum potential useable life that are critical for achieving positive NPV. A formal subject matter expert (SME) model may also achieve these goals at lower cost, though at higher risk. The informal champion model, however, is advised against.

The recommended path forward is to purchase one or two ambr systems to use in Commercial Process Development (CPD) and to establish whether they can be used for PC. Once it is established that the ambr 250 can be used for PC, it is recommended that the existing systems be used immediately thereafter on key projects for which increased development speed can increase speed to market, and that a third system be purchased to expand capacity.

Though this work focuses specifically on process development at Amgen, the frameworks developed herein are broadly applicable to many types of organizations, from R&D to manufacturing to the service sector. In any industry where high throughput technologies exist, these frameworks can be used to identify promising opportunities for their implementation, quantify the value they can provide to determine if investment is worthwhile, and decide how they should be supported to maximize the value realized by the organization.

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Summary of Abbreviations

API – Active pharmaceutical ingredient

BMS – Bristol-Myers Squibb

BiTE – Bispecific T-cell engager

CHO – Chinese hamster ovary

CLD – Cell line development

CPD – Commercial process development

CRO – Contract research organization

CTT – Commercial tech transfer

DOE – Design of experiments

DSD – Definitive screening design

DSP – Downstream process

DST – Drug substance technologies

FTEs – Full-time equivalents

HT – High throughput

HTT – High throughput technologies

LCM – Life-cycle management

mAb – Monoclonal antibody

MCB – Master cell bank

NME – New molecular entity

NPV – Net present value

OSE – Outside expense

PC – Process characterization

PD – Process development

PM – Preventative maintenance

PPQ – Process performance qualification

R&D – Research & development

siRNA – Short interfering RNA

SME – Subject matter expert

SSMQ – Small-scale model qualification

TT – Tech transfer

USP – Upstream process

1 Introduction

1.1 Context & Project Motivation

Historically biotech development pipelines have been dominated by monoclonal antibodies (mAbs), enabling the use of "platform" production processes that are relatively invariant between products and therefore fast to develop. As molecules more unique & structurally complex than mAbs become the norm for novel therapeutics in development, the traditional platform processes cannot be relied upon. As a result, unless a new approach is taken, the time & resources required for process development are bound to increase. This, in turn, would increase the cost and reduce the speed of bringing a therapeutic to market.

The trend of increasingly complex molecules is common across the biotechnology industry, thereby providing opportunity to forward-thinking firms. Being a leader in process development capabilities can be a valuable source of differentiation and competitive advantage for the company[1]. By reacting early to reduce the cost and increase the speed of process development (to counter the disadvantageous effects of the trend), firms can capitalize on existing expertise to maintain or increase their competitive advantage.

One potential means of achieving such improvements in process development is through the integration of high throughput technologies (HTT), equipment (and associated methods and software) used to generate and process large amounts of data in little time. However, where and how high throughput technology could be optimally implemented in biologics process development is not yet clear. Existing high throughput tools are often siloed, inefficiently applied, aging, and insufficiently supported[2].

Furthermore, there exist various models of staffing support for high throughput equipment that differ in the portion of an employee's time dedicated to supporting the equipment and the number of employees required for support. As formalized below in Chapter 5, they are: the dedicated team model, the formal SME model, and the informal champion model. These models feature varying degrees of success in achieving rapid adoption and long-term utilization of the equipment. Yet, the effect of high throughput support structures on the value solutions provide has never been formally assessed and it is therefore unclear whether existing structures are optimal or in fact inhibiting the realization of maximal value.

Recognizing these challenges, process development groups must identify ways to realize the value of high throughput technologies with a holistic view across the organization. This project aims to help achieve that by analyzing biologics process development workflows, considering interactions with partner groups and the context within the company more broadly. The analysis can then be used to identify promising opportunities for implementation of high throughput technology and quantify the value of implementation to determine whether or not to pursue particular solutions. Additionally, this project aims to examine the effect of equipment support structure on the value a firm is able to derive from high throughput technologies in order to determine the optimal support structure to employ.

1.1.1 Biopharmaceutical Industry Overview

The primary function of the pharmaceutical industry is to develop and market therapeutic drugs to treat, cure, and prevent disease. Therapeutics are broadly classified into two categories: small-molecule (synthetics) and large-molecule (biologics). The two categories are primarily distinguished by size, structure, and means of production[3]. Synthetic drugs are generally much smaller (the full structure, including every atom, could fit on a Powerpoint slide) and are traditionally produced by chemical synthesis processes, though some novel processes also employ enzymatic catalysis. Biologic drugs, by contrast, are 2 – 3 orders of magnitude larger, are often polymeric, and are produced within genetically engineered cells[3]. The term "biologics," also covers a wide range of very different types of molecules, or modalities. Modalities are classes of biologics with different structures and mechanisms of producing a therapeutic effect. Examples of different modalities include monoclonal antibody (mAb), bispecific antibody (bispecific), bi-specific T-cell engager (BiTE®), fusion protein, and short-interfering RNA (siRNA).

Since biologics are by definition produced by living cells, the processes are inherently variable. And because they are much larger, biologics have substantially more complex structures and are thereby often less stable to environmental fluctuations[3]. The efficacy of therapeutic proteins (a class of biologics), for instance, typically depends on the secondary and tertiary structure – the way the protein is folded – which can be disrupted by relatively moderate temperature or pH changes. Such conformational sensitivity is not, generally, a concern for

synthetics. Because of these structural sensitivities and the particularities of producing the product in living cells (which demand certain conditions to thrive), designing a process to manufacture biologic drugs is intricate. The process is heavily dependent on the host cell line used (whether mammalian, bacterial, or fungal) and the exact modality of the therapeutic molecule.

When the host cell and modality are standardized, biologics process development is greatly streamlined (reducing costs and increasing speed-to-market), as common steps and conditions can be used across molecules[4]. As a result, biopharmaceutical companies often develop and rely on "platform" processes, a set of steps and operating conditions using a standard host cell line, that works broadly well across projects provided the molecules are of the same (or similar) modality[4].

1.1.2 Amgen Overview

Amgen, headquartered in Thousand Oaks, California, is one of the world's fifteen largest biopharmaceutical companies[5,6]. Since its founding in 1980, the company has been an innovator focused on bringing to market therapeutics for indications with high unmet medical need. By 2021 the company employed 24,000 in over 50 countries around the globe, earned $26 billion in revenue, and spent $4.8 billion on research and development (R&D)[5].

Amgen has a diverse product portfolio comprising dozens of commercially-approved therapeutics spanning a range of therapeutic areas[7]. Between the commercial portfolio and molecules under development, Amgen products span over a dozen distinct modalities[8–10]. This wide range of modalities in use adds substantial complexity to process development and makes it increasingly difficult to rely heavily on one or two platform processes, especially as the prevalence of mAbs (historically the dominant modality for which platform processes are designed) is progressively declining[10].

1.1.3 Overview of Amgen Biologics Drug Substance Technologies

Amgen's Drug Substance Technologies (DST) is part of Process Development (PD) within the Operations branch of the company. DST is responsible for the development and

commercialization of the process for producing the therapeutic drug substance (DS), also known as the active pharmaceutical ingredient (API) or "target molecule."

In upstream processing, cells are cultivated and scaled-up from an initial cell-banked "seed" quantity to the required quantity for a "production batch" (Figure 1). In the production batch, the cells then actually produce the target molecule, which is then "harvested" from the cells. In downstream, the API collected during harvest is progressively purified through a series of steps (primarily column chromatography and filtration steps) to isolate the target molecule from product- and process-related impurities (Figure 2).

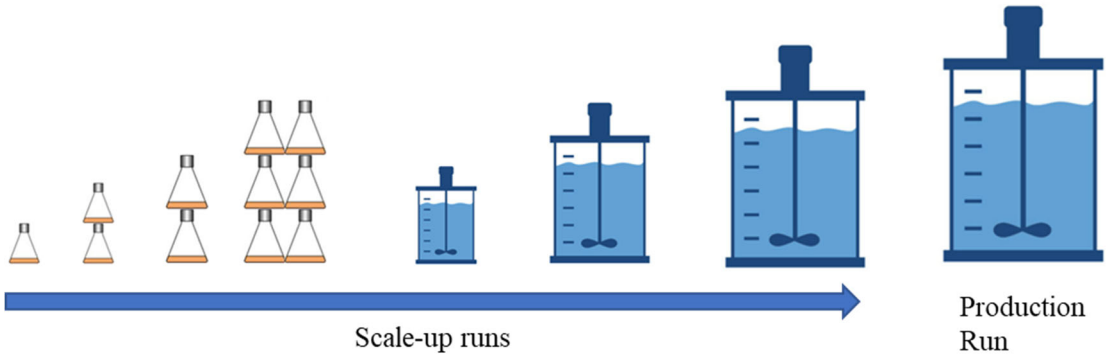

Figure 1: A high level picture of the scale-up process undertaken for each experiment in upstream process development from "seed" (far left) to production batch (far right). For each "production run," which generates the desired data, a long series of scale-up runs are needed. This process is typically done in parallel for 16 experiments at a time.

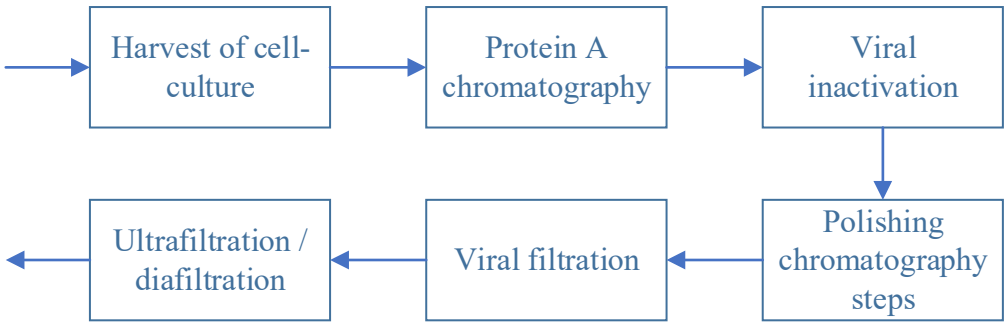

Figure 2: A high-level diagram of a typical biologics downstream process to recover the target molecule[11]. Downstream consists primarily of a series of filtration and column chromatography steps.

1.1.3.1 Early-stage Biologics Process Development

The generation of biologic drug substance begins with engineering host cells to produce the target molecule, selecting the cell line (originating from a single cell) to be used for pilot, clinical, and commercial production; and generating the master cell bank (MCB) from which all cells used in manufacturing batches will be derived. During this process, the downstream, drug substance isolation process will also start to be developed.

Cell line development (CLD) is the end-to-end process of generating productive cell lines and selecting the final cell line for commercial production. CLD activities are generally performed with small amounts of material (that is, at a small scale) to enable parallel examination of many candidate cell lines. Larger-scale production runs and purifications will also be performed at various points throughout early process development to produce quantities of drug substance to be used for clinical trials and other internal development activities (such as formulation development). These larger-scale runs are also used as experiments for the initial design and development of the upstream and downstream processes. Finally, when the set of candidate molecules has been narrowed down to only a handful, additional larger-scale batches of each candidate will be used to generate data facilitating the selection of the final cell line.

1.1.3.2 Late-stage Biologics Process Development

After the final cell line has been selected and the first-in-human (FIH) manufacturing process developed, the commercial manufacturing process will be refined and characterized, establishing which unit operations will be used to produce and isolate the API and setting ranges on each variable of each operation within which the process must be run during production to ensure quality product.

Late-stage biologics process development comprises two sub-stages, Commercial Process Development (CPD) and Process Characterization (PC). In CPD, the unit operations of the process and operating conditions of each step are determined. Subsequently, in PC, operating ranges for each variable are established and the process is stressed to ensure the commercial production process is robust. These development activities are generally done in parallel for upstream and downstream.

1.2 Problem Statement & Objectives

Trends in the biopharmaceutical industry are resulting in an increased prevalence of more structurally complex modalities and increased diversity of modalities in pipeline portfolios (as described in Section 1.1.1). This not only directly increases the cost and reduces the speed of development, but also reduces the ability for companies to rely on the platform processes that are optimized to rapidly develop similar processes, exacerbating the effect on cost and speed.

The implementation of high throughput technologies has the potential to better address the imposition from pipeline complexity, by increasing the flexibility and robustness of process development organizations.

The goal of this project is to provide a roadmap for improvement by analyzing the workflows of biologics drug substance process development, identifying promising opportunities for the implementation of high throughput technologies, quantifying the potential value, and describing the changes in processes, staffing and overall organizational resources required for optimal implementation. In particular, the project aims to examine the effect of equipment support structures on the value biologics developers derive from novel solutions. This would hopefully inform decisions of whether or not to pursue particular solutions and how to utilize them for maximal value. Moreover, through this exploration, a framework is developed to aid determination of the optimal support structure to employ for a particular technology in context.

1.3 Summary of Methods and Results

In Chapter 3, a framework is developed for identifying promising opportunities for use of high throughput technologies. To start, a detailed process map should be created to enable thorough process analysis. From there, stages of the process can be identified where tasks are repeated, work can be done in parallel, and low value-add tasks are done by highly skilled personnel. These will represent promising opportunities for implementation of HTT. Individual HTT solutions for these areas can then be identified and the value they can provide quantified.

In Chapter 4, a method for quantifying the value that can be derived from the implementation of high throughput technologies is described. The method accounts for all direct sources of value and cost, including FTE savings, cost of purchase, setup, qualification, support,

& maintenance. All direct sources are quantified and combined into a single net present value (NPV) for implementation of the technology. Importantly, the sensitivity of this NPV to assumed variable inputs should be assessed, particularly equipment lifetime and capacity utilization, which are likely to have a large impact. With the NPV as a starting point, the method then accounts for indirect sources of value and cost, including the cost of training and downtime, the value of savings from auxiliary functions required for the manual process, and the value from shortened project timelines.

Finally, in Chapter 5, a framework was also developed for assessing how three models of staffing support for high throughput technologies affect the value that can be derived from their implementation. In the "dedicated team" model, one or more job roles exist where the primary function of the role is to operate and maintain HT equipment. In the "formal SME" model, HT support is distributed among members of project teams. Individuals dedicated as subject matter experts (SMEs) will be trained on the equipment and be the primary responsible parties for the maintenance and operation of the equipment. In the "informal champion" model, HT support is carried out by individuals in the project team who choose to become trained on the equipment and support its use because they believe it to be a valuable tool for their primary job function. The ways in which these different models affect all sources of value and cost (both direct and indirect) can be considered in order to determine which enables the particular high throughput solution under consideration to provide the greatest possible value to the organization.

Throughput this thesis, these frameworks are applied to biologics drug substance process development at Amgen. A process map of the workflows in the organization was created and used to highlight promising areas for the use of high throughput technologies. In particular, upstream bioreactor experiments were found to exhibit a high degree of task repetition, work able to be done in parallel, and low-value-add tasks done by high-skill employees. The value of implementation of a high throughput technology for upstream bioreactor experiments, the ambr 250, was then quantified to determine whether or not to pursue the opportunity.

The NPV analysis showed that investment in ambr 250 systems is likely to yield a positive NPV. However, the expected NPV depends strongly on both the expected useful lifetime of the systems and their capacity utilization. In addition, through assessment of indirect sources of value and cost, the ambr 250 was found to provide substantial upside potential not captured in the NPV. Specifically, the ambr 250 is capable of cutting 6.5 weeks off development

time for projects where process development is on the critical path. Using ambr 250 for Process Characterization (PC) on such programs could increase highly valuable weeks of sales.

An assessment of the three different models of staffing support for the ambr 250 systems found that a dedicated team model is most likely to successfully facilitate the high capacity utilization and maximum potential useable life that are critical for achieving positive NPV. A formal subject matter expert (SME) model may also achieve these goals at lower cost, though at higher risk. The informal champion model, however, is advised against as it puts the value provided by the systems at risk.

Through applying the methodologies developed in this thesis comes a recommendation for Amgen to purchase one or two ambr systems to use in Commercial Process Development (CPD) and to establish whether they can be used for PC. Once it is established that the ambr 250 can be used for PC, it is recommended that the existing systems be used immediately thereafter on key projects for which increased development speed can increase speed to market, and that a third system be purchased to expand capacity.

2 Literature Review

2.1 Introduction

As discussed in the descriptively titled "Are Ideas Getting Harder to Find?" by Bloom et al., as technology has advanced over the last several decades it has required a progressively increasing amount of resources in order to achieve a given level of advancement[12]. This extends to the pharmaceutical industry, where, though the rate of new drug development, as measured by New Molecular Entities (NMEs) approved by the FDA, has remained strong over the last several decades, the effort per new drug has increased over time. Specifically, since 1970, productivity of pharmaceutical research has fallen by a factor of eight, and to compensate for this research effort has increased by a factor of nine[12]. For over 60 years this trend followed Eroom's Law, describing how the all-in cost of R&D for new drugs approved by the FDA has risen consistently and exponentially from 1950 - 2010[13]. Though it appears that since 2010 the trend has ceased to follow Eroom's law closely, this is due to lower rates of failure in the 2010's as the direct cost of bringing to market a new drug has continued to increase dramatically[13].

The pharmaceutical industry is also heavily competitive, even when narrowly considering companies like Amgen that focus on bringing to market innovative therapeutics (discounting firm's focused on generics). In 2021, over $100 billion was invested in research and development by 33 of the largest firms in the industry[14]. Moreover, competition from small, independent, venture-backed companies is rapidly increasing. In 2021, biotech companies raised more than $34 billion in venture capital funding, globally, far greater than the 2020 total of $16 billion and the 2019 total of $8 billion[15].

With heavy and increasing competition and productivity falling, Amgen must find ways to address increased development cost driven by competitive industry dynamics. One potential means to achieve this is through differentiation in process development capabilities, an important component of the operations excellence Amgen sees as providing a competitive advantage[1].

Much of the company's strength in process development has been founded on its robust platform process for producing monoclonal antibodies. But the prevalence of monoclonal antibodies in development pipelines is declining across the industry, as many of the indications for which the modality is effective have been addressed. Illustrative of this trend across the

industry, in 2021 monoclonal antibodies represented 21% of projects in Phase III (late-stage) clinical trials, but only 16% of projects in (earlier-stage) Phase I & II trials[16]. As a result, efforts to increase productivity in process development should be focused on methods that can achieve gains invariant of modality and improve the organization's capacity for flexibility in the array of molecules under development in a given year.

2.2 High Throughput Technologies in Drug Process Development

In drug process development, the term "high throughput" (HT) represents the combination of screening techniques and fast analytics that lead to a higher rate of experimentation, data generation, and data processing[17,18]. High throughput technology (HTT) is the equipment and associated software that enable this increased rate of experimentation and data generation. HT can achieve higher throughput through two primary means: parallelization and automation[19,20].

Parallelization represents the ability of HTT equipment to enable more experiments to be conducted at the same time ("in parallel"), than would otherwise be possible[21]. The link to increased throughput here is clear, as running a higher number of experiments in parallel results in more experiments complete in a given unit time (from an operations management perspective, this is comparable to increasing the number of servers).

Automation in drug process development is most commonly found in activities such as liquid handling and analytical detection[19]. Automation of the related processes, enabling them to run in the absence of hands-on labor, can increase the speed of execution, precision, and replicability.

Both parallelization and automation are in turn often enabled by miniaturization. Miniaturization of experiments reduces the amount of reagents and other inputs required per experiment, as well as the processing time and space requirements per unit capacity[19]. This reduces the cost per experiment, which may otherwise be prohibitive for running high numbers of experiments and enables more experiments to be run when there is limited material availability.

Comparability of results at smaller scale is crucial for HTT that employs miniaturization. If the data generated at the smaller scale are not representative of the results that would be

observed at standard lab scale, pilot scale, or commercial scale, additional development work would be required to understand the differences, thereby offsetting (perhaps entirely) the benefits of miniaturization.

2.2.1 Benefits of High Throughput Technology

One of the most direct and clear benefits of the implementation of high throughput technology is the reduction of labor costs. Through automation, parallelization, and miniaturization, fewer hours of labor are usually required to produce the same (and often greater) output.

The increase in speed of (reduction in time required for) process development is another important source of value added by HTT. Unlike in traditional manufacturing or service settings where increased speed allows for the production of a greater number of units of product or a greater number of customers able to be served, in the context of process development, increased speed allows a company to get the product to market faster. For "innovator molecules" (those with a novel biological structure[22]), this means patients with a previously unmet need can get treatment sooner. And regardless of whether the therapeutic is novel or generic (provided loss of exclusivity is not the limiting factor for launch timing), getting to market faster means more weeks of sales for the product before the end of the product lifetime. When it comes to innovator molecules with fixed patent lifetime each additional week of sales is highly valuable.

High throughput technology also increases the ability of a process development organization to balance workload for employees in the face of highly variable inputs. Large pharmaceutical and biotechnology companies acquire products at a wide range of stages in their development cycle, including in late-stage clinical trials when less time is available for process development than would be under standard timelines. Acquisitions are often not predictable with sufficient time for process development teams to plan capacity and can therefore cause a large surge in required workload.

Novel therapeutics undergoing clinical trials also have a high rate of failure, leading to development programs being cut at a moment's notice when data indicates the product is either inefficacious or unsafe.

In the face of high variability of workload, having higher capacity available for experimentation than the average amount required enables process development teams to increase experimental throughput as needed without sustained excess labor costs or burning out their highly skilled workforce.

What's more, the increase in molecule complexity and diversity is increasing both the mean and variability of the development time required for a project, a dangerous combination for any operation that can make it very costly to service all demand (or in this case, complete all projects in the desired timeframe). As discussed above, however, the increased speed and ability to flex in response to workload variability that high throughput technologies can provide is very beneficial for addressing this.

Outsourcing to contract research organizations (CROs) is another valuable means for these organizations to balance workload, but companies are often resistant to outsource projects that are either highly complex (requiring the higher levels of expertise found internally) or involve highly sensitive intellectual property (whether pertaining to the product or the process itself). Outsourcing to CROs, therefore, cannot be entirely relied upon for all requisite capacity flexibility.

Another benefit of high throughput technology is a reduction in R&D material costs. On account of miniaturization, if the same number of experiments are conducted during process development as would be at traditional lab scale, smaller amounts of materials are required. The savings from this can be substantial, as much of the material used for process development experiments can be very expensive, particularly the target molecule itself.

2.2.2 Costs of High Throughput Technologies

While high throughput technologies have multiple clear potential benefits, they also incur additional costs. Beyond the cost of the physical system itself, there are also auxiliary direct and indirect costs associated with the implementation of high throughput technologies that stem from:

- Setup & qualification
- Support & maintenance
- Training

- Downtime from equipment failure
- Downtime from lack of available users

Many of these different drivers of cost (such as the cost of training) will also vary substantially depending on the staffing model and support structure chosen. Therefore, in assessing the total cost of implementing high throughput technologies, one has to consider the model that will be employed to support the equipment. An analysis of the trade-offs of different models of support can then be performed to determine what model would fit best for a particular technology being adopted by a particular functional area.

2.2.3 Sartorius Ambr® Systems

The ambr 15 and ambr 250 systems are automated, HT arrays of single-use multi-parallel miniature bioreactors produced by Sartorius[23,24]. The individual single-use bioreactors are 15 mL in volume for ambr 15 systems and 250 mL in size for ambr 250 systems. The arrays of 24 or 48 (for ambr 15) or 12 or 24 (for ambr 250) single-use bioreactors are run in parallel in a highly automated fashion. The difference between the ambr 250 system and traditional benchtop bioreactors is shown below in Figure 3 and Figure 4. In past assessments of the use of ambr systems, the combined benefits of shorter setup times from the use of disposable bioreactors and automated sampling were found to reduce labor requirements by up to 66%[25].

These systems have the potential for use at any point where traditional benchtop bioreactors are currently used for upstream laboratory experiments. Implementation of ambr systems has the potential to increase the speed of and reduce the labor resources required for upstream research and development work.

Figure 3: A Sartorius ambr 250 system and an enlarged individual, 250 mL disposable bioreactor that is part of the automated array.[24]

Figure 4: A traditional (albeit state-of-the-art) benchtop bioreactor. Benchtop bioreactors range in scale from ~250 mL to 10 L and are traditionally each set up and run independently.[26]

Ambr systems have been in use in the biopharmaceutical industry for many years at multiple companies. In 2013, Bareither et al.[27] at Merck & Co., Inc. (Merck), a large pharmaceutical company, demonstrated proof of concept for ambr 250 use in upstream process development. Experimental results for process development were shown to be sufficiently similar to benchtop

bioreactor scale and pilot scale for the data generated to be used for regulatory filings (a requirement for the Process Characterization stage of process development). This was done for a diverse set of host organisms: Chinese hamster ovary (CHO) cells (mammalian), *Pichia pastoris* (fungal), and *Escherichia coli* (bacterial). Such demonstrations of comparability of ambr results to larger scale runs have also been replicated in other laboratories[28].

In 2015, Tai et al.[29] at Bristol-Myers Squibb (BMS), another large pharmaceutical company, built on this, and demonstrated how a definitive screening design (DSD) experimental protocol executed on ambr 250 can be used to combine CPD & PC into one study. A DSD is an experimental design that enables the researcher to study a large number of factors in a relatively small set of experiments while still detecting non-linear responses and still preventing confounding of factors. The BMS study was done in *E. coli* and results were then verified at traditional laboratory scale, demonstrating scale comparability for ambr 250 in PC-type applications.

In 2016, Pollard, McDonald, and Hesslein reviewed how pharmaceutical companies have set up and use HT equipment for process development[30]. They cite the ability of ambr systems to provide an eightfold increase in productivity (in runs per month) and a 66% reduction in resources while still generating representative data. They also highlight how, upon implementation of systems like ambr, the bottleneck can shift to analytical teams.

2.2.4 Three Models of Staffing Support for High Throughput Technologies

For this study, three different models of staffing support for high throughput technologies are compared, which we will dub: the "dedicated team" model, the "formal SME" model, and the "informal champion" model.

In the "dedicated team" model, one or more job roles exist where the primary function of the role is to operate and maintain HT equipment. The full-time equivalent (FTE) employees in these roles are the primary stewards of the HT solutions and will typically function as a service provider for the scientists and engineers primarily responsible for the development of a molecule or group of molecules (the "project team"). These teams may support only one type of equipment, but more commonly support multiple solutions.

In the "formal SME" model, HT support is distributed among members of project teams. Individuals dedicated as subject matter experts (SMEs) will be trained on the equipment and be the primary responsible parties for the maintenance and operation of the equipment. HT support is a formal part of the SMEs' responsibilities, but likely not their primary responsibility. Rather, HT support is most often a function to which a minority of their time is devoted. Because HT support can only be a certain percentage of their time, a higher number of SMEs is needed than would be for a dedicated team.

Finally, in the "informal champion" model, HT support is carried out by individuals in the project team who choose to become trained on the equipment and support its use because they believe it to be a valuable tool for their primary job function. There may be one or more informal champions for a particular solution, and the number is likely to vary as the opt-in nature of training new users is not tied to the turnover rate of existing users. The champions may operate the HT equipment in full for their peers or simply instruct their peers in how to use the equipment but leave them to carry out the bulk of the operations.

The model of HT support structure chosen can have a profound impact on the realized value derived from investment in HT solutions. In their review of high throughput technology implementation, Pollard et al. ultimately recommend investing in a dedicated team to overcome the "activation energy" of full-fledged adoption of the technology in order to reap the maximum benefits consistently[30]. This requires substantial investment in hiring and training, however, and may not necessarily be the optimal decision for all cases.

The optimal support model for the implementation of a particular instance of high throughput technology will depend on the structure of the functional area adopting the technology, the skillsets of the employees in the area, and even the scale of the implementation. For instance, investment in a dedicated team is likely to be much more cost-effective if the number of high throughput systems for them to support is higher to take advantage of a sort of economies of scale.

The optimal support model may also change over time as the workflows of the functional area evolve. For example, if the equipment is initially only planned to be used on side-projects to test the functionality, an informal champion model may be fitting at the time. But, as the technology becomes more trusted and the use cases expand such that it becomes core to the

workflows of the functional area, it may become sensible to invest in the establishment of a dedicated team.

3 Identification of Opportunities for HTT Implementation

In order to identify high-value opportunities for implementation of high throughput technology, a three-step framework was applied to generate and evaluate potential use-cases. First, an end-to-end process map of biologics drug substance (DS) process development (PD) was created to serve as a tool for analyzing the current state of workflows. Using this, the ways the organization currently uses high throughput technology could be assessed and opportune areas for implementing novel HTT solutions could be identified. Finally, a high-level strategic framework for determining where high throughput technologies provide the most value could be applied to the set of identified opportunities to determine the lead candidate on which to perform a detailed cost-benefit analysis.

3.1 Process mapping of Biologics Drug Substance Process Development

As it's not possible to find ways to improve a process without understanding it, the first step in finding high-value opportunities for implementation of novel high throughput technology in biologics DS PD would be to develop a detailed end-to-end process map of the workflows. A wholistic view was desired in order to avoid continuing to apply siloed solutions, so both early-stage and late-stage PD were included in the map, from transfection through process characterization.

The process map was developed through conversations with dozens of scientists, engineers, and project managers in order to obtain very detailed information on the order of operations, how long each operation takes, equipment used, resources required, and the nature of interactions between groups. The workflows of a project were divided into the following stages:

- Early-stage biologics DS PD
    - Transfection
    - Pool selection
    - Single-cell cloning
    - Clone screening
    - Master cell bank (MCB) creation
    - Larger-scale production runs for:

        - Material supply
        - Clinical trials
        - Initial process development
        - Final clone screening
- Late-stage biologics DS PD
    - Commercial process development (CPD)
        - For both upstream process (USP) & downstream process (DSP)
    - Process characterization (PC)
        - For both USP & DSP
    - Tech transfer (TT) & process performance qualification (PPQ)

Brief descriptions of each of the above stages of the process follow:

Transfection

In transfection, a specific DNA sequence is inserted into the chosen host cell line to engineer the cells to produce the target molecule. This is done multiple times to create multiple different batches, or "pools" of engineered cells.

Pool selection

In pool selection, the various pools generated in transfection are submitted to stresses that encourage only cells that are productive (i.e. that make the target molecule) to survive. The surviving cells are then propagated and analyzed to assess growth and productivity to select which will be used for single-cell cloning.

Single-cell cloning (SCC)

In single-cell cloning, hundreds or thousands of individual cells are isolated and propagated individually. The growth and productivity of each individual cell line are analyzed to select which cells will be further assessed at larger scale in clone screening.

Clone screening

In clone screening, dozens or hundreds of cell lines are grown further and used for a series of production batches at progressively larger scales, eliminating candidates along the way.

Through this process, the final cell line for commercial manufacturing will be selected on the basis of growth, productivity, and genetic stability (among other criteria).

Master Cell Bank (MCB) creation

The cell line selected for commercial manufacturing is propagated and many individual vials of these cells are frozen to create the MCB. Over the course of the lifetime of the product, individual MCB vials will be periodically thawed and propagated further to create a working cell bank (WCB) to be used for a series of commercial manufacturing batches.

Commercial Process Development (CPD)

In CPD, the unit operations of the process and operating conditions of each step are determined. CPD is generally done in parallel for upstream and downstream.

Process Characterization (PC)

In PC, operating ranges for each variable are established and the process is stressed to ensure the commercial production process is robust. PC is generally done in parallel for upstream and downstream.

Tech transfer (TT) & process performance qualification (PPQ)

In tech transfer, the internal process development team teaches the intended manufacturing site (internal or external) how to best run the process and consults on the setup of the manufacturing equipment train. In PPQ, a set of batches are produced under a standard protocol to prove sufficient control over the process. Results from the batches run during PPQ are submitted to regulatory agencies to gain approval for the manufacturing site.

3.1.1 Process maps

High-level views of the process maps for early-stage and late-stage DS PD are shown in Figure 5 and Figure 6, respectively. Though the details are not legible (to protect the proprietary information), the figures illustrate the structure of the workflows and how the broad structures of early-stage and late-stage DS PD differ. From these diagrams it is clear how the activities in

early-stage DS PD are predominantly done in sequence, while in late-stage DS PD there is a great deal of work that is (or can be) done in parallel.

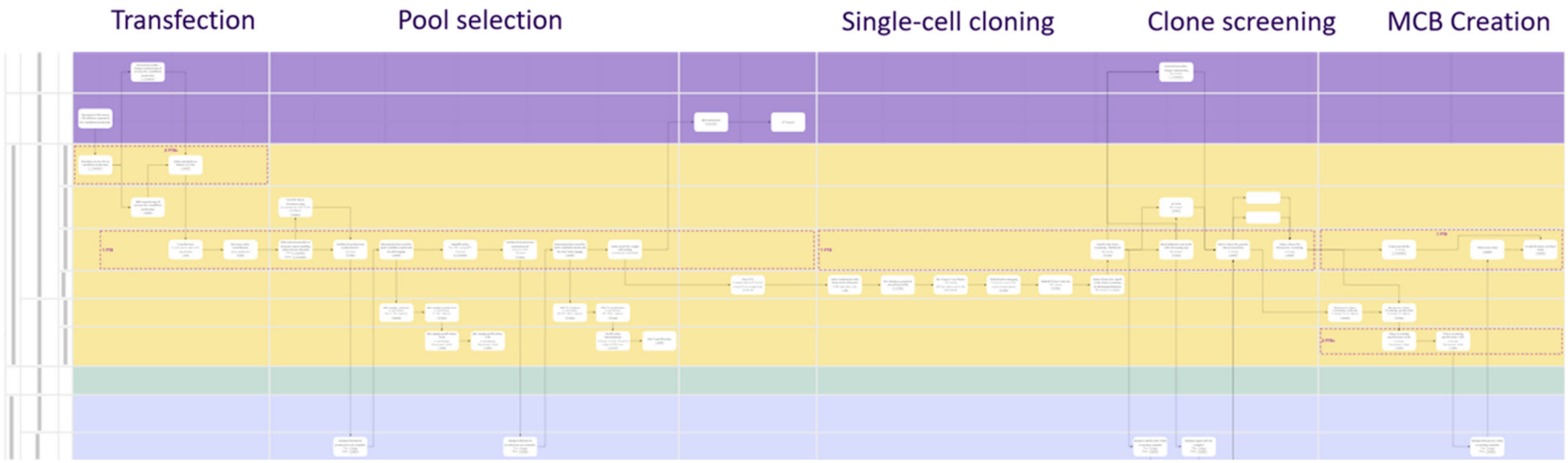

Figure 5: A high-level view of the early-stage DS PD process map, with stages separated into columns and groups organized into swimlanes.

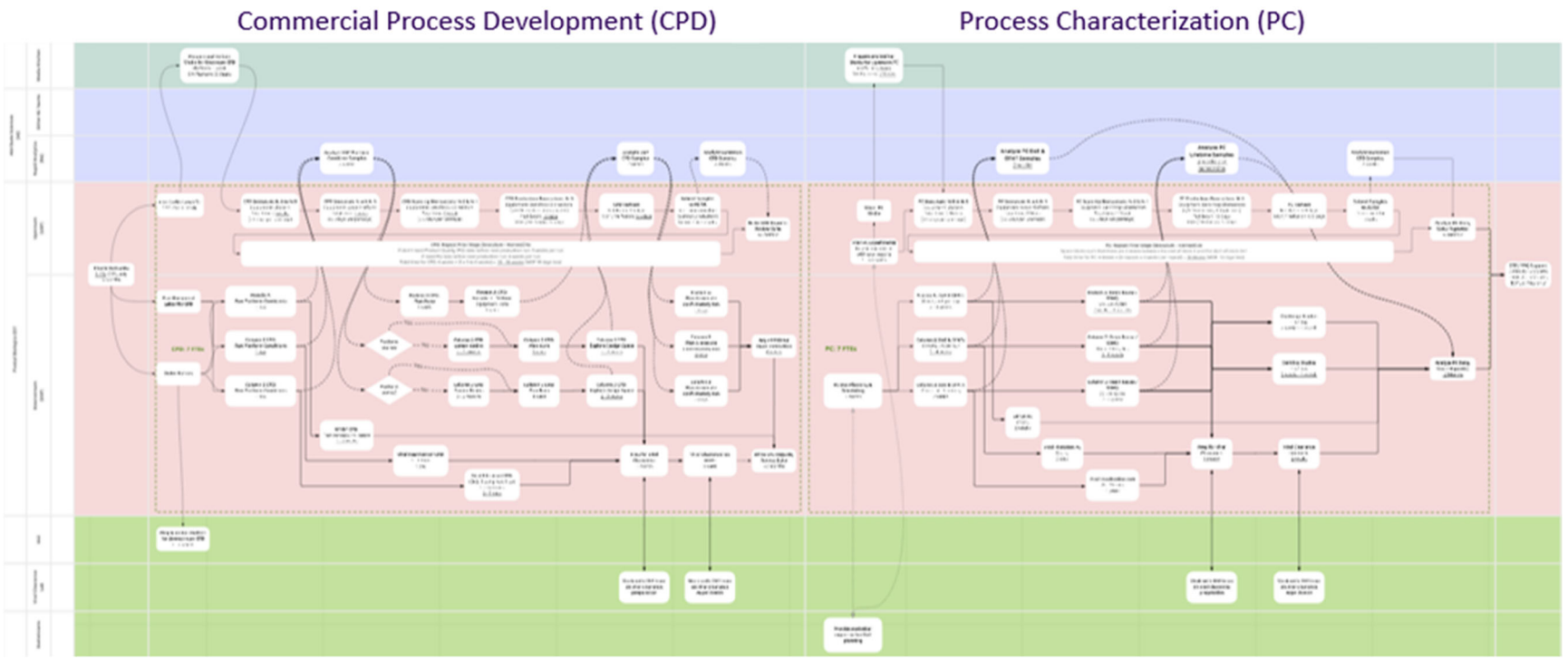

Figure 6: A high-level view of the late-stage DS PD process map, with stages separated into columns and groups organized into swimlanes.

3.2 Framework for assessing opportunities for HTT implementation

To assess which areas showed the greatest potential for benefit from the implementation of high throughput technology, a formal framework was developed focusing on the characteristics of a process that enable maximum realization of the value of HTT. Three primary characteristics were identified:

- Tasks are repeated
- Work can be done in parallel
- Low value-add tasks are done by highly skilled personnel

As discussed in Section 2.2, a key feature of high throughput technology is automation, where the technology can perform tasks without the need for hands-on labor. Automation is most successful when tasks are repeated with minimum variation because it allows for reduced scale, complexity, and cost of the equipment required to perform the tasks. The more frequently tasks are repeated, the higher the utilization of the equipment can be as well, thereby decreasing the cost per instance of usage. If tasks are not repeated at a high frequency, the equipment will spend much time idle (a waste of capacity) or will have to be very large, complex, and costly to be able to perform a wider variety of tasks at high capacity utilization.

Parallelization is another key feature of high throughput technology (also discussed in Section 2.2). The miniaturization employed in most high throughput technology enables the parallelization of similar or identical tasks that the equipment can perform. Because high throughput technology is designed with the ability to perform tasks in parallel, when tasks cannot be performed in parallel, available capacity is wasted. In the context of process development, this occurs when the equipment has the capacity to run multiple experiments simultaneously, but successive experiments depend on the results of prior experiments. In this case, because data from one experiment is needed in order to inform how a second experiment will be performed, the second experiment cannot be run at the same time as the first. As a result, the capacity for the equipment to run multiple experiments in parallel is wasted. High throughput technology is therefore most valuable when experiments can be run in parallel, and the full capacity of the equipment can be utilized each time it is employed.

Finally, high throughput technology has the greatest potential for benefits where high-skilled, high-cost employees are performing low-value-add tasks. When this is the case the maximum value employees are capable of providing is not being realized. By implementing HTT to perform the low-value-add tasks, the capacity for the high-skill employees to work on high-value-add activities is increased. As a result, either fewer of the employees are needed to complete the same amount of work (saving expensive labor hours) or the overall capacity of the organization can be increased without increasing labor costs.

In scientific laboratories the prevalence of high-skilled employees performing low-value-add tasks is very high. Experiments that require highly educated and experienced individuals to design and perform often involve numerous menial, manual steps. For instance, setting up equipment, measuring volumes of liquids, adding liquids to reactors, and sampling batches are all simple tasks that don't fundamentally require high-skilled individuals to be carried out. Through parallelization and automation (performing activities, often for numerous experiments simultaneously, without the need for an employee to be physically present), HTT can greatly reduce the hands-on time required of scientists and engineers per experiment.

Altogether, where tasks are repeated, work can be done in parallel, and low-value-add tasks are done by high-skilled labor, high throughput technology has the maximum potential for increasing throughput, increasing capacity, and decreasing costs.

3.3 Identification of opportunities for HTT deployment in biologics DS PD

When applying the framework from Section 3.2 to biologics DS PD through the process map (shown in Section 3.1), three areas stood out as showing the most promise for the deployment of high throughput technology. These three areas were:

- USP bioreactor experiments (in CPD & PC)
    - Exploring variable ranges and determining operating conditions for the bioreactors used to produce the target molecule
- DSP column experiments (in CPD & PC)
    - Exploring variable ranges and determining operating conditions for the chromatography columns used to separate the target molecule from impurities

- Clone screening
    - Assessing the productivity and growth of individual cell lines to determine which to use in production

Sections 3.3.1 to 3.3.3 outline the detailed analysis of these opportunities leveraging the framework described above.

3.3.1 USP bioreactor experiments

USP bioreactor experiments are used to explore variable ranges and determine operating conditions for the bioreactors used to produce the target molecule. These experiments are heavily repeated, can almost entirely be performed in parallel, and currently involve a great deal of low-value-add tasks done by high-skilled employees.

For both commercial process development and process characterization, large sets of experiments are designed upfront with knowledge of the variables and ranges of interest. There is minimal need to wait for results from one experiment or set of experiments before the next can be run. This is particularly true of process characterization, which typically employs a design of experiments (DOE) framework, in which conditions for a broad set of experiments are defined upfront and not subject to change based on the results of the initial runs.

For CPD, 96 benchtop bioreactor runs are typically done in six blocks of 16 parallel runs. For PC, another 64 runs, in four blocks of 16 parallel runs, is typical. Parallelization of both CPD & PC experiments is already standard, though experiments are currently run in sets of 16 at a larger “benchtop” scale with lots of hands-on time required from experimenters for setup, sampling, and breakdown / cleaning. Because of the manual nature of many of the operations, it is very common for experimenters to come in on weekends to collect the necessary samples.

A high throughput solution like the ambr 250 (introduced in Section 2.2.3) can enable increased parallelization (up to 24 runs at a time), automate necessary additions (such as CO_2) and sampling, and reduce the amount of time high-skilled labor has to spend on setup and breakdown. Reactors are single-use, disposable, miniature (such that they fit in a smaller footprint to minimize movement waste), and don’t require nearly as much preparation for setup since they come as a sterile single piece.

Altogether, USP bioreactor experiments meet all the criteria set out by the framework for identifying high-value opportunities for implementing high throughput technology.

3.3.2 DSP column experiments

DSP column experiments are used to explore variable ranges and determine operating conditions for the chromatography columns used to separate the target molecule from impurities. These experiments presented another strong potential opportunity for automation, as, like with USP bioreactor experiments, many have to be performed over the course of commercial process development and process characterization. For process characterization, depending on the exact column step (whether Protein A, Column 2, or Column 3), 20 – 40 runs are done for DOEs and one factor at a time (OFAT) experiments. Another 30 – 300 cycles will then be required for resin reuse and small-scale model qualification (SSMQ).

Much of this must be done on the same exact column, however, precluding the use of parallelization. In comparison to USP bioreactor experiments, not as much labor is required for setup and breakdown of experiments. When multiple runs need to be done successively, the Akta systems currently employed require minimal hands-on work between runs (mostly just ensuring enough mobile phase is available).

The ways in which downstream column experiments are suboptimal for high throughput technology are exemplified by resin reuse experiments. In these experiments, many runs must be done, taking up to 2 – 3 months, but all the runs must be done successively on the same column as the purpose is to explore how performance may change throughout the lifetime of a column in commercial production. Parallelization is therefore impossible. What's more, during these experiments, very little experimenter time is required. Samples only need to be taken roughly every ten runs and it only takes about 30 minutes for a single experimenter to take the sample and perform the analysis or submit a sample to the analytical support team.

Some phases of the commercial process development stage are a better fit for high throughput technology. For instance, the process of resin screening for Column 2 and Column 3 can take 2 – 3 months, or longer for high-complexity projects. As numerous different resins and conditions must be tested for this step, the different columns can be tested in parallel. And as many data points are needed for each column, tasks are highly repeatable and can be automated.

3.3.3 Clone screening

Clone screening is done to assess the productivity and growth of individual cell lines to determine which to use in production. This process presents a strong opportunity for use of high throughput technology, as it necessitates many candidates to be evaluated in the exact same manner in parallel. Under the current process, hundreds of clones are isolated. These clones must then be passaged for scale-up and evaluated for growth and productivity at progressively larger scales. All the while, candidates are eliminated but the number of the candidates remains large through the fed-batch small-scale clone screening, during which half the initial number of clones are evaluated with the end goal of selecting only a handful to advance to bioreactor clone screening.

During this process, a large amount of manual work is done by the cell line developer to passage all the cell lines in parallel for a few months. A high degree of parallelization is fundamental to the process. And though for each project the process is only completed once, the numerous projects typically undertaken annually, each requiring perhaps a month of equipment time, could likely provide sufficient capacity utilization for investment in HTT to provide a worthwhile return. This would especially be the case if the equipment is also utilized for technology development projects.

The ambr 15 currently in use for technology development projects presents a promising candidate for use in the clone screening process. Because of the range of scales the candidate cell lines must pass though, however, no single solution can be used for the entire process. The ambr 15 could be used for the fed-batch runs of small-scale clone screening. But intermediate scale-up steps would still be needed between single-cell cloning and ambr 15. Introducing ambr 15 for small-scale clone screening would also have effects on the subsequent bioreactor clone screening stage, as it would impact the scale and potentially number of candidates coming into this step. This may, in turn, impact the attractiveness of high throughput technology use in the bioreactor clone screening stage, perhaps even necessitating the use of HTT.

This is to say that for clone screening, no single technology can be considered in isolation. When evaluating potential implementation of high throughput technology in this space, all stages of scale up and evaluation must be considered in tandem. Instead of locally optimizing

an individual stage of the process, the end-to-end clone screening process should be optimized globally or maximum throughput and minimal cost. This must involve decisions about multiple pieces of equipment and processes across numerous groups.

3.4 Selection of opportunity for valuation analysis

Ultimately the implementation of ambr 250 for upstream bioreactor experiments was selected as the lead opportunity for deeper evaluation as the characteristics of the workflows in this area align perfectly with those established in Section 3.2 as optimal for realizing the benefits of high throughput technology. Tasks are repeated a multitude of times, experiments can mostly be done in parallel, and there is a large amount of low-value-add setup, breakdown, and cleaning work done by highly skilled employees.

The technology can also be seamlessly integrated into current workflows (simply acting as a substitution for benchtop bioreactors). Since the ambr 15 has been on the market since 2011[31], integration would be especially facile for firms that have already begun to develop expertise with ambr systems.

The next step in evaluation of the technology was to perform a full valuation analysis, quantifying all sources of cost and added value in order to determine the expected net present value of the investment as well as assess the potential downside risks and upside benefits.

4 Valuation of Ambr 250 Implementation

With the ambr 250 having been selected as the leading candidate for implementation, a thorough evaluation of all the sources of value and cost attributable to implementation of the technology was undertaken in order to assess whether or not it would be beneficial to pursue the opportunity. After considering all factors, if the total value of implementation of ambr 250 is positive (accounting for the cost of capital required for deployment), it is a worthwhile investment. If, on the other hand, the expectation of the costs is greater than the expectation of the value provided, then the investment should not be made.

The total value of implementing a high throughput technology like ambr 250 can be broken down into two components: the direct value and the indirect value. The direct value component comprises sources of value and cost that are quantifiable with a reasonable degree of certainty and can be combined into a net present value (NPV) calculation.

The indirect value component, on the other hand, comprises sources of value and cost for which quantification would carry high levels of uncertainty and thereby cloud the insights able to be derived from an NPV calculation if included. Instead, these factors can be considered as auxiliary to the direct NPV. With this approach, the NPV can be used as a reliable base figure for decision making and the indirect sources can be considered alongside, using judgement to determine how strongly to weight them relative to the NPV should the two provide conflicting indications.

The net value that can be derived from the implementation of ambr 250 systems for upstream process development can be broken down into the following component sources of value and cost:

- Value from FTE savings
- Value from speed increase
- Value from responsiveness / flexibility
- Cost of systems
- Cost of setup & qualification
- Cost of support / maintenance
- Cost of training

- Cost of downtime from failure
- Cost of downtime from turnover

4.1 The Direct Value of Investing in Ambr 250 Systems

Of the nine sources of value and cost listed above, the following four will be considered as direct sources of value and cost. These tangible, quantifiable factors will be used to calculate the NPV of ambr 250 implementation.

- Value from FTE savings
- Cost of systems
- Cost of setup & qualification
- Cost of support / maintenance

The remaining factors (listed below) are more difficult to quantify in a manner precise enough to be valuable for inclusion in the NPV calculation. Using the direct NPV as a foundation, the potential impact of these indirect factors can be incorporated on top for the purposes of decision-making.

- Value from speed increase
- Value from responsiveness / flexibility
- Cost of training
- Cost of downtime from failure
- Cost of downtime from turnover

The methodology used to calculate values for each value and cost component of the NPV calculation is outlined in the following sections. Other factors also incorporated in the calculation include:

- Tax rate: 21%
    - The nominal US federal corporate tax rate
- Discount rate: 8%

    - Calculated following the Capital Asset Pricing Model (CAPM), using the risk free rate and equity risk premium from Kroll and a beta value for Amgen from Yahoo finance.[32,33]
- Outside expense (OSE), the expected additional cost of outside equipment and consumables as a percentage of FTE cost
    - A value of 35% OSE was assumed
- Depreciation: straight-line over 10 years

Further details on the NPV calculations are provided in Appendix 1, including the equations used and a summary of the values of all factors incorporated. A description of how each figure was generated from these calculations is also provided therein.

4.1.1 Calculation of the Value from FTE Savings

To quantify the labor hours that could be saved by implementing the ambr 250 (for CPD, PC, or both) on a single project, a differential analysis was performed comparing current workflows to those that would be expected when utilizing ambr 250 systems. Each phase (CPD and PC) was divided up into three steps: initial scale-up, production runs, and the gap between production runs. The number of times each step would need to be completed was then determined for each phase with or without use of ambr 250. Finally, the time and resources required for each step (with or without ambr 250) was determined and the time and resource requirements for each step summed to arrive at the total time and resources required to complete CPD and/or PC for a single project.

The data for these calculations were drawn from the previously developed process map, as well as conversations with upstream process development SMEs, some of whom work extensively with ambr 15 systems.

To determine the total amount of FTE time that can be saved in a year by using ambr 250 for CPD, PC, or both (relative to a base-case of using benchtop bioreactors), the savings per project is multiplied by the number of projects that the system can be used for each year. The number of projects an ambr 250 can be used for each year is dependent upon which phases of development the system is used for (CPD or both CPD & PC), as well as the number of ambr

250 systems in use. This can be constrained either by the capacity of an individual ambr 250 (assuming 90% capacity utilization over 50 business weeks per year) or by the total number of projects to be completed per year (a maximum of six is assumed). These calculations are shown in Table 1.

The number of weeks of FTE time saved per year can then be translated into a cost savings assuming a comprehensive annual FTE cost of $250,000 per year for 45 weeks of labor (or $5556 per week). OSE of 35% is then included to represent auxiliary material and labor cost reductions associated with the decrease in direct labor hours.

Table 1: The total FTE savings that can be achieved by using a given number of ambr 250 systems for CPD only or both CPD & PC. FTE savings per project and weeks per project are estimated based on prior process mapping activities (Section 3.1). An ambr 250 capacity of 45 weeks per year (90% capacity utilization over 50 business weeks) is assumed. Assuming six new projects per year, this is the maximum number of projects per year that ambr 250 systems can be used for, regardless of how many are purchased. OSE of 35% is then included to represent auxiliary material and labor cost reductions associated with the decrease in direct labor hours.

	One Ambr		Two Ambr		Three Ambr	
	CPD Only	CPD & PC	CPD Only	CPD & PC	CPD Only	CPD & PC
FTE savings per project (FTE*wks)	13.6	22.4	13.6	22.4	13.6	22.4
Weeks per project	11	19.5	11	19.5	11	19.5
Projects per year	4.1	2.3	6.0	4.6	6.0	6.0
FTE savings per year (FTE*wks)	**55.6**	**51.7**	**81.6**	**103.4**	**81.6**	**134.4**
Weekly FTE cost	$5,556	$5,556	$5,556	$5,556	$5,556	$5,556
Cost savings per year	$309,091	$287,179	$453,333	$574,359	$453,333	$746,667
Cost savings per year (incl. OSE)	**$415,727**	**$386,256**	**$609,733**	**$772,513**	**$609,733**	**$1,004,267**

4.1.2 Calculation of the Cost of Systems

Each 24-way ambr 250 system is estimated to cost $1,000,000 – $3,000,000 to purchase. This purchase price will naturally depend on the configurations and features desired. The total cost of systems is simply the number of systems purchased multiplied by the cost per system.

4.1.3 Calculation of the Cost of Setup & Qualification

The initial setup of the first ambr system purchased is expected to require one FTE full-time for 35 weeks, plus a second FTE periodically on days runs must be set up or broken down (5 weeks total time over this period), for a total of 40 weeks of FTE time. After expertise has been gained setting up the first ambr 250 system, it is assumed that setup of additional ambr 250 systems that will be purchased would require only half the time. These figures are based on estimates of the time that was required to complete these actions for the ambr 15 currently in use in pre-pivotal biologics DST. Incorporating a comprehensive annual FTE cost of $250,000 per year for 45 weeks of work as well as the standard 35% OSE (as done in Section 4.1.1 above), results in the total setup and qualification cost, depending on the number of systems purchased, shown below in Table 2.

Table 2: Setup and qualification costs for ambr 250 systems depending on the number of systems purchased. Comprehensive annual FTE cost of $250,000 for 45 weeks of work and OSE cost of 35% are assumed.

	One Ambr	Two Ambr	Three Ambr
FTE*weeks required for setup	40	60	80
Weekly FTE cost	$5,556	$5,556	$5,556
Cost savings per year	$222,222	$333,333	$444,444
Cost savings per year (incl. OSE)	**$298,889**	**$448,333**	**$597,778**

4.1.4 Calculation of the Cost of Support & Maintenance

Sartorius provides a comprehensive maintenance and support package with the purchase of ambr 250 systems that covers all required replacement parts and maintenance costs for a fixed cost per system per year. With the purchase of an ambr system, the service contract for the first year comes free. Thereafter, it is assumed that the total cost of support and maintenance is equal to the annual cost per system times the number of systems purchased. This is conservative considering the comprehensive service contract may not be needed for the entire lifetime of the system and a company may find it worthwhile to discontinue the contract after the first several years.

4.1.5 Use Cases & Ambr 250 Implementation Scenarios

The first use case of the ambr 250 would necessarily be in the commercial process development (CPD) stage of upstream PD, as this process requires many repeated sets of experiments, and the results of these experiments are used to define the upstream process but do not go into regulatory filings. Thus, for CPD, ambr 250 can be used without previously establishing the level of comparability to manufacturing scale runs. For process characterization, the subsequent stage of upstream PD, however, experimental results are used in regulatory filings. Therefore, comparability of results from the small-scale ambr 250 runs to results from benchtop bioreactor and/or manufacturing-scale runs must be established before ambr 250 can be used for PC. As discussed in Section 2.2.3, above, evidence that ambr 250 can indeed be used for PC experiments has been published by large biopharmaceutical companies such as Merck.

For ambr 250 to be used on all projects across the DS PD space multiple systems would have to be purchased as a single system does not have sufficient available capacity to service all projects. As the purchase of each ambr 250 system can be considered as an independent decision, separate NPV calculations were done for the following three implementation scenarios:

- One ambr 250 system is purchased for use on CPD experiments on some projects
- Two ambr 250 systems are purchased for use on CPD experiments on all projects
- Three ambr 250 systems are purchased for use on both CPD and PC experiments on all projects

4.1.6 NPV of One Ambr 250 System for CPD

As the capacity required for CPD on pipeline projects exceeds the capacity available on a single ambr 250 system, if a single ambr 250 is purchased and used for CPD it can be presumed to have fairly high capacity utilization. 90% capacity utilization over 50 weeks per year was used for the purposes of the NPV calculations in this case.

The NPV of the investment depends strongly on the expected lifetime of the system (Figure 7). But ultimately, even with a conservative lifetime assumption of 10 years the NPV of the direct costs and savings of investing in a single ambr 250 system is positive, at $348,000.

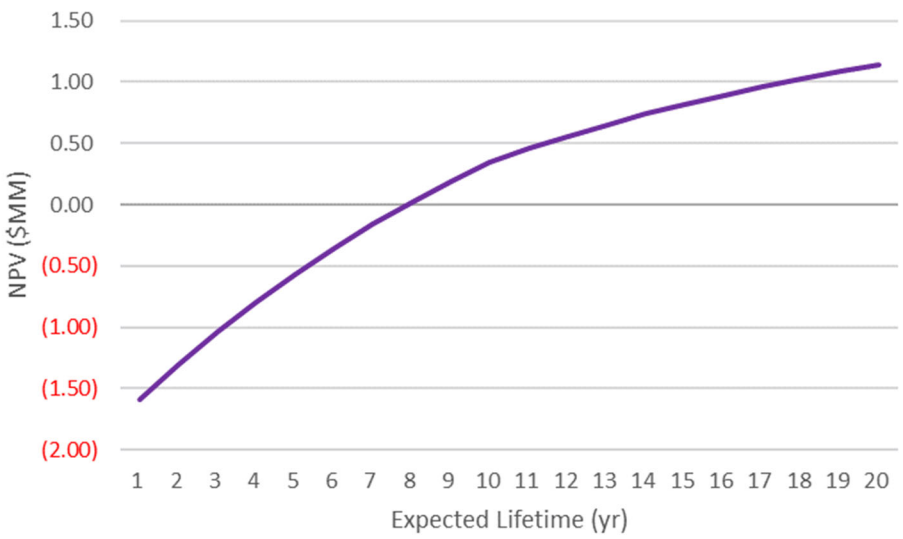

Figure 7: NPV of investing in one ambr 250 system for use in CPD experiments by expected system lifetime

4.1.7 NPV of Two Ambr 250 Systems for CPD

Purchasing a second ambr 250 system would provide sufficient capacity to use an ambr system for CPD on all pipeline projects. A result of this is that the capacity utilization of the ambr 250 systems under this scenario would be substantially lower than that achieved in the one ambr scenario described above. And in order for the investment in the second system to be a positive NPV decision, the NPV of the two-ambr scenario must not only be positive but must also be greater than the NPV of investing in only one system.

The principal source of direct value in the NPV calculation is the hours of FTE labor saved per year, which is lower for the marginal additional system than for the first purchased system that could achieve near-full utilization. The principal drivers of cost (system purchase price and maintenance contracts), on the other hand, are perfectly proportional to the number of systems purchased. Altogether this means that the direct NPV of investing in two ambr 250 systems for CPD is strongly dependent on the capacity utilization (in addition to the expected lifetime) and not necessarily higher NPV than investing in just one system.

As shown in Figure 8 below, the direct NPV of investing in two ambr 250 systems for CPD is positive with capacity utilization of at least 74% if the system has a 10-year lifetime. But 10 years is a conservative estimate. And if the system lifetime reaches as high as 20 years (an

optimistic but not outlandish target), capacity utilization must only reach 54% for NPV to be positive. With lifetimes beyond 20 years, NPV does not change meaningfully as the present value of cash flows over 20 years away is small.

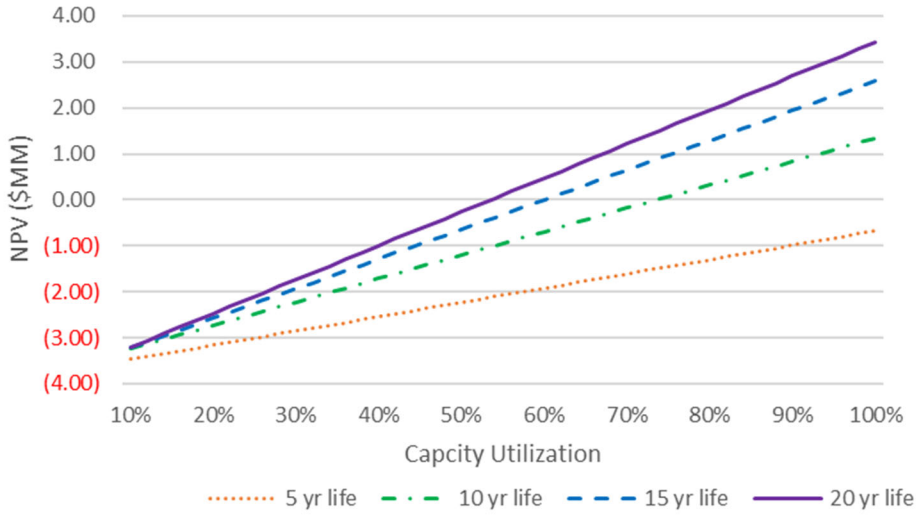

Figure 8: NPV of investing in 2 ambr systems to use on all projects for CPD only versus the capacity utilization obtained from those systems for varying expected system lifetimes.

For the marginal NPV of purchasing a second ambr 250 system to be positive, however, meaning it is beneficial to purchase a second system in addition to a first, capacity utilization must be higher (Figure 9). With an expected lifetime of 10 years, utilization must reach 82% to achieve this. Though with an expected lifetime of 20 years utilization must reach 70%.

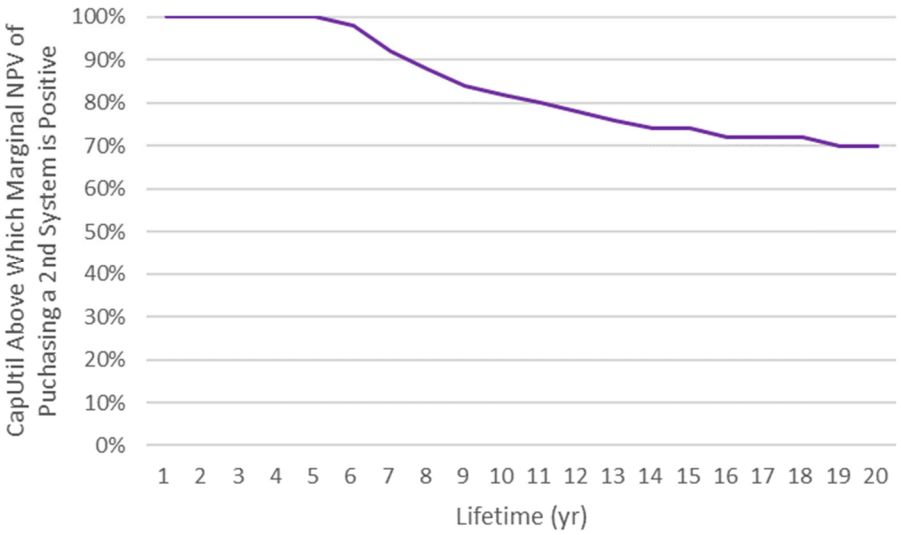

Figure 9: For varying expected lifetime, the chart below shows the capacity utilization above which investing in a second ambr 250 system for CPD will yield a positive marginal NPV and therefore should be done

If two ambr 250 systems are used for CPD experiments on all pipeline projects (assuming 6 projects per year entering the pivotal space), capacity utilization should reach ~66% for pipeline projects only. And in addition to pipeline projects, the ambr systems can also be used for life cycle management (LCM) programs (products already on the market) and technology development projects. With these included utilization above 70 – 80% could likely be achieved, rendering investment in the second ambr 250 system worthwhile.

4.1.8 NPV of Three Ambr 250 Systems for CPD & PC

Purchasing a third ambr 250 would likely provide enough capacity to use ambr systems for both CPD and PC on all pipeline projects. The calculations to determine whether purchasing this third system would provide a positive return are similar to those above for the second system.

As shown in Figure 10 below, the direct NPV of investing in three ambr 250 systems for CPD & PC is positive with capacity utilization of at least 80% if the system has a 10-year lifetime. And if the system lifetime reaches as high as 20 years, capacity utilization must only reach 58% for NPV to be positive.

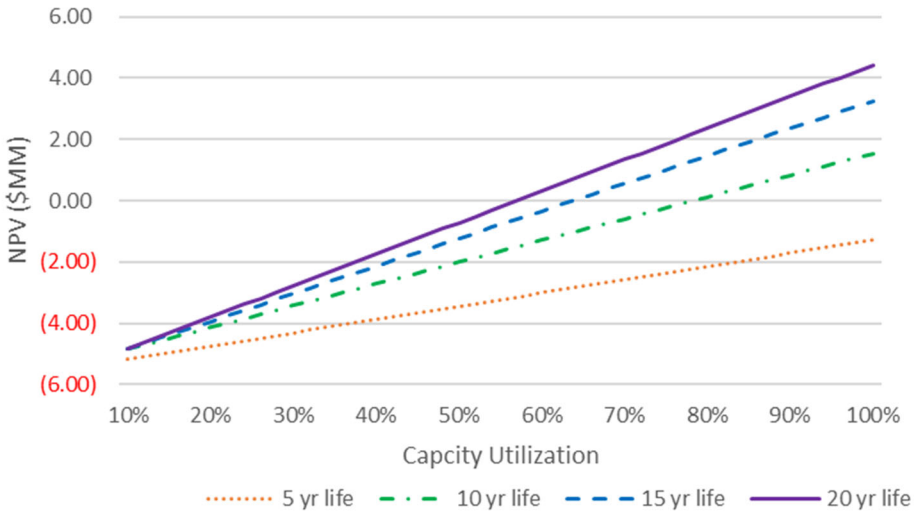

Figure 10: NPV of investing in 3 ambr systems to use on all projects for both CPD & PC versus the capacity utilization obtained from those systems for varying expected system lifetimes.

For the marginal NPV of purchasing a third ambr 250 system to be positive, however, meaning it is beneficial to purchase a third system in addition to a first and a second, the NPV of purchasing three systems must be higher than both the NPV of purchasing two systems and the NPV of purchasing one system. To achieve this, capacity utilization must be higher (Figure 11). With an expected lifetime of 10 years, utilization must reach 92%, a lofty goal. With an expected lifetime of 20 years utilization must reach only 70%.

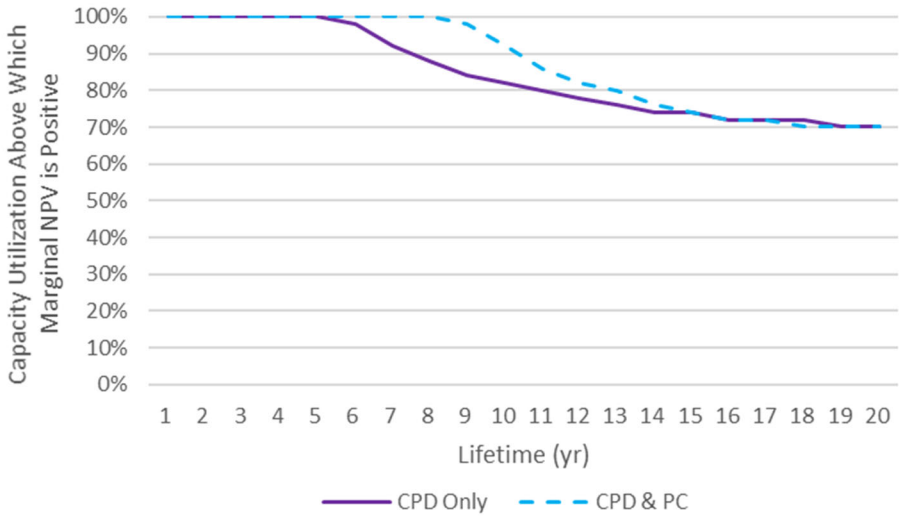

Figure 11: For varying expected lifetime, the capacity utilization above which the marginal NPV of investing in a second ambr system (CPD Only) or a third ambr system (CPD & PC) is positive. Above this expected level of capacity utilization, it is beneficial to purchase the marginal additional system.

If three ambr 250 systems are used for CPD & PC experiments on all pipeline projects (assuming 6 projects per year entering the pivotal space), capacity utilization should reach ~78% for pipeline projects only. With this level of utilization, purchasing three ambr systems is the optimal decision if the expected lifetime is 14 years or higher, not an unreasonable goal for the lifetime of the ambr systems. And since the ambr systems can also be used for LCM molecules and technology development projects, even higher levels of utilization could potentially be achieved.

Altogether, investing in three ambr 250 systems for use in both CPD and PC is likely the optimal decision with the highest NPV. Amgen would have to establish that results from the ambr 250 can indeed be used for regulatory filings before it can be used for PC, though. So, purchase of the first two systems, to be used for CPD while establishing that they can be used for PC, would be the necessary first step before investing in a third system.

4.2 The Indirect Value and Cost Derived from Ambr 250 Implementation

Beyond the value quantifiable in the above NPV calculations, there are also additional, indirect, ways that ambr 250 systems would provide value or generate costs that are not considered in the NPV. This is because quantification of these values would carry high levels of uncertainty and thereby potentially cloud the insights derived from looking only at direct sources of cost and value that carry higher certainty. Several of the most important such indirect sources of cost and value are discussed below.

4.2.1 Cost of Training

Employees experienced with the ambr 15 system estimate that it takes roughly 6 weeks of employee time to train a new user to be self-sufficient. This would come out to $33,000 worth of time per employee trained (using the same standard $250,000 comprehensive annual FTE cost). The number of employees trained would depend on the support structure instituted for the

equipment, but assuming 5 employees were trained upfront to become part-time ambr specialists, that comes out to a meaningful $167,000 worth of employee time in training.

Of those that are initially trained when the equipment first arrives, however, much of their hands-on-training time would occur during the system setup and qualification (expected to take approximately 40 weeks of employee time total). Therefore, there's substantial overlap in the resource cost of training and the resource cost of setup and qualification that would be hard to disentangle but likely decreases substantially the expected cost of upfront training. Assuming 3 of the 5 are trained during the setup and qualification period brings the cost of upfront training down to ~$67,000, which is a very uncertain estimate and not likely to make much of an impact in the decision of whether or not to invest in the equipment. If fewer employees were dedicated full-time to ambr support, their upfront training time would likely entirely overlap with the time spent on setup and qualification.

There is an additional training cost associated with upskilling new users after turnover, but this would be expected to be less than the upfront training cost, particularly because the costs come later and their present value is substantially discounted. Altogether the cost of training, upfront and continuous, is not a major driver of cost that meaningfully influences the net value of investment in ambr systems.

4.2.2 Cost of Downtime

Downtime has both direct and indirect costs. The cost of downtime impacts the direct NPV of investment in ambr 250 systems through the capacity utilization of the equipment. If the equipment is down, its capacity is not being utilized during that time. This direct impact is baked into the above NPV calculations by assuming that capacity utilization will not reach 100%. It is not assumed above for the purposes of decision making that capacity utilization will be greater than 90%. This is done to reflect a conservative assumption that the equipment may be down and waiting to be serviced for up to one month per year.

There is the possibility that complex maintenance issues may take up to a few months to fix, but this is not likely to happen frequently enough to be a significant contributor of cost over the 10+ year lifetime of the systems (one extra 12-week disruption over 500 weeks is only a

2.4% impact and more likely to occur when the system is older and the present value of this disruption will be of smaller magnitude).

The indirect costs of downtime relate to a disruption of the speed increase provided by the ambr 250. As the value of the speed increase (to be discussed below) is not included in the NPV calculation, a reduction in the speed increase obtained due to downtime would merely reduce this additional indirect source of value. It does not add any new cost but rather diminishes indirect value and does not merit inclusion in the NPV calculation.

Downtime can also occur due to lack of available users to operate the equipment on account of employee turnover. The cost of this will vary substantially depending on the HT support structure chosen, and is highly uncertain, so would not be prudent to include in the direct NPV calculation. The costs of downtime due to employee turnover, and the impact HT support structure has on these costs, are discussed in more detail in later sections.

4.2.3 Value from Reduced Bioreactor Cleaning & Sterilization

One indirect source of value not accounted for in the direct NPV calculations above comes from a reduction in the need for bioreactor cleaning and sterilization with implementation of ambr 250. Between uses, benchtop bioreactors must be delivered to a bioreactor support team for thorough cleaning and sterilization, which of course requires FTE resources to complete. The bioreactors of the ambr 250 system, on the other hand, are single-use and therefore do not require these steps.

Using ambr 250 systems for both CPD and PC on 6 pipeline projects per year which each require 10 total blocks of experiments of 16 bioreactors each would obviate the need for cleaning and sterilization of 960 bioreactors per year. The FTE time that would be reduced by avoiding this step for 960 bioreactors per year was not accounted for in the above NPV calculations because these numbers are not known, but it is likely to be a meaningful source of additional indirect savings. The reduction in the use of energy, water, and chemicals would be another source of savings from avoiding these steps.

4.2.4 Value from Shortened Development Timelines

One very meaningful source of value that was not included in the NPV calculations due to difficulties in quantification and high levels of uncertainty is the value derived from the shortened development timelines provided by implementation of ambr 250. Using ambr 250 has the potential to reduce the time required for upstream CPD by approximately 10 weeks and the time required for upstream PC by 6.5 weeks (as estimated by the process mapping discussed in Section 3.1). The value that comes from this depends strongly on two factors: whether process development is on the critical path for the project and whether timelines can also be adjusted in the concurrent downstream CPD or PC.

If adjustments cannot be made in the downstream timelines, then the overall program timeline will not change meaningfully as downstream will be the bottleneck for process development. For downstream CPD, there are no clear options for finding the same level of improvement as ambr 250 would provide for upstream. It is possible, however, that downstream CPD could be started earlier (somewhat increasing at-risk work) in order for CPD to be done sooner. Devoting additional resources to the downstream development team for CPD could potentially provide some speed increase as more unit ops could be developed in parallel with more hands to do so. Finally, for complex programs where screening is required for column selection or other purposes, the existing Tecan automated liquid handlers can be better utilized to achieve some speed increase.

For PC, on the other hand, downstream time savings can be accomplished by shifting around the timing of activities in order to get to commercial tech transfer (CTT) and process performance qualification (PPQ), the stage after PC, more quickly. Several of the downstream activities that are currently done before CTT & PPQ, including small-scale model qualification (SSMQ), resin reuse, stability studies, and viral clearance studies, can instead be done during or after CTT & PPQ. The results generated in these experiments are not required for CTT or PPQ but are needed for the filing which does not take place for one year after the start of CTT. As by the current late-stage DS PD resource model only some team members are staffed on CCT & PPQ, the other downstream engineers on the project can complete these activities during CTT & PPQ. This approach has been successfully undertaken by companies such as Eli Lilly seeking to achieve accelerated timelines for high priority projects.

Even if downstream timelines can match the improvements to upstream timelines provided by ambr 250 implementation, if process development is not on the critical path,

shortened development timelines cannot improve speed to market. There is still value in the increased speed for these projects, however, as if process development takes less time, it can be started later and still meet the same deadlines. This increases the information available about the chances of success for the project (in extreme cases the program may even be terminated in the intervening time) and serves to reduce at-risk work. It also pushes back the date at which the investment in process development is made, serving to reduce the present value of the cost of this investment.

Where downstream timelines can match improvements in upstream timelines and process development is on the critical path, there is enormous value in increased development speed. In these cases, any savings can translate into increased speed to market. And each additional week of sales a company is able to gain on a product can mean millions of dollars in additional sales revenue.

If over the 10+ year lifetime of the ambr 250 systems Amgen was able to gain even one additional week of sales on a single product, the millions of dollars in increased sales from this alone would make the investment in ambr 250 systems for CPD and PC a worthwhile investment. If 20% of products gained 2 weeks of sales from this change over a 20-year lifetime, this would translate to over $100 - $200 million in additional sales.

Late-stage acquisitions may prove a case where the use of ambr 250 for upstream process development can increase speed to market and gain additional weeks of sales. For some such products, process development is on the critical path because clinical trials are already in an advanced stage and substantial development work is needed to fit the manufacturing process to company standards on short timelines.

Given this upside potential on top of the already likely positive NPV from the direct sources of cost and value, implementing ambr 250 systems for upstream process development is a strong investment. One or two ambr systems should be purchased for use in CPD and to establish whether they can be used for PC. Once it is established that the ambr 250 can be used for PC, the first use case of ambr 250 for PC should be undertaken on a project where PC is on the critical path soon thereafter and a third system should be purchased to expand capacity.

4.3 Valuation Conclusions and Recommendations on Path Forward

Altogether this analysis establishes that investment in ambr 250 systems for use in upstream CPD & PC is a worthwhile investment. From the FTE savings alone, the investment is likely to yield a positive NPV, though the expected NPV depends strongly on both the expected useful lifetime of the systems and their capacity utilization.

On top of this, implementing ambr 250 systems for upstream process development has the potential to increase development speed, cutting 6.5 weeks off PC, and therefore 6.5 weeks off total development time for projects where process development is on the critical path. Examples of programs where this may be the case are late-stage acquisitions. Using ambr 250 for PC on programs for which shorter program timelines lead to gaining weeks of sales could translate to millions of dollars in increased sales per week of sales gained.

The recommended path forward is to purchase one or two ambr systems to use in CPD and to establish whether they can be used for PC. Once it is established that the ambr 250 can be used for PC, it is recommended that the existing systems be used immediately thereafter on projects for which increased development speed can increase speed to market, and that a third system be purchased to expand capacity.

5 Determining the Optimal Support Structure for Ambr 250

In Section 2.2.4, three opposing models of support structures for high throughput technology were discussed: the "dedicated team" model, the "formal SME" model, and the "informal champion" model. The choice of support model will ultimately impact many of the different drivers of value and cost of implementing a particular technology.

When considering adopting a new technology, it is prudent, therefore, to analyze how the value of that technology may vary depending on the support structure chosen. And ultimately, a support structure can be chosen that, for the particular technology and the particular functional area at the particular time of adoption, achieves the optimal balance of value and cost.

In the following sections, an analysis is presented of the ways in which the three aforementioned models of support structure impact each variable driving the value derived from and the cost associated with implementation of ambr 250 systems. Following this analysis, a recommendation is presented as to which model of support would be optimal for ambr 250 systems in Amgen biologics drug substance process development.

5.1 System Lifetime

As the expected ambr system lifetime affects multiple sources of both value and cost, the impact of HT support structure on system lifetime, and the associated impact on the net value of the system, should be discussed upfront before discussion of the individual sources of value and cost. The following sources of value and cost are all affected by the expected system lifetime:

- Value from FTE savings
- Value from speed increase
- Value from responsiveness / flexibility
- Cost of support / maintenance
- Cost of training
- Cost of downtime from failure
- Cost of downtime from turnover

While the exact lifetime of the ambr 250 system is unknown, estimates range from ten to twenty years. With a dedicated team or formal SME model of support, the system would likely be used frequently with appropriate levels of care and maintenance (both preventative and corrective) would likely be carried out as needed in a timely manner. Thus, under these models the system can be expected to live up to its full potential lifetime of ten to twenty years.

Under an informal champion model, however, upkeep of the equipment does not fall under the users' formal responsibilities, and it may be difficult to attribute misuse or poor clean-up practices to a particular individual within the informal network of users. Thus, users are less likely to use the system with appropriate levels of care or to ensure necessary maintenance is done in a timely manner. The system may have substantial periods of disuse under an informal champion system as well, if employees don't choose to become trained at least as fast as users leave their role or if by chance no user has a need for the equipment for their projects for some time. Without frequent use, HT equipment is more likely to fall into disrepair, experience more downtime, and require more maintenance (as discussed in more detail in later sections). These factors altogether may lead to a substantial decrease in the effective lifetime of the equipment.

The aggregate impact of system lifetime on the net value of the system can be determined through a sensitivity analysis. Figure 12 shows the capacity utilization Amgen would need to achieve to breakeven on investment in ambr systems for various values of expected lifetime, looking exclusively at the direct sources of cost and value (system cost, maintenance cost, & value from FTE savings). With good support and maintenance, as could be expected under the dedicated team or formal SME models, ambr lifetime is estimated to be between 10 and 20 years. With a lifetime of 10 years, the systems would need to be utilized 74 – 80% in order to breakeven on the investment from the value of FTE savings alone (Figure 12). But with a lifetime of 20 years, only 54 – 58% utilization would be required to achieve this. These levels of capacity utilization are certainly achievable.

If the informal champion model is used, however, a lower useable lifetime is a definite possibility, either because the equipment was used and upkept improperly or because knowhow is lost upon turnover. Below 10 years of lifetime, there is a steep dependency between lifetime and breakeven capacity utilization such that even cutting only a few years off the expected lifetime makes breakeven utilization difficult to achieve. With 8 years of lifetime, 86 – 92%

utilization is required to breakeven, and below 7 years of lifetime breakeven becomes impossible.

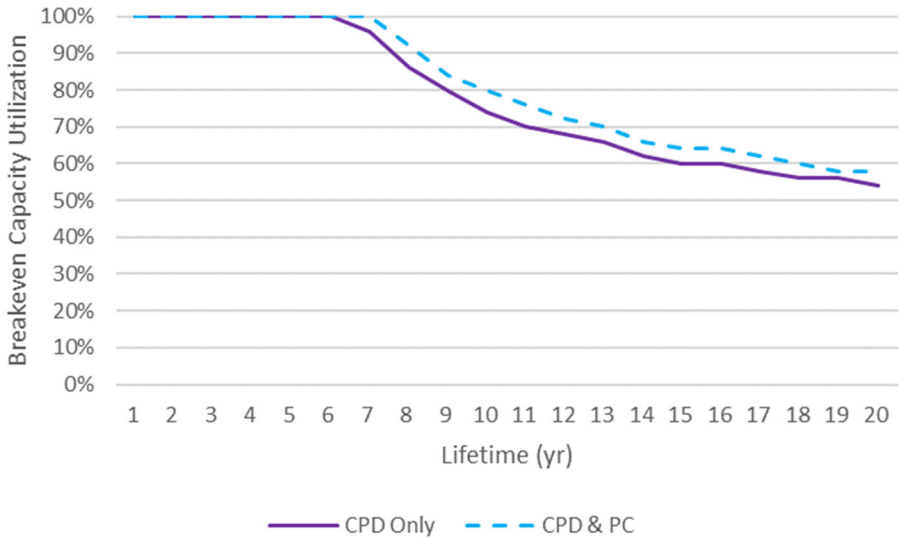

Figure 12: Breakeven capacity utilization by expected ambr lifetime if using ambr for CPD only on all projects or using ambr for both CPD & PC on all projects. If capacity utilization is higher than the breakeven percentage, NPV is positive for investing in the requisite ambr systems.

The figures below illustrate the strength of the dependence of NPV on lifetime and capacity utilization for the situations where Amgen invests in two ambr systems for use on all projects for CPD only (Figure 13) or invests in three systems for use on all projects for both CPD & PC (Figure 14). With a lifetime of 15 – 20 years and utilization of 75 – 90%, the NPV of the investment can surpass $2 million. These ranges of lifetime and utilization should be achievable with a dedicated team or formal SME support structure.

It is impossible to breakeven on the investment, however, with a lifetime under 7 years (regardless of capacity utilization) or capacity utilization under 55% (regardless of lifetime). And with an informal champion support structure, lifetime or capacity utilization may very well be below these cutoffs.

Thus, on account of the benefits derived from increased lifetime and capacity utilization, the value of pursuing a dedicated team or formal SME model rather than an informal champion model could be on the order of $2 million.

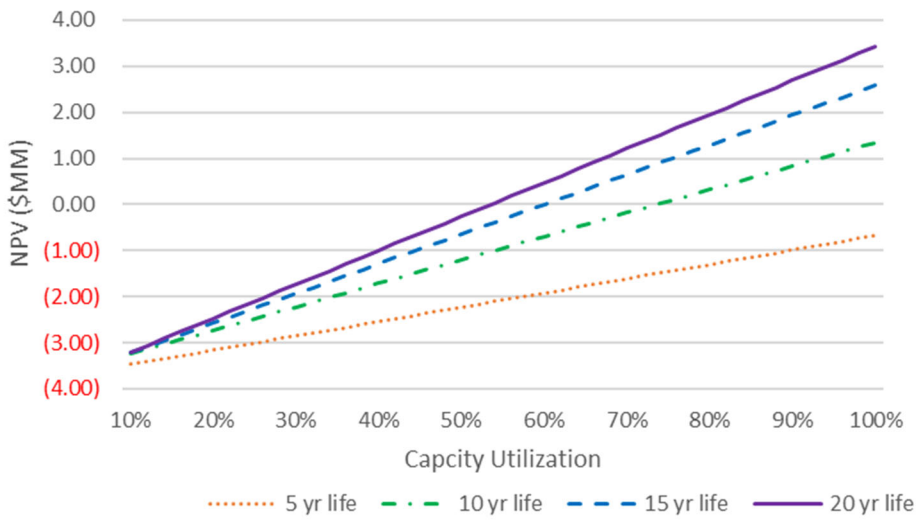

*Figure 13: A duplicate of **Figure 8** above. NPV of investing in 2 ambr systems to use on all projects for CPD only versus the capacity utilization obtained from those systems for varying expected system lifetimes.*

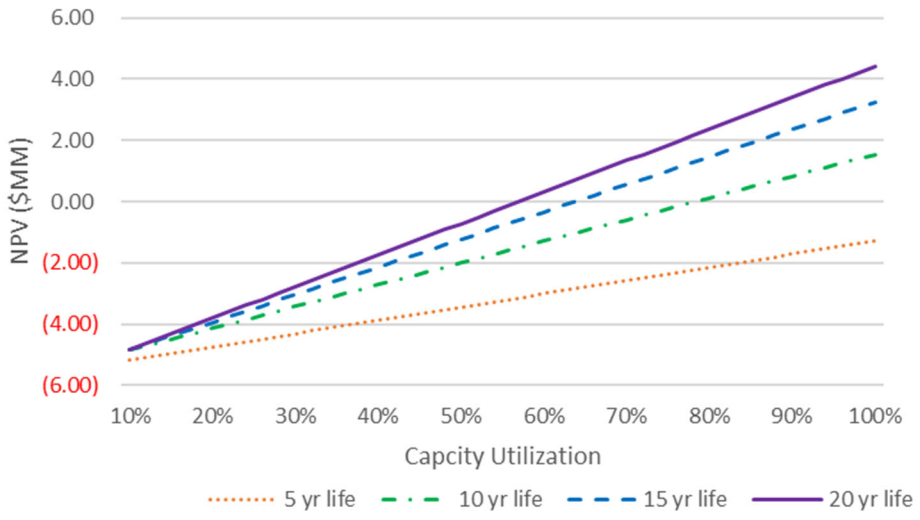

*Figure 14: A duplicate of **Figure 10** above. NPV of investing in 3 ambr systems to use on all projects for both CPD & PC versus the capacity utilization obtained from those systems for varying expected system lifetimes.*

5.2 Value from FTE Savings

Assuming a trained user comes at equal cost to Amgen and takes approximately equal amounts of time to perform operations using the ambr and complete work regardless of whether the user is an informal champion or a dedicated SME, the only means by which HT support structure can affect the value from FTE savings is through the number of projects for which the equipment can be used. The ability of the ambr to achieve the target level of capacity utilization depends on there being sufficient availability of trained users. And the availability of trained users will, in turn, depend on how many users are trained initially and the relative rates with which trained users leave their role and new users are trained.

With a dedicated team or formal SME model, both of which would feature a relatively rapid replacement of trained users following turnover, the system will be supported by less than the target number of users for only a small percentage of the lifetime. As a result, the system can be expected to achieve capacity utilization close to target levels.

With an informal champion model, however, the probability of insufficient support is much higher, as when a trained user leaves the role, a new user is not trained until another employee takes an interest in the system and chooses to become trained. This is likely to be substantially slower than under the other two structures where management would replace a lost user as soon as possible. The probability of capacity utilization below target levels on account of insufficient support is therefore substantially higher under an informal champion model.

5.3 Value from Speed Increase

The value derived from an increase in program speed is affected by HT support structure in the same way as is the value from FTE savings, through the number of projects for which the equipment can be used each year. With the same assumptions on how the informal champion model may reduce the number of projects completed per year relative to either the dedicated team or formal SME models, one may conclude that use of an informal champion model would decrease the value derived from ambr 250 implementation. If the equipment is utilized for fewer projects per year, however, it may be possible to prioritize the projects where process

development will be on the critical path and thereby still achieve most of the value that comes from increased speed.

5.4 Value from Responsiveness / Flexibility

As discussed in Section 2.2.1, high throughput technologies can increase an organization's ability to handle a variable workload with variable project types and the potential for sudden increases in workload. This we term increased responsiveness and flexibility. The value provided by increased responsiveness and flexibility is affected by HT support structure through the likelihood there is support staff available to utilize the ambr system. As discussed in the section on system lifetime above, under the informal champion model, if employees don't choose to become trained at least as fast as users leave their role the equipment may experience extended periods of lack of user support that are unlikely under a dedicated team or formal SME model. Accordingly, if the informal champion model is followed, when there is a sudden influx of work, the ambr may not be used to reduce FTE capacity utilization (and increase the likelihood of on-time delivery) if no users are trained at the time.

Furthermore, even if under the informal champion model there is never a period without any users, if there are a smaller number of users than under other models there may still be reduced value from responsiveness. Under this model, the users will almost always be working on other projects at the time of a sudden project influx, and the chance one can take on a sudden project is lower the fewer users are trained. Under the formal SME model, it can be ensured that there are sufficient number of trained users that there is reasonable chance one may be able to operate the ambr for a project that appears suddenly, but there still may not always be availability (or other projects may experience delays instead if the new work takes priority). In contrast, if there is a dedicated HT team, they can very likely fit it in if capacity utilization of the ambr for pipeline programs is not excessively high.

5.5 Cost of Systems

The cost of ambr systems is a fixed, upfront cost and is not impacted by the HT support structure employed.

5.6 Cost of Setup / Qualification

The cost of setup and qualification of ambr systems is a fixed upfront cost and is not likely impacted by the HT support structure employed.

5.7 Cost of Support / Maintenance

The cost of support and maintenance is affected by HT support structure through the lifetime of the system, as discussed above. Beyond this, it may also be affected through the annual maintenance contract. The cost of a comprehensive maintenance contract with Sartorius is $40,000 per year. This contract includes all required maintenance, replacements needed due to wear and tear, and yearly preventative maintenance (PM). There are cheaper maintenance contract options that are not comprehensive, however, and depending upon the extent of Amgen user expertise, the savings from these cheaper contracts may be attainable.

Under an informal champion model, the users are unlikely to develop and maintain sufficient levels of expertise such that the comprehensive service contract is unnecessary. Yet under a formal SME model, the users are likely to reach higher degrees of expertise so that they are able to deal with a broader set of maintenance issues themselves (thereby reducing the value of the comprehensive service contract). And under a dedicated team model, the support team is likely to develop still higher levels of expertise and obviate the need for Sartorius support for most issues.

Thus, while under the informal champion model the full modeled cost of maintenance can be expected to be realized, under the dedicated team model, there may be substantial savings in the cost of maintenance. And the formal SME model may provide an intermediary level of savings.

5.8 Cost of Training

HT support structure can have a substantial impact on the cost of training users to operate automation equipment. With a dedicated team model, training costs are straightforward. The number of individuals that comprise the team will all have to be trained as users, and when one leaves the team, a new individual must be trained. The cost structure is the same for a formal SME model, though since SMEs have other functions and operating automation equipment may not be their primary responsibility, a greater number of users will need to be trained to ensure sufficient availability for support. As two to four times the number of users may be required under the formal SME model than under the dedicated team model (depending on the desired percentage of formal SME time to be devoted to automation support), the total cost of training will be two to four times higher.

Under the informal champion model, the expected training cost is mor difficult to predict as it depends on the rate employees choose to become trained as users (an inherently hard to predict variable for any given technology). For the equipment to receive sufficient trained user support, a higher number of trained users are required than by the formal SME model as the percentage of their time that can be expected to be dedicated to supporting the equipment is smaller.

Thus, if users choose to become trained at a high enough rate that the equipment receives sufficient support, training costs are expected to be higher under this model. If, on the other hand, users choose to become trained at a lower rate (particularly if a rate lower than turnover), training costs can be expected to be lower than under other models, but the cost reduction here is substantially lower in magnitude than will be the increased cost of downtime and reduction in value gained from FTE savings or program speed.

One notable factor also involved here is that under the dedicated team and formal SME models, the chance of losing all knowledge and experience is strongly dependent on the target number of trained users. If the chance of losing knowledge and experience can be approximated by the chance of losing all users in a single calendar year, it can be calculated as follows:

$$P_{KL,x} = {r_{Turnover}}^{N_T}$$

Where $P_{KL,x}$ is the probability of knowledge loss in year x, $r_{Turnover}$ is the turnover rate, and N_T is the target number of trained users. This can then be extended to calculate the probability that knowledge loss occurs at any point over the lifetime of the equipment:

$$P_{KL} = 1 - (1 - P_{KL,x})^t$$

Where P_{KL} is the probability of knowledge loss occurring at any point over the lifetime of the equipment and t is the expected lifetime of the equipment.

Using these equations one can find that even with two trained users, the probability of losing all knowledge at any point over the lifetime of the equipment is slightly lower than the turnover rate itself. With three trained users the probability of knowledge loss becomes a fraction of a percent, and with even higher numbers of users the chance is vanishingly small.

As a result, though there can be a substantial cost to get formal training from the equipment vendor if knowledge is lost, even with only two or three trained users that are replaced promptly after turnover, the expected value of this cost is insignificant. Though if new users are not being trained promptly when users turnover, as may occur under the informal champion model if the voluntary training rate is lower than the turnover rate, this training cost may need to be paid several times over during the lifetime of the equipment.

5.9 Cost of Downtime from Failure

Due to variation in the degree to which the equipment is properly maintained, HT support structure may have a meaningful impact in the expected cost of downtime due to failure. As touched on above in the section on support and maintenance costs, a dedicated team will know the equipment and the proper ways to use and maintain it very well. As a result, they are unlikely to misuse the equipment in a way that results in failure and are likely to keep the equipment maintained at the highest possible levels. This, in turn, leads to relatively low levels of expected downtime and correspondingly low associated cost.

Under a formal SME model, users are likely to have good understanding of the equipment and use good practices in equipment handling. If some aren't using the equipment frequently, though, they will be more likely to misuse the system in a way that causes downtime than would be users on a dedicated team. Formal SME users will also not be as familiar with equipment maintenance as a dedicated team, which may result in a greater number of failures

due to suboptimal maintenance and a greater average duration of failures if more issues must be solved by provider support staff that may not be able to provide on-site support for a month or more. Altogether, these factors will lead to increased frequency and duration of downtime, and accordingly a higher cost of downtime.

Under an informal champion model, the average level of expertise in equipment use and maintenance will be even lower than for the formal SME model. As such, the cost of downtime due to failure will be highest for an informal champion model due to increased frequency and duration of downtime.

5.10 Cost of Downtime from Turnover / Insufficient User Support

The cost of downtime due to insufficient user support will strongly depend on the HT support structure chosen. As with other factors, it will be low for a dedicated team model, high for an informal champion model, and intermediate for a formal SME model.

With a dedicated team, if a project has a need to use the equipment there will almost always be a team member available to support equipment use if the equipment itself is available. If the team is small and their capacity utilization is high, then one may expect some periods where insufficient support is available but provided a reasonable turnover rate these periods should not be frequent (with 2 team members and a turnover rate of the industry average 9.4%[34], the probability of user turnover any given year is 17.9%). They may, however, be of a moderate-to-long duration if the hiring and training process must be done end-to-end in order to restaff the team after turnover.

A formal SME model has an advantage in this aspect relative to the dedicated team model, as after turnover new users are likely to be recruited from the existing pool of department FTEs and thus only a short training period will be required to re-establish the target number of trained users. As the number of users needed under this model is higher, though, turnover will occur more frequently (with 5 SMEs and a turnover rate of 9.4%, the 2020 voluntary turnover rate in Process Development, the probability of user turnover any given year is 39.0%). Unless the target number of FTEs is set accounting for some amount of turnover, the incidence of insufficient support may be more frequent than desirable.

When the system is needed for a project, a user is also quite likely to be available to support the equipment. But the SMEs will be staffed on projects and have other demands on their time, and if FTE capacity utilization is high in the department, it may be tough to find an FTE with the capacity to support another project. The probability of finding available support will depend on the target number of trained users, which may need to be adjusted if the trained users are not available as often as would be desired.

The informal champion model is likely to result in the highest cost of downtime due to turnover and insufficient user support. As with the formal SME structure, users may have other high priority responsibilities to attend to and be unable to support when needed. There is also a higher likelihood that there are not enough trained users to support all need as the number of users is to some extent left up to chance (as it will depend on the relative rates of turnover and voluntary training). As discussed above in the section on the cost of training, with this model there is a higher likelihood of losing SME knowledge and support entirely. Should this occur, there would be no users at all to support any equipment need. And without internal trained users, the barrier to becoming trained is higher (as one must request and receive vendor training), further lowering the rate of voluntary training.

Even if the rate of voluntary training matches the rate of turnover, the number of trained users will fluctuate substantially as users that leave will not simply be immediately replaced as with a formal SME or dedicated team model. There is an element of stochasticity in user training. Accordingly, just by chance it can be expected that there will be frequent periods of insufficient support, the cost of which will not be made up for by the periods where the number of trained users exceeds the need. Though in the situation where turnover rate matches training rate one expects the same amount of time with excess users as with too few users, there is no value to excess users, but there is a cost to too few users. Also, if the average user number is sufficiently low that just by normal variability the user count may hit zero, the rate of voluntary training will then drop, and the original average user number will likely not be re-achieved.

Relatedly, an analog to downtime from insufficient user support is when, despite having available trained users, equipment is not used for a project because the scientist leading development is not familiar or comfortable enough with the high throughput technology to trust its use. A dedicated team can effectively counteract this hesitancy by taking time to educate other scientists and engineers across the department about the high throughput equipment and how it

has been used effectively on other projects. In helping them understand the advantages of the equipment and build trust that it can generate data that is equally reliable to conventional workflows, education can increase the speed of adoption and increase the rate of high throughput use on suitable projects.

Under a formal SME model, the SMEs may also have the time and expertise to employ education to increase adoption and use, even if not to the same extent of a dedicated team. Under an informal champion model, however, the champion(s) are likely to have less time to dedicate towards educating others. As a result, the departmental level of comfort with using high throughput technology for projects may be lower, adoption will be slower, and capacity utilization across the lifetime of the equipment may be lower as more scientists and project managers opt to use traditional workflows instead (even if trained support is available).

5.11 Ambr 250 Support Model Recommendations

Given the high potential value of investing in ambr 250 systems for CPD & PC, there is substantial value in ensuring the equipment receives proper support to allow it to operate at high capacity utilization and achieve its maximum potential useable life. Instituting a dedicated team model is most likely to successfully facilitate achieving high capacity utilization and maximum potential useable life, though a formal SME model would also serve the purpose well. Relying on an informal champion model, on the other hand, leaves much more up chance and puts the potential value attainable from implementing ambr 250 systems at risk. An informal champion model is therefore not recommended for the support of this equipment.

6 Applicability Across Firms and Industries

Though this work focused specifically on process development at Amgen, the frameworks developed herein are broadly applicable to many types of organizations, from R&D to manufacturing to the service sector. In any industry where high throughput technologies or automation exist, these frameworks can be used to identify promising opportunities for their implementation, quantify the value they can provide to determine if investment is worthwhile, and decide how they should be supported to maximize the value realized by the organization.

6.1 Biopharmaceutical Industry

There are a range of connections of this work to biopharmaceutical R&D across firms. To start, those which conduct a large series of experiments in traditional benchtop bioreactors should apply the methodologies described here to their own operations to determine whether ambr 250 can provide substantial value in their organizations.

As illustrated in Chapter 3, however, there may be numerous promising opportunities for implementation of high throughput technologies across an organization. This is particularly true of biopharmaceutical companies, for which there is a high prevalence of repeated, parallelizable tasks done by high-skilled employees. Biopharmaceutical companies should investigate these opportunities in all aspects of R&D: in designing novel therapeutics, in evaluating therapeutic performance in-vitro, and in process development for both drug substance and drug product. Another function where promising opportunities may exist is in quality control.

Biopharmaceutical companies should also apply the framework for determining optimal staffing support structures not only to new equipment under consideration, but also to existing systems. It should not be presumed that legacy support structures (which may have been selected initially for convenience) are optimal in the long-term.

6.2 Other R&D-Focused and Laboratory-Based Organizations

In the same way that the frameworks developed here are applicable to the biopharmaceutical industry, they are also applicable to all other organization with substantial R&D operations. The connection to the chemicals industry is most direct, but these tools can also be used in industries such as flavors and fragrances, cosmetics, packaged foods, and even some consumer packaged goods (such as toothpaste) that involve substantial formulation development and product testing.

Other organizations with heavy laboratory operations could also benefit from the use of these frameworks. Companies such as LabCorp and Quest Diagnostics run a wide variety of laboratory tests on countless specimens daily. Such organization could follow these methodologies to determine which tests on which equipment would be most promising for implementation of high throughput technologies, which solutions provide the most value, and how to provide staffing support for optimal return.

6.3 Manufacturing

Manufacturing is fundamentally characterized by repeated, parallelizable tasks and large capital expenditure on equipment is generally necessary for the operation. As such, manufacturing operations can apply the frameworks described above to help guide equipment purchasing decisions, both in the initial build-out of the manufacturing site and in considering where it might be worth upgrading legacy equipment. In particular, the framework for identifying promising opportunities for high throughput technologies described in Chapter 3 can help existing operations with long, complex processes and aging equipment determine what stages of the operation would be a good place to start integrating novel technologies. And in evaluating options and making purchasing decisions, the framework from Chapter 4 can be used to make sure all relevant factors, both direct and indirect are accounted for.

6.4 Warehousing

With the growing availability of warehousing automation technologies, warehouses facing capacity and labor constraints are increasingly turning to automation to increase space efficiency and reduce labor requirements[35]. Decisions of whether to adopt expensive automation

technologies that are core to the business should not be made without considering all associated sources of cost and value. The framework established in Chapter 4 for quantifying both direct and indirect costs and savings can be used for assessing different technologies and determining whether it would be valuable to make the investment in implementing automation.

What's more, these automation technologies are likely to be core to the operation if implemented. As such, a dedicated team staffing support model is likely to be important for maximizing the value realized from investment in warehousing automation, particularly through minimizing the costs of downtime. The framework developed in Chapter 5 can be applied to an operation's individual case, though, to make sure that the additional labor cost is worth employing this model over the formal SME model.

6.5 Service-Sector Industries

Automation is also becoming increasingly available and valuable in service-sector businesses. While the number of unemployed workers had dropped back to pre-pandemic levels, the number of unfilled jobs has increased substantially, leaving a labor supply gap of over 5 million positions, much of this in the service-sector[36]. For businesses that may not be able to afford raising wages enough to attract sufficient labor in such a market, automation provides an attractive alternative and has been increasingly utilized in service roles where complex social and emotional skills are not required[37].

One example of such automation use comes from Spyce, a Boston-based salad & bowl restaurant that developed a technology to automate the entire process of building a customized bowl, which is done manually at competitors. In 2021, Spyce was acquired by the salad chain Sweetgreen with the intention to implement Spyce automation technology in its restaurants[38].

The framework described in Chapter 4 above for quantifying the direct value that can be derived from high throughput technologies and factoring in indirect sources of cost and value could be very helpful for service-sector businesses considering adopting automation in light of labor supply shortages. This is true both for individual service sector businesses evaluating the purchase of external automation equipment and for large organizations like Sweetgreen evaluating the acquisition of a company for the use of its automation technology or determining whether and where to integrate the technology once the acquisition is a sunk cost.

6.6 Emerging Cell-Based Tech Industry

Many new cell-based technology companies have recently been founded to use engineered cells to produce a wide range of products, including egg and milk proteins, sweeteners, flavors, leather, fibers, collagen & gelatin, human breast milk, and even meat[39,40]. These are often categorized under the umbrella "cellular agriculture," defined as the controlled manufacture of agricultural products with cells and tissues without plant or animal involvement[39]. Such businesses require extensive R&D in developing products and gaining regulatory approval for their processes. And as their products are produced through the culture of cells in bioreactors, the parallels to the biologics drug substance process development analyzed above are strong.

As these companies are young and fast-growing, they are not burdened by legacy systems and equipment. They can therefore design R&D groups with high throughput technology integrated from the outset. The frameworks developed in Chapters 3 and 4 can help these firms identify promising opportunities to integrate HTT into their workflow design and evaluate the various available solutions to guide investment decisions.

And since these companies are fast-growing their organizational structures may change rapidly. When these organizational changes occur, the staffing support model for high throughput technology that optimizes value for the organization may changes as well. From the initial design and as these changes occur, the framework developed in Chapter 5 can be applied to ensure any high throughput technology invested in is appropriately supported.

7 Conclusions

In the face of increasing competition, increasing pipeline complexity, and increasing resource requirements for bringing new drugs to market, streamlining process development is an important means of controlling costs and achieving competitive advantage in the biopharmaceutical industry. And given the waning dominance of the monoclonal antibody modality in the pipelines of biologic drug developers, biotechnology companies with a history of operational excellence can no longer rely on their platform processes and mAb expertise to maintain process development advantage.

One potential means of achieving the necessary improvements in process development is through the implementation of high throughput technology. It is important, however, that implementation of these solutions is globally optimized across the process development organization rather than having applications deployed piecemeal within specific functions.

To determine how to ensure high throughput technologies are deployed intelligently, a framework was developed for identifying promising opportunities for use of high throughput technologies and quantifying the value that can be derived from their implementation. This framework was then applied to Amgen's Biologics DST group.

Through mapping and analyzing the workflows of Amgen's Biologics DST group, the implementation of Sartorius ambr 250 systems for upstream process development and characterization was identified as a promising high opportunity for use of high throughput technology. A detailed NPV analysis was then performed to show that investment in ambr 250 systems is likely to yield a positive NPV, though the expected NPV depends strongly on both the expected useful lifetime of the systems and their capacity utilization.

The systems were also found able to provide substantial value not captured in the NPV calculations, including cutting 6.5 weeks off development time for projects where process development is on the critical path. Using ambr 250 for PC on such programs could translate to over $10 million in increased sales per week of sales gained.

A framework was also developed for assessing how three models of staffing support for high throughput technologies affect the value that can be derived from their implementation. This framework was applied to the use of ambr 250 in upstream process development to determine how to realize the maximum possible value from investment in these systems. This

assessment found that a dedicated team model is most likely to successfully facilitate the high capacity utilization and maximum potential useable life that are crucial for achieving positive NPV. A formal SME model may also achieve these goals at lower cost, though at higher risk. The recommended path forward is to purchase one or two ambr systems to use in CPD and to establish whether they can be used for PC. Once it is established that the ambr 250 can be used for PC, it is recommended that the existing systems be used immediately thereafter on projects for which increased development speed can increase speed to market, and that a third system be purchased to expand capacity.

Though this work focused specifically on process development at Amgen, the frameworks developed herein are broadly applicable to many types of organizations, from R&D to manufacturing to the service sector. In any industry where high throughput technologies exist, these frameworks can be used to identify promising opportunities for their implementation, quantify the value they can provide to determine if investment is worthwhile, and decide how they should be supported to maximize the value realized by the organization.

Appendix 1 – NPV Calculations for Figures

To calculate NPV for a given investment in ambr systems, the following factors were accounted for. Precise values are not provided for some variables to protect proprietary information.

Factor	**Value**
Value of labor cost reductions	$390,000 – $1,010,000 per year
Sartorius maintenance contract cost	$20,000 - 50,000 per year per ambr
Labor cost for setup & qualification	$220,000 for one ambr plus $110,000 for each additional ambr
Ambr purchase cost	$1,000,000 - $3,000,000 per ambr
OSE	35% of labor costs or savings
Lifetime for depreciation	10 years
Tax rate	21%
Discount rate	8%
FTE labor cost	$250,000 per year (for 45 weeks of labor)

Based on the above factors, cash flows from costs and savings were estimated for each year over the lifetime of the system. The NPV was then calculated according to the following formula, where n is system lifetime in years and r is the discount rate:

$$NPV = \sum_{t=0}^{n} \frac{Cash\ flow_t}{(1+r)^t}$$

If it is assumed that each ambr has a maximum of 45 weeks of available capacity per year and the equipment is fully utilized if there are sufficient pipeline projects, the following NPV was calculated for expected lifetime values ranging from one to twenty years. The below data, for the use of one ambr for CPD only, were used to generate Figure 7.

Table A1: NPV of investing in varying numbers of ambr systems for use in CPD and/or PC experiments by expected system lifetime

	NPV ($MM)																			
Expected Lifetime (yr)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1 ambr for CPD only	(1.59)	(1.31)	(1.04)	(0.79)	(0.56)	(0.35)	(0.16)	0.02	0.19	0.35	0.46	0.56	0.65	0.74	0.82	0.89	0.96	1.03	1.08	1.14
ambr for all projects, CPD only	(3.26)	(2.83)	(2.44)	(2.07)	(1.74)	(1.42)	(1.13)	(0.87)	(0.62)	(0.39)	(0.21)	(0.04)	0.11	0.26	0.39	0.51	0.63	0.73	0.83	0.92
ambr for all projects, CPD & PC	(4.73)	(4.03)	(3.39)	(2.79)	(2.23)	(1.72)	(1.24)	(0.80)	(0.40)	(0.02)	0.28	0.56	0.82	1.06	1.28	1.48	1.67	1.85	2.01	2.16

To generate NPV as a function of both capacity utilization and lifetime, (used for Figure 8, Figure 10, Figure 13, & Figure 14), the data in Table A1 were adjusted to reflect different levels of capacity utilization ranging from 10% - 100% (in increments of 2%). This resulted in a 20-cell x 46-cell table of NPVs for each configuration of ambr use. The NPV values across different configurations were then compared to find breakeven capacity utilization for investment in an additional ambr system (used for Figure 9, Figure 11, & Figure 12).

References

1. Using pharmaceutical manufacturing to compete | McKinsey. https://www.mckinsey.com/industries/life-sciences/our-insights/operations-as-a-competitive-advantage-in-biotechnology.
2. IDBS, R. Q. Integrating Siloed Systems: Making The Most Of Automation. *Pharmaceutical Processing World* https://www.pharmaceuticalprocessingworld.com/integrating-siloed-systems-making-the-most-of-automation-2/ (2018).
3. Kesik-Brodacka, M. Progress in biopharmaceutical development. *Biotechnol. Appl. Biochem.* **65**, 306–322 (2018).
4. Timmick, S. M. Strategies for the Development of Integrated Purification Processes for Non-Platform Biologic Therapeutics. (Rensselaer Polytechnic Institute, 2017).
5. About Amgen. *Amgen* https://www.amgen.com/about.
6. Dunleavy, K. The top 20 pharma companies by 2021 revenue. *Fierce Pharma* https://www.fiercepharma.com/special-reports/top-20-pharma-companies-2021-revenue (2022).
7. Amgen Products. *Amgen* https://www.amgen.com/products.
8. The Shape of Drugs to Come. https://www.amgen.com/stories/2018/08/the-shape-of-drugs-to-come.
9. Learn More About the Shape of Drugs to Come on AmgenScience.com. https://www.amgen.com/stories/2017/07/the-shape-of-drugs-to-come.
10. Amgen Pipeline. https://www.amgenpipeline.com.

11. Shukla, A. A., Hubbard, B., Tressel, T., Guhan, S. & Low, D. Downstream processing of monoclonal antibodies—Application of platform approaches. *J. Chromatogr. B* **848**, 28–39 (2007).

12. Bloom, N. Are Ideas Getting Harder to Find? *Am. Econ. Rev.* **110**, (2020).

13. Ringel, M. S., Scannell, J. W., Baedeker, M. & Schulze, U. Breaking Eroom's Law. *Nat. Rev. Drug Discov.* **19**, 833–834 (2020).

14. Industry Profile 2022. https://phrma.org/resource-center/Topics/Research-and-Development/Industry-Profile-2022.

15. Next-generation platform technologies are driving the biotech VC surge | McKinsey. https://www.mckinsey.com/industries/life-sciences/our-insights/what-are-the-biotech-investment-themes-that-will-shape-the-industry.

16. Innovation in the Biopharmaceutical Pipeline. https://phrma.org/resource-center/Topics/Innovation/Innovation-in-the-Biopharmaceutical-Pipeline.

17. Hanke, A. T. & Ottens, M. Purifying biopharmaceuticals: knowledge-based chromatographic process development. *Trends Biotechnol.* **32**, 210–220 (2014).

18. Diederich, P., Hoffmann, M. & Hubbuch, J. High-throughput process development of purification alternatives for the protein avidin. *Biotechnol. Prog.* **31**, 957–973 (2015).

19. Bhambure, R., Kumar, K. & Rathore, A. S. High-throughput process development for biopharmaceutical drug substances. *Trends Biotechnol.* **29**, 127–135 (2011).

20. Gardner, C. R. *et al.* Application of high throughput technologies to drug substance and drug product development. *Comput. Chem. Eng.* **28**, 943–953 (2004).

21. Rustia, M. D. B. Augmenting drug process development capacity through applications of lean principles and high throughput technology. (Massachusetts Institute of Technology, 2018).

22. Sharma, A., Kumar, N., Kuppermann, B. D., Francesco, B. & Loewenstein, A. Biologics, biosilimars, and biobetters: different terms or different drugs? *Eye* **33**, 1032–1034 (2019).

23. Ambr® 15 Cell Culture Bioreactor System. *Sartorius* https://www.sartorius.com/en/products/fermentation-bioreactors/ambr-multi-parallel-bioreactors/ambr-15-cell-culture (143AD).

24. Ambr® 250 high throughput - Multi-Parallel Bioreactor. *Sartorius* https://www.sartorius.com/en/products/fermentation-bioreactors/ambr-multi-parallel-bioreactors/ambr-250-high-throughput (2021).

25. Bareither, R. & Pollard, D. A review of advanced small-scale parallel bioreactor technology for accelerated process development: Current state and future need. *Biotechnol. Prog.* **27**, 2–14 (2011).

26. Bench-scale bioreactors for research and development | INFORS HT. https://www.infors-ht.com/en/bioreactors/bench-top-bioreactors/.

27. Bareither, R., Bargh, N., Oakeshott, R., Watts, K. & Pollard, D. Automated disposable small scale reactor for high throughput bioprocess development: A proof of concept study. *Biotechnol. Bioeng.* **110**, 3126–3138 (2013).

28. Delouvroy, F. *et al.* ambr™ Mini-bioreactor as a high-throughput tool for culture process development to accelerate transfer to stainless steel manufacturing scale: comparability study from process performance to product quality attributes. *BMC Proc.* **9**, P78 (2015).

29. Tai, M., Ly, A., Leung, I. & Nayar, G. Efficient high-throughput biological process characterization: Definitive screening design with the Ambr250 bioreactor system. *Biotechnol. Prog.* **31**, 1388–1395 (2015).

30. Pollard, J., McDonald, P. & Hesslein, A. Lessons learned in building high-throughput process development capabilities. *Eng. Life Sci.* **16**, 93–98 (2016).

31. Bulletin, L. N. from L. TAP Launches New Micro Bioreactor System featuring Vi-CELL. *www.labbulletin.com* https://www.labbulletin.com/articles/tap-launches-new-micro-bioreactor-system-featuring-vi-cell (2023).

32. Amgen Inc. (AMGN) Stock Price, News, Quote & History - Yahoo Finance. https://finance.yahoo.com/quote/AMGN/.

33. Recommended U.S. Equity Risk Premium and Corresponding Risk-Free Rates. *Kroll, LLC* https://www.kroll.com/en/insights/publications/cost-of-capital/recommended-us-equity-risk-premium-and-corresponding-risk-free-rates.

34. Turnover Rates by Industry, Location & Role in 2022. https://www.praisidio.com/turnover-rates.

35. State of the Third-Party Logistics Industry Report. https://www.extensiv.com/resource-library/report/state-of-the-third-party-logistics-industry-report.

36. Ferguson, S. Understanding America's Labor Shortage. https://www.uschamber.com/workforce/understanding-americas-labor-shortage (2023).

37. Wirtz, J., Kunz, W. & Paluch, S. The Service Revolution, Intelligent Automation and Service Robots. 38–44 (2021).

38. Heater, B. Salad chain Sweetgreen buys kitchen robotics startup Spyce. *TechCrunch* https://techcrunch.com/2021/08/25/salad-chain-sweetgreen-buys-kitchen-robotics-startup-spyce/ (2021).

39. Eibl, R. *et al.* Cellular Agriculture: Opportunities and Challenges. *Annu. Rev. Food Sci. Technol.* **12**, 51–73 (2021).

40. Cellular agriculture industrial biotechnology for food and materials | Elsevier Enhanced Reader. https://reader.elsevier.com/reader/sd/pii/S0958166919301417?token=5B41C97C8A30AC8D762BCBF08FAA3B3A336494C4BB2FB486DFD2EA4D4BF91D21F1D82D25F2B2EB0B10A71035C18D8DCC&originRegion=us-east-1&originCreation=20230312121021 doi:10.1016/j.copbio.2019.12.003.