Alignment Strategies for Drug Product Process Development and Manufacturing

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By Christopher Garvin

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Abstract

The transfer of information between the drug product development and manufacturing organizations is fundamental to drug product commercialization. This information is used to characterize the product-process interaction and ensure manufacturability, and to set operating ranges at fill/finish sites. Amgen has successfully commercialized drug products for years, yet opportunities exist to improve the efficiency of process development and technology transfer, and to better align the equipment, procedures, and data collection of the groups involved in these activities.

We identify improvement opportunities and develop a strategic approach, which we term the "Pilot Plant Cooperative," to enable more efficient and effective commercialization. The benefits of this strategy are assessed in three case studies: (1) a capital investment project for new laboratory filling equipment, (2) enhanced data generation in clinical manufacturing, and (3) efficiency improvements in early-stage process development studies. Based on these studies, we make specific recommendations for future work. We make additional procedural and cultural recommendations, including revising capital investment processes and implementing alignment-focused incentives and hiring practices, to ensure widespread alignment is achieved and maintained.

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1 Introduction

1.1 Project Drivers

Amgen has experienced rapid growth over the past two decades, with revenues increasing more than 100-fold since 1995[1]. Accompanying the growing sales has been a quickly expanding workforce; during that same time frame, the number of employees has risen from fewer than 3,000 to nearly 20,000[1]. Fueling the growth has been Amgen's successful product portfolio and pipeline, both of which have necessitated operational expansion to keep pace with patient and clinical demand. However, Amgen's growth, while a boon to the company's financial position, has brought with it challenges unprecedented in the company's short history.

Among the challenges facing Amgen is the increasing complexity of the company's drug product development and manufacturing operations network. These organizations have expanded globally, creating geographic and cultural barriers to accompany already-existing functional barriers. As a result, effective communication has been inhibited, and the organizations have followed progressively divergent paths, leading to misalignment of procedures, equipment, and data collection. Former CEO Gordon Binder acknowledged that this reality had set in throughout the company, asserting that "at times, our policies didn't keep pace [with the rapid growth] (Binder, 2008)." He further noted that consensus, at one time a tenet observed by most Amgen employees, became chaotic as the company grew, resulting in more independent decision-making (Binder, 2008).

Despite the mounting complexity and misalignment, Amgen has continued to produce high-quality drug product while meeting customer demand. However, the drug product development and manufacturing organizations find themselves at the precipice of a tipping point. Further global expansion is underway, and the company's pipeline is filling with promising products. As of early 2012, Amgen has 18 products in Phase 1, 13 in Phase 2, and 12 in Phase 3 (Amgen, Inc., 2012). Assuming typical clinical

[1] Source: COMPUSTAT

success rates[2], the current pipeline should yield roughly 13 commercial products over the next decade. Even after subtracting the existing commercial products in trials for other indications, seven new molecular entities are likely to join Amgen's commercial product portfolio. To further compound the challenges presented by a suite of new products, many of the products are formulated at high concentrations and require an array of new SKUs, each increasing the already heavy development and manufacturing workload. To effectively handle these new products while continuing to support existing commercial products, Amgen will need to operate more efficiently. This means maintaining high quality standards and operational consistency while reducing time, labor, and cost per unit.

Amgen's mission is "serving every patient every time." Accomplishing this will require a dedication by all groups across the Drug Product Network to institute a more efficient and robust commercialization process, ensuring that product launches are successful and patient supply is maintained. This project aims to create a strategy that does just that. The intended outcome is enhanced collaboration among the Drug Product Network groups and promotion of more efficient generation and transfer of the highest quality data possible to abet commercialization. In order to have a complete and lasting impact, the strategy must be holistic, covering the entire network, and should be forward-looking, setting in motion steps to sustain long-term alignment and efficiency regardless of Amgen's future path.

1.2 Problem Statement

Amgen's drug product manufacturing and development network is faced with growing organizational complexity and operational challenges that could impede efficient process scale-up and commercialization. This project investigates strategies that would improve process robustness, reliability, and consistency while minimizing cost. In doing so, these strategies should also promote better understanding of process-product interdependencies and facilitate cross-network communication.

[2] Eventual commercialization probabilities = ~15% for Phase 1 drugs, ~24% for Phase 2 drugs, and ~60% for Phase 3 drugs (Bogdan & Villiger, 2010).

2 Background

2.1 Biotechnology Industry

The healthcare biotechnology industry consists of companies that participate in the development, manufacturing, distribution, and/or sale of biologics. Biologics are drugs derived from living organisms and include therapeutic proteins, DNA vaccines, monoclonal antibodies and peptibodies, as well as newer modalities such as gene therapy and stem cell therapy (Data Monitor, 2011). A biologic typically requires 10-15 years to transition from discovery to market, including clinical trials and FDA approval, and companies incur significant costs in doing so. Furthermore, only a fraction of drug discoveries ever reach the commercial marketplace, so healthcare biotechnology companies must rely on the revenues from the drugs that do to cover the costs associated with both the successes and failures (Suresh & Basu, 2008).

The biotechnology industry first emerged in the 1970s with the development of recombinant DNA technology and the generation of monoclonal antibodies (mAbs). The recombinant techniques allow for the transformation of DNA sequences into protein-based drugs that resemble natural substances and have been shown to work with higher potency and more precision than traditional "small-molecule" drugs (Kamarck, 2006). In addition, these drugs have the potential to cure diseases rather than just treat symptoms (Sekhon, 2010). The biotechnology market has grown steadily over the past five years (CAGR ~10%), resulting in U.S. healthcare biotechnology revenues of $57 billion in 2010 (Data Monitor, 2011). As a result, biologics constitute roughly one-third of all drugs currently in development (Sekhon, 2010). This growth is attributed to new product development, a favorable regulatory environment, an aging population, and increased access to capital (Snyder, 2011).

The future of the biotechnology industry will likely be shaped a combination of emerging and long-standing factors. The new trends include the threat of biosimilars after patent expiry, the increasingly active mergers and acquisitions environment, consolidation with large pharmaceutical companies, government and consumer demand for lower prescription drug prices, the impact of demand

for personalized medicine, and changing disease trends (Silver, 2012). Additionally, the importance to the industry of the regulatory environment is ever relevant. How a company navigates this environment while dealing with the emerging trends will largely dictate that company's long-term success (Silver, 2012).

2.2 Amgen, Inc.

Amgen, Inc. was founded in 1980 and has grown to become the world's largest independent biotechnology company, with $15.3 billion in revenue during the 2011 fiscal year. The company's sole business unit is human therapeutics, and within this segment sales are dominated by five products: Aranesp, Epogen, Neulasta, Neupogen, and Enbrel. Research and development efforts are focused on "novel therapeutics for the treatment of grievous illness in the areas of inflammation, oncology and hematology, neuroscience, and metabolic disorders (Amgen, Inc., 2012)."

Amgen has experienced rapid sales growth over the past two decades and has responded by expanding its operations from its headquarters in Thousand Oaks, CA, to other parts of the U.S. and world, including drug product manufacturing facilities in Juncos, Puerto Rico, and Dun Laoghaire, Ireland. In recent years, growth has been accompanied by stagnant operating margins (Figure 1), and Amgen has responded by undertaking a number of cost-cutting measures as a way to improve operational efficiency. With over forty drug candidates in its pipeline, the degree to which this efficiency can be improved will play an important role in the company's long-term financial and operational well-being.

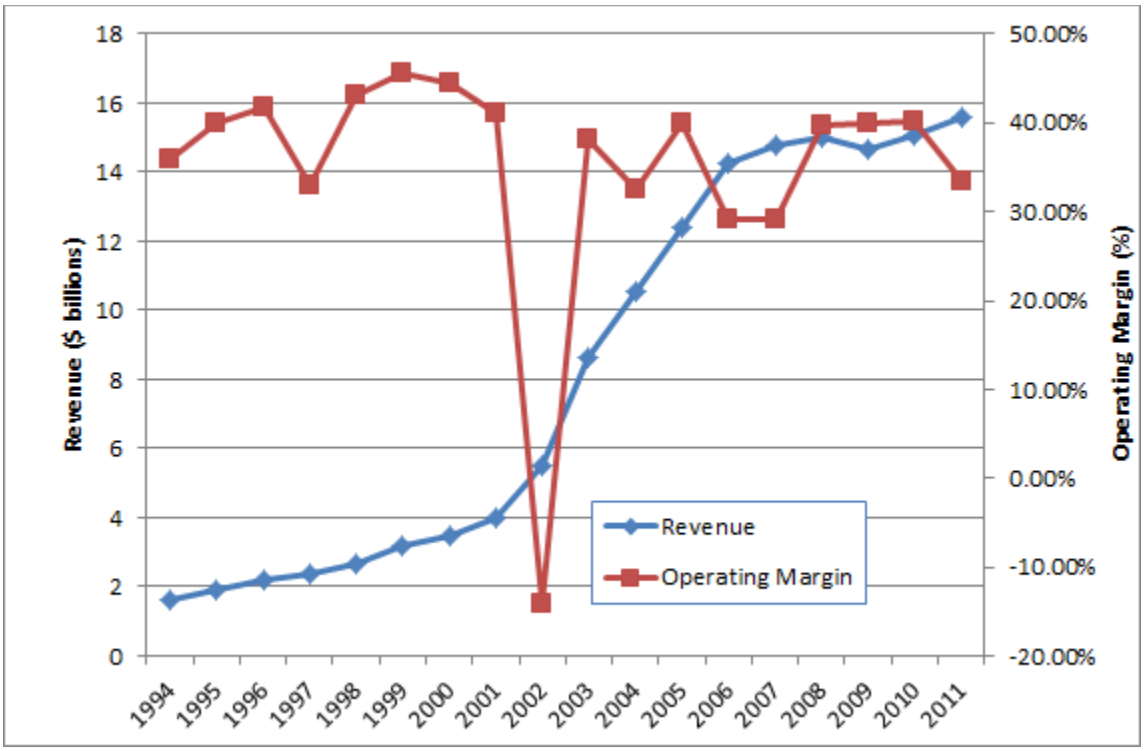


Figure 1: Amgen's annual revenue and operating margin since 1994 (Edgar Online, 2012).

2.2.1 Drug Product Development and Manufacturing Network

The Drug Product segment of Amgen's business is comprised of the formulation, fill, and finish (FFF) activities. Typical FFF processing includes Drug Substance (DS) freeze, storage, transport, and thaw; Drug Product (DP) formulation and mixing; bioburden filtration, cold room hold, and sterile filtration; product filling (into vials, syringes, or cartridges); lyophilization (i.e., freeze-drying); manual or automatic inspection for particles and defects; labeling, packaging, cartoning, and shipping. The purpose of these activities is to convert bulk drug substance into the dosage and presentation required by the doctors and patients around the world to which the product is ultimately shipped. In essence, the Drug Product organization is tasked with "assuring that Amgen medicines rapidly, reliably, and safely reach patients (Amgen, Inc., 2012)."

The project scope is centered on a network of four functional groups – known collectively as the Drug Product Process Development and Manufacturing Network (shortened here to "DP Network") – that

work together to commercialize[3] Amgen's drug products. These groups are Drug Product Development, Drug Product Engineering, Clinical Manufacturing, and Commercial Manufacturing. Other groups (e.g. Quality Assurance) are also involved in drug product commercialization but fall outside the scope of this project.

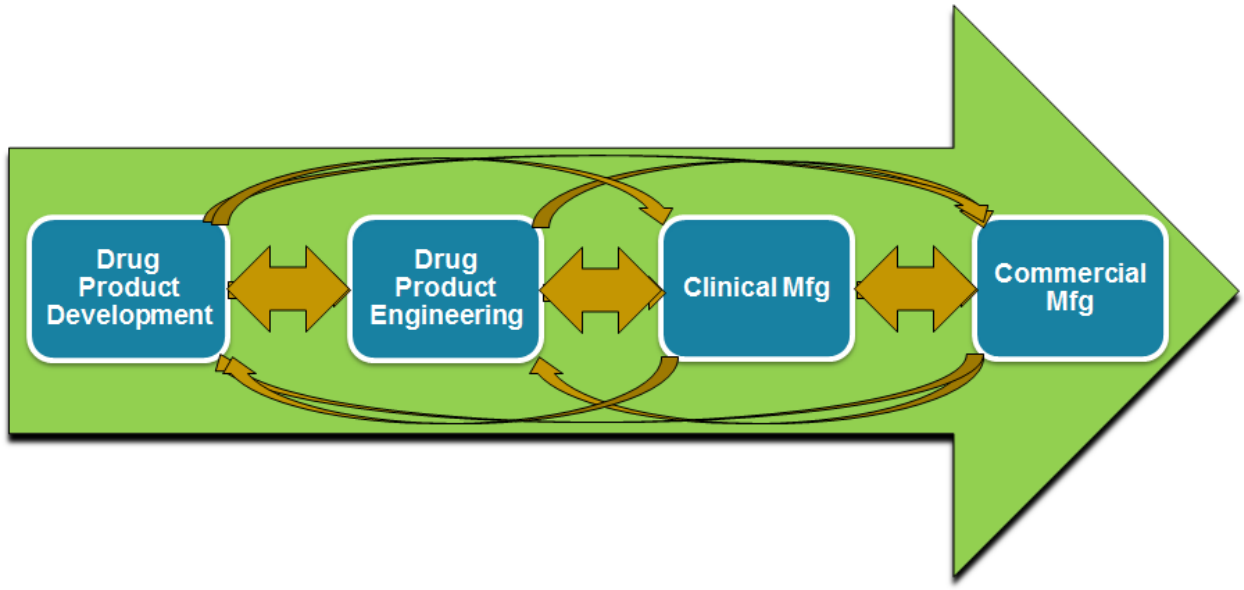


Figure 2: Schematic diagram of information flow during drug product commercialization

Amgen employs a decentralized development and manufacturing network; drug product development work is performed at Thousand Oaks, CA (ATO), and Seattle, WA (AWA), clinical manufacturing takes place in ATO, commercial manufacturing in Juncos, PR (AML) and in Dun Laoghaire, Ireland (ADL), and the warehouse and distribution centers are located in AML, ADL, and Breda, Netherlands (ABR). These geographically diverse groups and linked together through "Global Network Teams," a recently-introduced concept that encourages sharing of information and best practices across Amgen's network. Each of the four major groups in the DP Network is described in the following sections.

[3] We define "commercialization" as the act of developing a process and transferring it to a commercial manufacturing site

2.2.1.1 Drug Product Development

Drug Product Development (DPD) is responsible for developing and evaluating formulations for Amgen's pipeline products. In the early stages, this means ensuring platform formulation[4] compatibility with each new drug product through stability studies. Later, during commercial formulation development (CFD) activities, DPD performs a set of studies on commercial formulation candidates to identify the most robust formulation for a given product. DPD's CFD studies typically include a kinetic particle study (to define particulation propensity in a formulation), a buffer study, a pH and excipient study, and a protein concentration study. The combined results from these studies are used to pare down the list of candidate formulations to a subset that will undergo scale-down studies. DPD also develops appropriate assays and determines acceptable assay result ranges to support product characterization activities. Finally, DPD continues its support post-commercialization in areas such as clinical dosing, non-conformance investigations, and life-cycle management activities.

2.2.1.2 Drug Product Engineering

Drug Product Engineering (DPE) acts in a process development and manufacturing support capacity. DPE performs process evaluation studies to assess drug product manufacturability of the formulation recommended by DPD. Based on its studies, DPE makes procedural and equipment setting recommendations to Clinical and Commercial Manufacturing and then continues to support DP manufacturing through technology transfer and non-conformance investigations.

During early-stage (FIH) development, DPE typically performs a set of studies to prepare for product introduction to Clinical Manufacturing. DPE performs an expanded set of studies during Commercial Process Development (CPD), using DPD's recommended formulation. Additionally, in CPD, DPE makes a commercial DP container (SKU) recommendation. During Process Characterization (PC), the final development stage prior to validation, DPE conducts characterization studies to prepare for

[4] Monoclonal antibody products will often use Amgen's "platform formulation," a solution with a defined combination of components with set concentrations at a specific pH.

manufacturing at the commercial site. DPE's output includes identification of relevant performance and operating parameters for the commercial process, along with characterization of each parameter as "critical," "key," or "non-key," In-Process Control (IPC) definition and action limit determination, operating parameter ranges, and data to support regulatory filings.

2.2.1.3 Clinical Manufacturing

Clinical Manufacturing produces material using commercial-like equipment for Amgen's clinical drug trials, as well as for toxicology and stability testing. The group is able to perform all unit operations from DP thaw through inspection and has the capability to fill both vials and syringes. The final few unit operations – labeling, packaging, and shipping – are also conducted by the Clinical Manufacturing group, albeit in a separate building on the ATO campus.

Clinical Manufacturing also participates in technology transfer activities, ensuring all manufacturing concerns are addressed prior to introduction of a new product to the facility. During product manufacturing, the group performs all required procedures and files non-conformances when appropriate. The group then plays an important role in investigating root causes of issues (working closely with DPE or DPD while doing so) and making sure the process is completed while adhering to Amgen's quality requirements.

2.2.1.4 Commercial Manufacturing

Amgen currently produces drug product for commercial sale internally at AML and externally at a number of contract manufacturing facilities. With the recent purchase of a commercial manufacturing and warehouse facility in Ireland, however, Amgen's internal capabilities are expanding. This project's scope includes all of Amgen's internal facilities but excludes contract facilities.

In Amgen's manufacturing model, commercial manufacturing begins with production of drug substance at one of the company's manufacturing sites (Rhode Island, Colorado, or Puerto Rico), where, upon completion, it is frozen and shipped to a DP manufacturing site. Commercial Manufacturing thaws,

formulates, filters, fills, lyophilizes (when appropriate), and inspects the product. The finished product is then shipped to ABR for international distribution, or shipped to customers directly from AML.

2.2.2 Stages of Development

While the FFF process is generally consistent from one product to the next, the specific processing conditions may differ depending on unique product needs. Once a product's formulation is determined, process development studies are designed to gain an understanding of manufacturing equipment and procedural requirements. These requirements are refined over the course of three development stages and through clinical manufacturing experience. The three stages are known as First-in-Human (FIH), Commercial Process Development (CPD), and Process Characterization (PC). Each of the three stages is described below.

2.2.2.1 First-in-Human

The purpose of the First-in-Human (FIH) development stage is to prepare for manufacturing of Phase 1 drug product material for clinical trials. It includes a formulation recommendation and assay development by DPD, a set of process evaluation studies performed by DPE to ensure manufacturability in the chosen formulation, and production of drug product by Clinical Manufacturing (including a reference standard, lead lot for stability testing, definitive toxicology lot, and clinical fills for Phase 1a/1b).

2.2.2.2 Commercial Process Development

Commercial Process Development (CPD) includes all activities required to develop and scale-up the DP manufacturing process for late-stage clinical and commercial production. During CPD, the anticipated commercial process is developed prior to manufacturing Phase 3 clinical supplies. CPD formally starts with the Commercial Formulation Recommendation (CFR) from DPD (see "Drug Product Development" section above for additional information on the CFR). The CFR is based on three factors: a recommendation of three-to-five top formulation candidates (based on screening studies); formulation

scale-down studies that include a transportation and handling assessment and a stability evaluation; and verification of resource availability from all functional areas.

From the standpoint of the development timeline, CPD is initiated at the start of Phase 2. The planning and implementation occurs throughout Phase 2 and leads directly to Pivotal Campaign Initiation, and Process Characterization, at the start of Phase 3. During this timeframe, additional CPD studies are performed and used to provide data that feed into the Process Characterization risk assessment. Concurrently, a commercial DP container recommendation is also made based on the CFR and the pivotal SKU recommendation. Finally, transportation, and primary and secondary packaging tests are conducted to close out the required CPD activities.

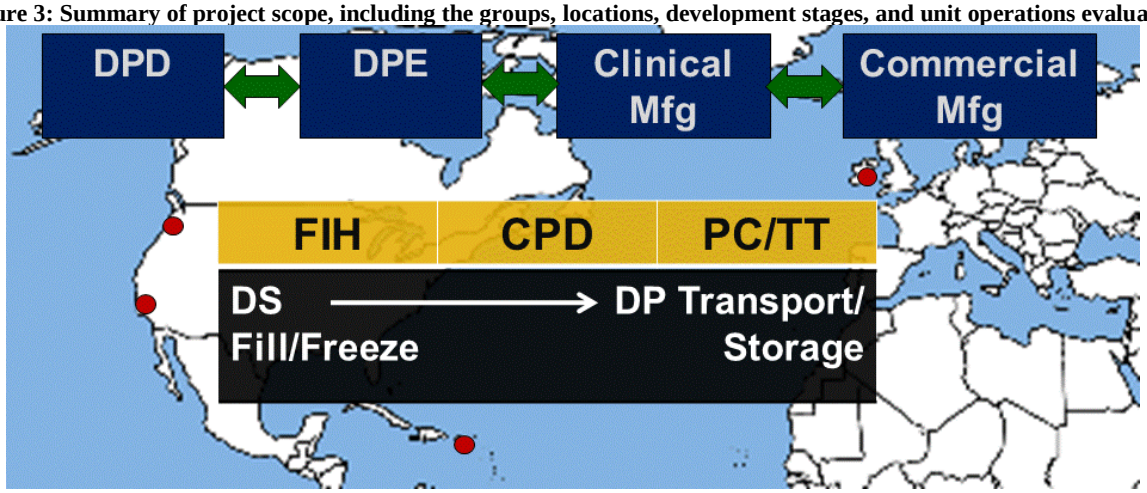
2.2.3 Process Characterization

Process Characterization (PC) is the final stage of development prior to process validation and takes place during Phase 3. It involves the additional studies and technical assessments required to characterize the commercial process before validation commences. The work performed during PC helps Amgen develop a thorough understanding of the manufacturing process parameters for each product as it approaches commercial launch. In principle, the goal of PC is to implement a well-designed and robust commercial process and control strategy. More specifically, this means identifying relevant operating and performance parameters; categorizing parameters as critical, key, and non-key; setting action and control limits; and defining operating parameter ranges (which include a characterization range, an acceptable range, and an operating range).

PC generally involves studies and technical assessments designed to characterize and investigate the robustness of the commercial process. The studies to be performed are documented in a PC plan after being determined based on the output of a risk assessment. The process development and manufacturing groups work together to determine the process operating and performance parameters, and risk assessments are performed based on available development and manufacturing information.

PC studies are performed at both the development site (in labs or a pilot plant) and at the commercial site. The latter is needed because of equipment design and capability differences between the development and commercial site and are only performed once a commercial site has been selected and commercial SKUs and manufacturing scale have been confirmed. The PC and CPD study results, along with FMEA (failure mode and effects analysis – a risk assessment method) input, and manufacturing and development history, are used by process development to generate technical assessments and a process characterization summary report in which the important parameters, limits, and ranges are identified. The studies performed can differ for each new product and are based on FMEA-determined high-risk areas.

Figure 3: Summary of project scope, including the groups, locations, development stages, and unit operations evaluated.



3 Project Motivation and Literature Review

"The traditional, nonintegrated, hierarchical life science organizations tend to work in a Commons-like way. The pool of resource is absorbed to further the aims and interests of individual functions rather than ensuring the greatest benefit to the overall organization." (Allport & Cooke-Davies, 2010)

This statement, referring to the "Tragedy of the Commons" (Hardin, 1968), succinctly summarizes the challenges facing Amgen and many other large biotechnology and pharmaceutical companies. These companies must create strategies to integrate diverse global functions and align them toward a common goal. This situation, in essence, is the driver for this project. In the remainder of this section, we review academic literature on this and related topics, including the roles of process

development and manufacturing and the connection between them, the financial stakes of this relationship, common challenges faced in trying to align these groups, approaches recommended for alignment, and the potential benefits of an integrated and aligned organization.

Process Development

In general, the role of process development is to translate product design into the "technical knowledge, organizational capabilities, and operating processes needed to create the product (Pisano, 1997)." As such, the earlier development studies are performed, the sooner crucial information on a unit operation is known. However, process development is also tedious and time and resource intensive, and as a result it has been suggested that biotechnology process development is less advanced than in other industries (Leila & Henry, 2003). Furthermore, since process development can affect both the time to market and the quality of manufacturing, it therefore has influence over commercialization efficiency and cost.

Manufacturing

The goal of manufacturing is to efficiently and consistently provide product that closely matches the material used in clinical trials (Kozlowski & Swann, 2006). Comparability to clinical material is achieved through a combination of product testing, process validation, and process control. While it is widely acknowledged that drug manufacturing is vital to product quality, cost, and commercialization speed, it has been noted that the importance of biotechnology manufacturing is often overlooked by firms (Suresh & Basu, 2008). After spending money on discovering, developing, and commercializing a new drug, the drug is frequently manufactured inefficiently, with a high degree of waste and variability (Suresh & Basu, 2008). This is especially important because low manufacturing costs are increasingly seen as a source of competitive advantage, offsetting the mounting costs of commercialization, shorter exclusivity periods, and dwindling returns on R&D investment (Basu, Joglekar, Rai, Suresh, & Vernon, 2008).

Financial Stakes

Biotechnology companies are generally under the competing pressures of innovating, increasing growth, and accelerating time to market while maintaining high levels of product quality (Suresh & Basu, 2008). Compounding the challenges faced by these companies is the massive cost of developing and commercializing a new drug, estimated in 2008 to be $2-3 billion (Suresh & Basu, 2008). This amount is largely a consequence of the relatively low (10-20%) clinical success rate of new molecular entities (Bogdan & Villiger, 2010; Steinmeyer & McCormick, 2008). Since the majority of products do not make it to market, it may seem imprudent to front-load costs during development. However, this approach is not completely unwarranted, since early investment in characterization may prevent costly manufacturing and quality issues later (Kozlowski & Swann, 2006). This is not the only example of how a strong relationship between development and manufacturing can minimize costs. "Hidden" costs, such as those related to validation and regulatory issues, are often underestimated by biotechnology companies and can contribute to the overall cost of commercialization (Farid, 2007). Another important cost consideration is the cost of operating imperfect processes, which can manifest internally (as rejected units), externally (as recalls, penalties, etc.), or as appraisal costs (quality labor and prevention) (Cogdill, Knight, Anderson, & Drennen III, 2007). In short, responsibility for developing and commercializing a drug more quickly, at lower costs, and with consistently high quality falls on the shoulders of the Development and Manufacturing organizations, and this can best be achieved by aligning these groups toward a common goal.

Alignment Challenges

Despite the clear importance of development-manufacturing alignment, it is not uncommon in large organizations for a divide to form between the two. There are many symptoms of such a divide; a common one is that specifications may be "thrown over the wall" leaving little time for process engineers to optimize the process for manufacturing (Lu & Botha, 2006). Another is that development work is

often performed using methods, technology, and workers that differ from those used at the manufacturing site (Hayes, Pisano, Upton, & Wheelwright, 2005). A complication that compounds the effects of this dynamic is that once a manufacturing process is set, it is difficult to change due to regulatory approval requirements. For this reason, it is of great importance for Process Development and Manufacturing to coordinate early in the drug development cycle. Process Development and Manufacturing alignment is further tested when the groups are dispersed globally. Without face-to-face meetings, access to people, shared resources, a common language, and frequent informal conversations, the amount of collaboration and integration can drop precipitously (Allport & Cooke-Davies, 2010).

A final and often overlooked challenge is the way in which accounting practices handle development costs. Despite the importance of development-based innovation to a firm's long-term success, these costs are expensed as incurred (Lev & Zarowin, 1999). As such, investment in development will often have a short-term adverse effect on earnings and a time lag of uncertain duration before these development efforts bear their fruit (Hall & Bagchi-Sen, 2007). Allport and Cooke-Davies (2010) add that typical financial metrics, such as ROI and NPV, are rarely integrated with R&D contribution.

Alignment Approaches

The academic literature contains many examples of ways in which Process Development and Manufacturing can be aligned to the benefit of a firm's total costs, commercialization efficiency, and product quality. Pisano (1997) offers as a solution shifting development work as close as physically possible to the final production environment. However, this is only possible if the manufacturing site has the capacity to allow experimentation on its equipment, or if a company has access to representative equipment in a pilot plant or other facility.

Over the past decade, the U.S. FDA has spearheaded a number of efforts aimed at improved process understanding through alignment. For instance, the agency prefers that product quality and

operational performance are "achieved and assured by design of effective and efficient manufacturing processes," which requires close coordination between Process Development and Manufacturing (Hussain, 2004). Furthermore, the FDA's Janet Woodbury has emphasized that "new scientific understanding and new technologies [in Process Development] can provide science-based approaches [in Manufacturing] (Cohen, 2005)." Indeed, new FDA initiatives, such as 'cGMP for the 21st Century' (USFDA, 2003), Process Analytical Technology (PAT) (USFDA, 2004), risk-based quality, and Quality by Design (QbD) (ICH, 2005), encourage companies to better use information to support commercialization and allow for regulatory flexibility (Kozlowski & Swann, 2006). PAT, in particular, is implemented with the goal of improving efficiency and profitability, as long as there is a positive effect on product quality assurance (Cogdill, Knight, Anderson, & Drennen III, 2007).

One way in which greater commercialization efficiency can be achieved is through increasing a product's speed to market without sacrificing quality. Pisano and Wheelwright (1995) theorize that to do so, a company's focus should be more on improving the patterns and channels of communication, rather than on organizational structure. Creating a climate of enhanced communication between Development and Manufacturing, particularly in a global company, calls for facilitation tools (Lemon & Carl, 1991) like video conferencing and virtual workspaces. High levels of communication can lead to consensus if the groups are given shared objectives, creating a singleness of purpose (Brethauser, 2002). Other techniques include planned visits, informal phone conversations, milestones, and progress discussions (Lu & Botha, 2006).

According to Kennedy (1997), an efficient process development organization is one that minimizes iterative work, avoids unnecessary costs, and applies capabilities across projects. Moreover, the right facilities are required. This includes labs, pilot plants, clinical manufacturing plants, and commercial manufacturing plants that are closely aligned (Carson, 2005). In addition to their cross-organization consistency, the facilities should be flexible enough to support a variety of programs, but only to the extent that operational efficiency is not sacrificed (Steinmeyer & McCormick, 2008).

Finally, a critically important concept is that local sacrifices must often be made in order to achieve widespread effectiveness and efficiency. If groups are not aligned toward a common, firm-level goal, some may feel that they lost out to other groups. It is therefore essential that the cost-benefit assessment be made not on the individual level but on "tangible and measureable organizational benefits (Allport & Cooke-Davies, 2010)."

Benefits of Alignment

The literature contains numerous examples of the benefits resulting from better alignment of development and manufacturing, including less risky product launches, a higher degree of process robustness, a lower cost of compliance, decreased development cycle time, improved manufacturing flexibility and efficiency, and a lower cost of goods sold (Suresh & Basu, 2008), as well as a smoother production ramp-up (Terwiesch & Bohn, 2001). Other studies have added that development and manufacturing alignment could lead to increased revenues, due to a faster time to market, and thus a reduction in the time required to reach peak sales (Tollman, Guy, & Altshuller, 2003; Burchill & Fine, 1997). Additionally, learning induced by early process development can ultimately reduce manufacturing costs and provide a strategic advantage because process development capabilities can act as a potential barrier to imitation (Pisano & Wheelwright, 1995) (Hayes, Pisano, Upton, & Wheelwright, 2005).

One of the most important benefits of collaboration and alignment between development and manufacturing is an improved process understanding across both organizations. A solid comprehension of the interdependence of product and process can enable a company to maximum run rate and minimize cost of goods manufactured (Han, Nelson, & Tsai, 2010). As others have noted, process understanding can also lead to reduced process variability, which can positively influence both product quality and productivity (Suresh & Basu, 2008). In this way, better process understanding is a win-win for any firm able to achieve it.

In summary, the importance of development-manufacturing alignment is widely understood, and firm-wide benefit has been demonstrated in many industries. As a result, many efforts have focused on initiating alignment in the biotechnology and pharmaceutical industries, but without an over-arching alignment strategy, there has been minimal documented success.

4 Project Approach

We organized the project to evolve in four sequential stages (Figure 4). First, we built a foundation of information to map out the current state – which groups run which procedures, on which equipment, to generate what data. Next, we analyzed the current state map for misalignments and other inefficiencies, and evaluated possible improvement opportunities. Then, based on the analysis, we developed a high-level alignment framework to be applied across the DP network. We used case studies based on existing areas of need to demonstrate the potential benefit of implementing this framework. Finally, we investigated the causes underlying misalignment and inefficiencies in the Amgen DP network and developed a set of recommendations to mitigate these existing issues and to establish the means for sustaining long-term alignment. The actual work performed in each of these four project stages is now described in detail.

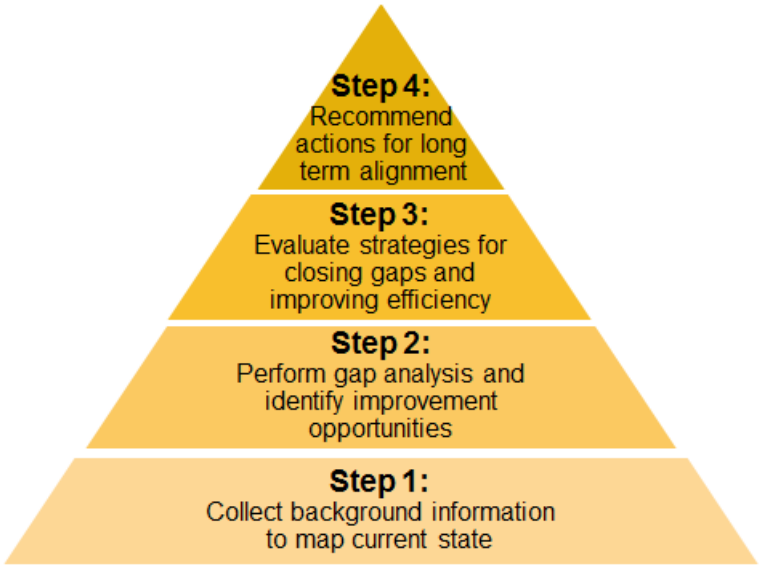


Figure 4: Visual representation of project plan

4.1 Setting the Foundation

We sought to understand what each of the four groups in the network does, the equipment on which they do it, and the data they generate. When the project began, there was no single source of this information, and, in fact, some of the information was not recorded at all. As such, the project's first step entailed collecting this information in its entirety. Once collected, this information would form the basis for the remainder of the project.

We collected information in three ways – by reading Amgen's internal documentation, interviewing personnel in the four groups, and touring the facilities. The first approach involved locating and then reading relevant Standard Operating Procedures for Clinical and Commercial Manufacturing, Study Guidelines for DPE and DPD, as well as Technical Reports, and Business Processes. This process primarily yielded detailed and up-to-date procedural information, particularly for the Manufacturing groups. The second approach consisted of identifying knowledgeable points of contact within the four groups and asking for information that could fill as many of the holes as possible in the current state map. Once these two approaches had been exhausted, we had a nearly complete understanding of the procedures and data collected, but were still uncertain about some of the equipment used. To close this remaining knowledge gap, we scheduled tours of the Clinical Manufacturing facility and of the DPE and DPD laboratory areas. The tours allowed us see the equipment used in these facilities. Since we were not able to visit the commercial manufacturing sites, we had to rely on the equipment information collected for those sites by the first two approaches.

The resulting current state map is a single source that provides insight into the detailed procedures, equipment, and data collected by the groups in the DP network. Previously, this information was spread among hundreds of documents, sometimes only in personal files, or, in some cases, not recorded anywhere. As such, combining the information into a single document allows for straightforward comparison across all DP network groups and phases of development, a task of immense complexity prior to the creation of the map.

4.2 Analyzing

We took advantage of the current state map to perform such a comparison of the DP Network. In particular, the information in the map allowed us to conduct two straightforward analyses of network inefficiencies. First, we identified redundancies – tasks that are performed by multiple groups during the same stage of development, or tasks performed by the same group during different stages of development. For instance, both DPD and DPE might measure product viscosity during their First-In-Human evaluations. Or, perhaps DPE performs a filterability assessment on the same product during different stages of development. These hypothetical examples would both constitute redundancies and would be highlighted during our analysis. Second, the current state map also allows us to identify gaps. Gaps can appear in a few different forms: equipment or procedural differences between development/engineering and manufacturing, or missed opportunities to collect data in one group when it would be useful to another group. Of course, some gaps and redundancies exist by design and are therefore not 'inefficiencies.' For this reason, all inefficiencies identified were sent for review to subject matter experts within each group. These experts were able to distinguish between acceptable and unacceptable gaps, as well as determine the completeness of our analysis. This latter point is particularly important, since the current state map was developed solely from sources to which we had access. This does not include the files of, or knowledge accumulated by, Amgen staff. For example, the documents we reviewed might have indicated that two inspection machines have matching model numbers, leading us to conclude that they are in fact identical. However, a staff member familiar with the machines might remember that one machine had a software upgrade that expanded its capabilities beyond that of the other machine. This is a gap that would have gone unidentified without the input of the process expert(s).

We also interviewed process experts and stakeholders to collect information on other inefficiencies that might not have been apparent during our document review. In particular, we were interested in understanding potential process improvements that could be achieved with different

equipment, better communication, improved process flow, or a reallocation of workload. We chose to focus the next part of the project on three of the areas identified.

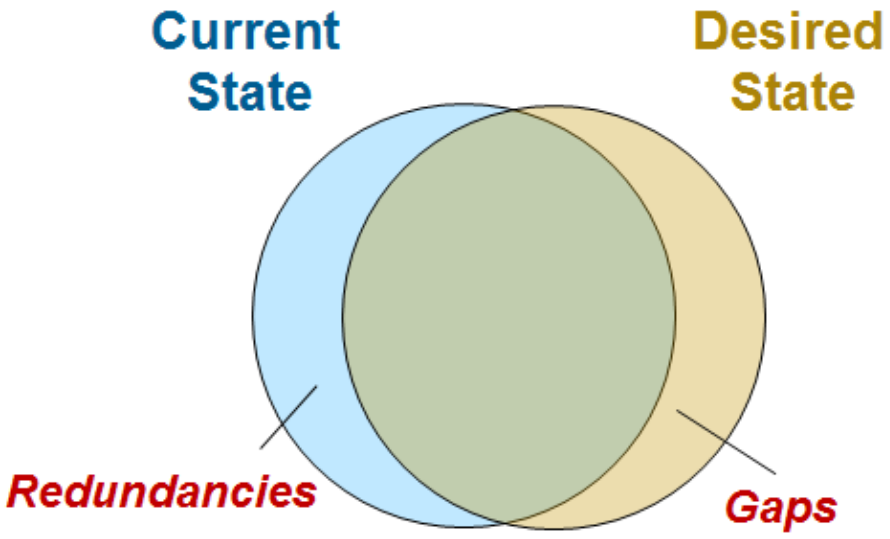


Figure 5: Conceptual view of types of inefficiencies present in the DP Network

4.3 Strategies and Case Studies

In order to tie the analysis findings (inefficiencies and other areas of improvement) to realizable benefits for Amgen, a strategy or set of strategies is needed. We started by setting the following as an objective that the strategy would be designed to help meet: ***we want the right group to be running the right procedures, on the right equipment, to generate the right data***. Put another way, whenever data is required, the group that can generate that exact data most efficiently should perform the data generation task. Achieving this state would mean that all data required for commercialization is generated as efficiently as possible, where efficiency is defined by cost, time, and labor. For example, data on product shear sensitivity may be generated by a study in which the product is exposed to representative shear rates and durations, after which critical product quality attributes are tested to determine the shear impact. While DPD and DPE may have the capability to perform a bench-top shear test using a rheometer, it could be that Clinical Manufacturing is able to more efficiently test the shear simply by running its normal process operation and then sending filled vials for product quality analysis. In this case, Clinical

Manufacturing can produce more representative data, since it is running the product through actual process equipment, and it can do it in less time with fewer resources by including the 'study' as part of its normal operation. This is only a hypothetical example, but it demonstrates our point; we need to consider all options to reach a state where the right group is always running the right procedures on the right equipment to generate the right data.

Reaching our desired state requires more than a procedural change or two; it requires a paradigm shift. Therefore, our strategy must be broad and impactful, affecting all groups in the DP network and changing their collective mindset. To achieve this, we propose as our strategy a framework that we call the Pilot Plant Cooperative (see Section 5.1 below for a full description) to provide the landscape on which the desired state can be built.

We chose to test the framework on case studies to prove the concept and demonstrate its potential benefits, as well as identify possible drawbacks. We selected for our case studies the three subjects suggested to us by our stakeholders: (1) DPE filling equipment evaluation to support Clinical and Commercial Manufacturing, (2) generation and transfer of useful from Clinical to Commercial Manufacturing, and (3) improvement of DPE's First-In-Human process evaluations.

The first case study targets what is arguably the most critical unit operation: drug product filling. This is an important step during which a precise amount of liquid product is added to a vial or syringe at high speed. If the amount added is incorrect, or the filling operation adversely impacts product quality, the product must be rejected. For these reasons, it is crucial that the filling operation and its interaction with the product are well understood prior to filling actual product. Currently, this is done through a combination of filling studies in DPE labs, evaluations at a few filling machine vendor sites, and on-site evaluations using the Commercial filling equipment. In this case study, we apply the Pilot Plant Cooperative concept to the filling unit operation to determine the best location for these studies and evaluate the costs and benefits of a few of the top options.

The second case study is based on the premise that Clinical Manufacturing, while creating material for use in clinical trials, also generates data that may be applicable to Commercial Manufacturing. Theoretically, Clinical Manufacturing data can be used to replace or augment datasets generated in DPE labs or at the Commercial site, thus saving time and supporting a more robust transfer to the Commercial sites. Currently, however, very little data is generated at the Clinical sites due to equipment and procedural differences relative to the Commercial site, and also because of an incomplete understanding of what data is needed and how that data can be generated. Our case study applies the Pilot Plant Cooperative approach to determine how Clinical Manufacturing can best support Commercial Manufacturing. More specifically, we seek to understand which data would be most efficiently generated by Clinical Manufacturing with the existing equipment and procedures, and which additional data could be generated by Clinical Manufacturing if equipment were purchased or procedures updated. Based on the assessment, we make recommendations for achieving a more collaborative relationship between Clinical and Commercial Manufacturing.

Finally, DPE's First-in-Human process evaluations were chosen because there is general acknowledgement that some of the current practices are inefficient, imperfect, or both. Our analysis involves in-depth looks at each of the eight process evaluations, from which we seek to understand the reason for performing the evaluation (i.e., what is the data generated used for) and how the evaluation is performed. Given this information, we applied the Pilot Plant Cooperative concept to determine whether better options for generating the data are available, or, if the data is not really needed, how the study can be eliminated. We developed recommendations for each of the eight studies and performed preliminary calculations to demonstrate the benefit of taking the suggested actions. Furthermore, evidence of the Pilot Plant Cooperative's benefit to the FIH stage can serve as a strong indication that even greater gains can be made by applying it to other stages, such as CPD or PC.

4.4 Sustaining

The first three project stages focus on building a foundation of background information and then making strategic recommendations aimed at a more efficient commercialization process. However, the goal of the project is not just short-term progress but long-term, sustained improvement. This requires additional measures to ensure continued ownership of project-borne initiatives, business processes to align all groups in the DP network toward a common commercialization approach and goals, as well as other culture-based changes.

Our approach during this stage was to set in motion some of these measures, while making recommendations for others. For example, the current state map contains a wealth of information not currently available from a single source. It is of great value not just to DPE, but to all DP network groups, as it provides details on how each group compares to all the other groups. As such, it should be made available to all groups and kept up-to-date so that it remains just as useful in the future. To this end, we created a website on Amgen's intranet to share all project documents, including the current state map. We also developed a plan to maintain the document's relevance through annual updates based on a review of procedural changes and equipment purchases each year. Similar plans were put in place for other project documents containing useful data.

We divided our recommendations for this stage into two categories – Procedural and Cultural – to distinguish between simple document changes and deeper mentality shifts. The procedural category includes suggestions to update SOPs and guidelines to achieve more aligned practices between groups and to collect more relevant data, as well as to modify business processes to ensure alignment implications are considered when making equipment purchase decisions, for instance. The cultural category, on the other hand, includes recommendations regarding behavioral incentives, hiring practices, and encouragement of cross-functional interaction. These are potentially more challenging because the cause-and-effect may not be fully understood (e.g. does hiring a strong a communicator mean that he/she will be more likely to build cross-functional relationships, or does an employee's behavior depend more

on the environment into which he/she is placed?). Our recommendations touch on these uncertainties but focus more on initial steps to reach an improved state of alignment.

5 Analysis and Results

5.1 Strategic Alignment: Pilot Plant Cooperative

Achieving meaningful, widespread, and long-lasting commercialization efficiency improvement requires more than a few small projects targeting specific areas of process development or manufacturing. Rather, a framework is needed to fundamentally change the way commercialization is undertaken. As discussed earlier, the existing commercialization process has a number of inefficiencies that must be addressed. For example, the commercial site equipment is used to perform process characterization and other studies, which reduces the time available to formulate and fill commercial product.

Any framework that attends to this and other commercialization inefficiencies should meet a few important criteria. First, it must be simple; otherwise its adoption across the DP network is unlikely. It must also be inexpensive, or it risks rejection by management due to budgetary limitations. Finally, it should reduce boundaries between groups in the DP network and benefit all groups equally.

A traditional approach to improving the ability to perform commercialization-supporting studies – and the approach we initially investigated during this project – is to build a pilot plant. Pilot plants typically contain scaled-down versions of the commercial equipment and can be used to generate data to improve understanding of process behavior for a given product. Amgen has a few pilot plants fitting this description for its bulk drug substance process. However, its sole drug product pilot plant contains only a subset of the commercial process equipment, and this equipment does not fully represent all commercial processing conditions. For these reasons, an improved pilot plant with more representative equipment could provide the foundation for a vastly improved commercialization process.

While a new pilot plant has many benefits, it also requires significant investment in capital equipment, as well as allocation of floor space in Amgen's already full campus. However, we believe we can meet the user requirements while limiting (or perhaps reducing) costs through an alternative approach. Rather than investing in a physical pilot plant, we instead propose a Pilot Plant Cooperative.

The Pilot Plant Cooperative, as we envision it, is similar to a traditional pilot plant in that it facilitates the commercialization process by providing the means to generate all required data to support process scale-up and transfer. The difference is that it is not a single facility of scale-down equipment but a set of facilities and tools in multiple locations. Furthermore, like a traditional pilot plant, it consists of equipment (hardware), but it also includes models and a knowledge management system (software). In essence, the Pilot Plant Cooperative is a toolbox available to anyone in the DP network who requires data in support of process scale-up and transfer.

The way we foresee it working is as follows. A member of the DP Network would choose from among the Pilot Plant Cooperative's available options (Figure 6) to generate any required data in the most efficient way possible. The most efficient way, typically, would be to use a model and/or historical data. This would require only a small amount of labor, no equipment, no additional investment, and would produce the necessary information (assuming the model had already been created and approved by Amgen Quality). If no such model was available, the next option would likely be to use existing equipment from somewhere in the network. One might first try to use equipment in a DPE or DPD laboratory, since this equipment has a greater likelihood of being idle and available than would other equipment in the Network. If not, the Clinical Manufacturing equipment might be used, or, as a last resort, the Commercial Manufacturing equipment. Neither of these latter two options is desirable when their use for a study means that clinical or commercial production would be delayed. Alternatively, an external vendor or a contract site could be used if the proper equipment is available. This option, of course, has a cost associated with it, and spending money for a study might not always be feasible. Finally, if all other options have been exhausted, or if a strong business case can be made, new equipment

can be purchased. The ultimate location of the equipment depends on the needs of the network. However, the Pilot Plant Cooperative approach would encourage sharing of this equipment, regardless of its location.

Figure 6: Schematic of the Pilot Plant Cooperative

As an example of how the Pilot Plant Cooperative can be used, consider that a member of the DPE group requires information on a product's freeze-thaw sensitivity. In the current setup, he or she performs a study using a controlled rate freezer in DPE's laboratory. The Pilot Plant Cooperative would expand the DPE scientist's options by providing access to existing data (e.g. freeze-thaw sensitivity of similar past products, or freeze-thaw data for this product generated by DPD), directing the scientist to a model that predicts freeze-thaw sensitivity based on other known product characteristics, or pointing the scientist to other equipment in the network, such as a Cryovessel in a DPD lab, or full-scale carboys in Clinical or Commercial Manufacturing, or even to outside vendors with appropriate equipment. In short, the Pilot

Plant Cooperative expands the current capabilities in two key ways: providing access to data and models that can be used to replace or augment studies; and by changing the virtual structure of DP Network. This latter point may seem trivial – after all, nothing is actually being done to expand the physical capabilities of the DP Network – but it fosters a mindset adjustment that encourages "network thinking" in a way that helps break down superficial barriers between groups. A Pilot Plant Cooperative, once made available to all groups in the DP Network, opens doors to collaboration and cooperation in a way that would likely improve learning and mutual understanding, but that also as a byproduct increased efficiency due to equipment sharing and redistribution of workload based on time availability and relative equipment and personnel capabilities. These are all important points and will be discussed in more detail later.

5.2 Case Studies

To demonstrate possible applications of the Pilot Plant Cooperative, we chose three case studies, each designed to address an area of actual need within the DP Network. The first is an evaluation of the a filling equipment gap in DPE, the second is an investigation of ways in which Clinical Manufacturing can better support the commercialization process, and in the third we look at potential efficiency improvements in early-stage process development studies. Each is discussed in detail in the following sections.

5.2.1 Case Study #1: Filling Equipment Investment

In our first case study, we investigate DPE's support of the drug product filling unit operation. This unit operation is of great importance to Amgen, as it doses product into the presentation ultimately delivered to customers, and it therefore must conform to strict quality and procedural specifications.

Summary of Findings: Based on our analysis of DPE's filling gap from the perspective of the Pilot Plant Cooperative, we recommend that Amgen purchases an automated filler for use by the DP Network during process development and characterization. This section describes the filling unit operation background, along with our analysis and more specific recommendations.

5.2.1.1 Background

Filling of the formulated product into primary containers is arguably the most critical drug product manufacturing unit operation. In this process step, product is dispensed into vials, syringes, or cartridges in precise amounts and at high speeds. Filling must be accomplished without dripping, spilling, or damaging the primary containers. Additionally, the filling process itself must not adversely impact product quality through exposure to high shear rates, incompatible materials, or excessive light and temperatures. As such, the process must be sufficiently well understood by the development and manufacturing groups so that it can be properly controlled and monitored.

Amgen currently develops its initial understanding of a product's "fillability" (i.e. the ease with which a product can be filled in the manufacturing environment) through fill assessments in the DPE pilot laboratory. In these tests, DPE typically fills a number of vials or syringes of the size and fill volume expected to be used during manufacturing and notes any observations of dripping, foaming, product adhesion (i.e. the tendency of the product to adhere to and/or dry on the equipment and tubing), and fill speed limitations. The DPE evaluator also checks the fill weight to ensure the fill targets are consistently met with the given equipment settings and change parts. If any adverse observations are made, the evaluator may adjust the filling speed or switch to a different fill nozzle to improve the filling quality. Final filling equipment and procedural recommendations are then delivered to the manufacturing groups for use in their operations.

While the current system for performing fill evaluations in DPE works relatively well (few changes to DPE's recommendations are typically required in manufacturing), the capabilities of DPE's equipment do not sufficiently meet all of manufacturing's needs. This is particularly true when preparing to transfer a product and process to commercial manufacturing. As a result, new commercial products require development time on the commercial filling equipment in order to better characterize the filling process and prepare for process validation. This situation presents commercial site scheduling challenges to accommodate fill characterization activities without disrupting the production schedule for other

commercial products. Scheduling conflicts have the potential to cause a delay to either the development work or the commercial production, each with significant associated costs. Additional costs have arisen in the past when commercial line time was not available and Amgen was forced to use equipment vendors for product-specific testing.

Filling Process Description

The filling unit operation is set up in generally the same way at Amgen's clinical and commercial manufacturing facilities, for both syringes and vials. Formulated drug product, stored in a stainless steel hold tank in a 2-8° C cold room, is transported with the tank into the filling suite. In the suite, the tank is elevated to an appropriate height for transfer and then connected to a filtration skid. The tank is pressurized, forcing the product out through a silicone hose and through a sterilizing filter. After filtration, the product continues through another hose and into a glass surge vessel, where it is temporarily stored before filling. From the surge vessel, the product enters the filler and can follow one of a few different routes to the filling needles, depending on the machine used and its components. Amgen's fillers use three different dosing mechanisms: a rolling diaphragm pump, a rotary piston pump, and time-pressure, all of which are described in detail later. The product dose flows through the filling needles (which can number anywhere between 1 and 16, depending on the filler and setup) and into the primary container. Amgen products are usually filled into vials between 3- and 20-cc and 1-mL syringes, and all Amgen's filling machines are able to accommodate these sizes. Once filled, vials are stoppered and capped, and syringes are plungered. The sealed containers are later visually inspected (either by machine or operator), packed, and sent to the warehouse.

Product Quality and Process Performance

As described above, the drug product is dispensed into its final container (usually a vial or syringe) during the filling operation. Thus, the filling process constitutes the last time the product undergoes physical manipulation outside the final container. Up to this point, significant time and material, both with substantial associated costs, have gone into manufacturing the product. In most cases,

the product has undergone cell culture scale-up, harvest, purification, and drug product formulation – in total, months of production time – before reaching the filling operation. A performance issue or adverse product quality impact at this point could mean discarding material that has a high production cost and even higher sales value. It is therefore of great importance that the filling operation and its product impact are well understood prior to manufacturing initiation.

In general, the filling unit operation can impact product quality in two ways. First, shear stress is placed on the product by the dosing mechanism and the nozzle head. Shear-sensitive products may incur protein damage due to shear rates above a certain product-specific threshold. Second, the environment to which product is exposed can affect the product. This includes product contact materials – stainless steel, silicone tubing, and glass – as well as oxygen, light, and room temperature.

Just as critical as product quality to the success of the filling operation are process performance and consistency. Performance is measured, for example, in terms of the percentage of rejected units (a lower number obviously being preferred), while consistency can be determined by fill weight precision relative to the target (a small spread represents a higher consistency). Other performance and consistency metrics include percent unplanned machine downtime, number of broken or scratched vials/syringes, amount of discarded product, total fill rate (units per minute), and a host of others.

Product quality impact and process performance and consistency are of such importance for the filling operation, additional discussion is devoted below to describing some of the mechanisms of product impact and the potential consequences to the drug product, as well as the controls and limits in place for ensuring a consistent and robust process.

Shear

The most relevant factor affecting product quality during filling is shear stress, or the force per unit area acting on a fluid due to the presence of a velocity gradient and depends on both the shear rate and the fluid viscosity (Macosko, 1994). Shear rates for unit operations, such as filling, can be estimated

based on a characteristic velocity and a characteristic length scale. Velocity is not the same at all points in the unit operation (it exists as a gradient, starting at zero at the fluid-equipment contact point), so a range of shear rates are present. The velocity change from zero to the maximum velocity, divided by the characteristic length (the distance from minimum to maximum velocity), gives the unit operation shear rate.

Shear sensitivity of drug products depends on two factors in particular. First, products with higher protein concentrations tend to exhibit higher shear sensitivity. Shear sensitivity in a product often manifests itself as protein aggregation, which is driven by inter-molecular collisions. Since higher protein concentrations increase the probability of molecular collisions (more molecules per volume results in more collisions), these products are more likely to experience shear-induced aggregation. The collision probability is further increased at higher shear rates, such as those encountered during filling. Second, non-Newtonian drug product behavior also tends to increase the likelihood of shear-induced degradation (Shire, Shahrokh, & Liu, 2004). Non-Newtonian fluids are those for which viscosity changes as a function of shear rate. For instance, many drug products made with the surfactant polysorbate 80 are prone to non-Newtonian behavior. Both of these factors are becoming more prevalent at Amgen, as product concentrations are continually pushed higher and therapeutic monoclonal antibodies with polysorbate 80 dominate the pipeline portfolio (Shire, Shahrokh, & Liu, 2004).

The filling unit operation exposes drug product to the highest shear rates it experiences during formulation/fill/finish, but only for a brief time (less than one second). In Amgen's older filling equipment, which uses positive displacement pumps (such as rotary piston or rolling diaphragm), product is exposed to shear rates at the filling needle as high as ~2,000/s. Amgen's newer filling equipment uses

Time-Pressure technology, which exposes the product to significantly higher shear rates than the pump technology (~20,000/s)[5]. Each of the three dosing technologies is described in detail in following section.

Dosing Technologies

Amgen's older vial fillers typically use rolling diaphragm pump technology (Figure 7) to dose the product. This is a positive displacement pump where product flow is generated by the sweeping action of the diaphragm, which is controlled by a rotating cam. The diaphragm is attached to a piston and pump locking ring. The piston moves up and down while a vacuum is pulled on the back of the diaphragm; this allows the pump to maintain accurate dosing. Dosing is controlled by the piston stroke and vacuum pressure (as well as drip retraction from the filling needles); deliverable volume per stroke is the most critical process parameter. As such, accurate dosing requires vacuum control, stable feed pressure from the surge tank, and an understanding of the diaphragm thickness and product density.

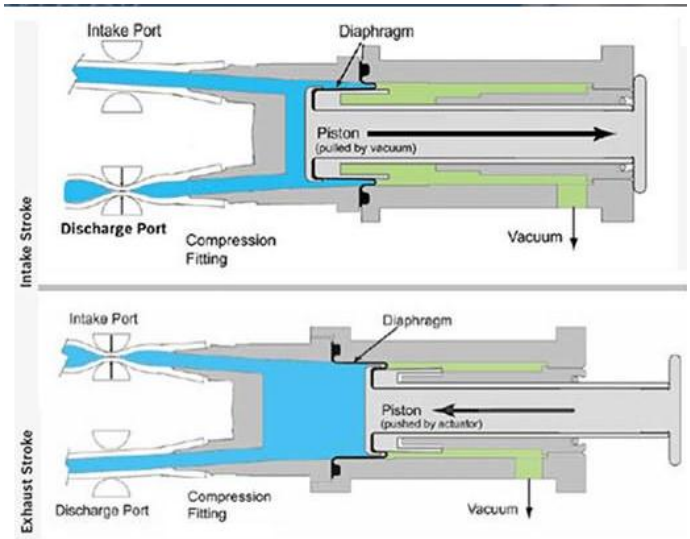


Figure 7: Rolling Diaphragm dosing technology
(Source: http://www.overlookindustries.com/services/application_development/pump_types.htm)

The rolling diaphragm pump is a robust dosing technology: there is little or no drift in dosing amount over time, it is unaffected by liquid temperature shifts, and it has little impact on shear-sensitive products. However, cleaning and assembly of the pumps is complicated, requiring significant time and

[5] For comparison, the product also undergoes shear stress during the mixing unit operation, but at a rate of just 25/s However, the mixing duration can be more than one hour, which accentuates the effect of the shear on aggregate formation (the longer the shear duration, the greater the number of molecular collisions).

expertise. Additionally, the diaphragms must be replaced frequently, adding a recurring expense and necessitating adjustments to the pump stroke to account for varying diaphragm thickness.

The rotary piston pump (Figure 8), like the rolling diaphragm pump, is present in many of Amgen's older filling machines (in syringe fillers, in particular), but also serves as the backup technology in Amgen's newer machines. In the rotary piston setup, a displacement pump doses the product through the filling needles and into the syringe barrels. Specifically, the linear displacement of the piston stroke drives the cylinder upwards, which generates a vacuum that pulls product from the filling manifold into the pump. The cylinders are then driven downwards by linear displacement, which displaces the product, forcing it out of the pump and into the fill line. As with the rolling diaphragm, the critical process parameter is the deliverable volume per pump stroke. In this case, though, dosing is controlled by the piston stroke length, as well as pump diameter. Since there is little or no dosing drift over the course of a manufacturing lot, the stroke length is typically set just once per lot. Dosing accuracy requires stable feed pressure and adjustments for product density.

The piston pump is slightly less robust than the rolling diaphragm. It has an elevated shear rate associated with its use, which may not be suitable for extremely shear-sensitive products. Furthermore, particles in the drug product or crystallization of product in the pump could cause friction within the pump that affects dosing accuracy. It is, however, suitable for a wide range of dosing volumes and liquids, including those with foaming tendencies, and, importantly, can be cleaned and sanitized using traditional CIP/SIP techniques.

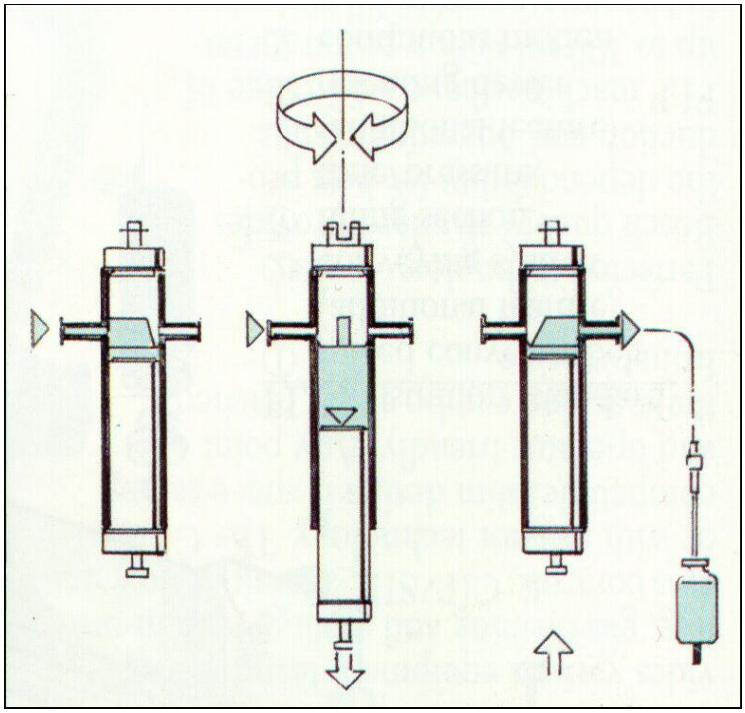


Figure 8: Rotary Piston Pump dosing technology
(Source: http://www.overlookindustries.com/services/application_development/pump_types.htm)

All of Amgen's recent filling equipment purchases, including both syringe and vial fillers, use time-pressure (T-P) dosing (Figure 9), which was recently declared Amgen's filling technology "standard." T-P dosing is a departure from traditional dosing methodologies in that it uses pinch valves instead of pumps to control product flow into primary containers. More specifically, product flows from the surge vessel into the filling manifold. From there, PLC-controlled valves regulate the flow of product from the manifold through flexible tubing and into the fill needles. The T-P technology works by placing the contents of the surge vessel under constant pressure and then opening the pinch valves (which are regulated using a fast-acting stepper motor) for a predetermined amount of time. The pinch valve timing is optimized to ensure the proper amount of product is allowed through based on knowledge of the desired fill weight, flow rate, and product density and temperature. Dosing adjustment can be made automatically during processing using the PLC and process fill weight checks. This is especially important for large lots for which product temperature (and thus density) may change from the beginning of the lot to the end. This is achieved with In-Process Controls (IPC) that monitor the fill weight and then

feed the data back to the filling controller. For systems with multiple needles, the fill weights are monitored for each needle, and adjustments are made only for the needles requiring them.

For T-P dosing, the critical process parameters are the manifold pressure and the time the pinch valve is open. Unlike the pump technologies, there is the possibility of dosing drift over the course of a lot; IPC with feedback is used to correct for this. Therefore, the filling accuracy is dependent upon the IPC accuracy, as well as the filling hardware characteristics. Filling accuracy can be affected by other factors, as well, including pressure and level in the surge vessel, air bubbles in the fill hose or at the orifice (due to the high pressure drop), wear of the fill hose, and changes in product viscosity and density due to temperature changes.

The T-P hardware is comparatively simple versus traditional pump dosing, while the software is much more complex. Cleaning of the hardware requires just CIP/SIP, and, while the tubing must be frequently replaced, it is relatively inexpensive. The technology can be used to fill a wide range of products and fill volumes and works particularly well with high speed fill machines. One drawback is the extremely high shear it places on products. It is therefore less suitable for filling shear-sensitive products than are either of the pump technologies.

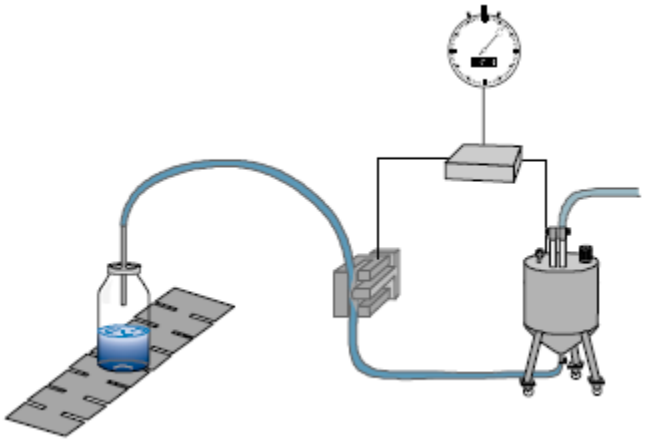


Figure 9: Drawing of Time-Pressure dosing technology

Other Important Equipment Components

In addition to the dosing technology, there are other important differences between the equipment used during the filling unit operation across Amgen's manufacturing and development network. Some of the most critical differences, from an operational perspective, are the checkweigh system, the general process flow – including vial washing, and stoppering and capping – and the operating environment (clean room vs. isolator technology). Each of these is briefly discussed below.

Fill volumes are checked routinely during the filling unit operation for any given production lot in order to maintain consistent and accurate fill amounts, while also ensuring the volume in the container matches the label claim. The checkweighing procedure, however, varies due to machine capability and procedural differences. For instance, Amgen's new filling equipment automatically weighs syringes and vials before and after filling to determine fill weight, while older machines that lack this functionality require manual vial taring and weighing post-fill, or destructive weighing of expelled syringe contents. These manual approaches are time intensive, and, in the case of the syringes, wastes valuable drug product.

The process flow in Amgen's newer facilities is highly automated, with extensive use of conveyors and robots, relative to its older commercial and clinical manufacturing facilities. Much of the operation in the newer facilities is in-line, which allows for a smooth, continuous process flow. The older facilities use a more stepwise flow, in which the filling unit operation machines are not all connected. For example, in the commercial facilities, vial preparation (washing and depyrogenation) is in-line with the filling equipment; vials continue straight from a depyrogenation tunnel into the isolator system, where they are filled. In the clinical filling areas, vials are run through a stand-along washer, and then depyrogenation occurs in an oven. Afterward, the vials are staged in a clean area before being manually transported to the filling area.

There are other differences between filling unit operations across the network, as well. Stoppers are placed mechanically in manufacturing, while they are placed using forceps in DPE. Capping may be done with spring-loaded pressure or pneumatically. Syringe tubs are automatically debagged, de-lidded, and de-lined in the newer filling areas, while those tasks are performed manually in the older areas. Additionally, the tubs are decontaminated via electron-beam irradiation in the new areas and by a series of wipings in older areas. Also, stopper, cap, and plunger presence and placement are automatically detected in the newer areas. In short, there are many operational differences, some of them significant, across the drug product manufacturing and development network that can affect process performance and consistency.

One important consideration is the filling environment. Filling must take place in an ISO 5 (also referred to as Grade A or Class 100) production environment. In Amgen's older filling areas, this state is achieved through use of clean rooms with HEPA-filtered air, controlled access, and strict gowning procedures. Clean rooms allow for relatively easy access to process equipment but are highly energy intensive and require extensive cleaning and tight controls. Amgen's newer filling areas use isolators that separate the filling equipment from the surrounding environment. This enables filling to continue to take place in an ISO 5 environment, but with that environment constrained to the small area within the isolator. By using an isolator, gowning requirements and access controls can be reduced, since personnel do not directly interact with the filling equipment or containers until after filling and capping has taken place, when the product is safely sealed within its container. As such, the surrounding environment does not need to be ISO 5, which in turn reduces energy usage and cleaning requirements.

The isolator brings with it a host of challenges, too. Its interior must be decontaminated between lots with vaporized hydrogen peroxide (VHP). A VHP cleaning cycle can take up to 12 hours, which increases equipment changeover time. Using VHP also means that all materials and equipment within the isolator environment must be compatible with VHP. In addition to requiring VHP sterilization, the isolator inhibits access to the filling equipment, which can only be reached through material transfer

isolators (MTI), rapid transport ports (RTP), and mouse holes, as long as positive pressure is maintained within the isolator (to make sure that the ISO 8 air in the surrounding environment does not flow into the ISO 5 isolator). And, finally, despite the convenience that the isolator provides to manufacturing personnel, aseptic techniques must still be used, particularly during manipulations through the MTI, RTP, and mouse holes.

Table 1: Selected attributes of Amgen's dosing technology.

	New Technology (Time-Pressure and Rotary Piston)	AML1 – Syringe Filling (Rotary Piston)	AML 1 - Vial Filling (Rolling Diaphragm)
Work Mode	Electrical Controls	Cam driven	Cam Driven
CIP / SIP	Yes	No	No
IPC Feedback for Auto-adjustment	Yes	No	No
In-line check weighing	Yes	No	No
Dose Adjustment	Servo Motor	Manual Mechanical	Manual Mechanical
Filling Parts	Simple (2 Piece Pump)	Multiple Parts	Multiple Parts

5.2.1.2 DP Network Filling Equipment Inefficiencies

The need for development work on the commercial line exists because of equipment differences between the DPE labs and the manufacturing sites, combined with the lack of an adequate model for scaling up study results from the DPE equipment to the manufacturing equipment. The DPE labs have bench-top filling units for both vials and syringes. These units require manual filling (a technician places the syringe or vial below the fill nozzle and presses a button or foot pedal to fill the container) and are therefore slow, time intensive, and create the opportunity for human error. Conversely, the filling units in the manufacturing suites fill the containers automatically at high speeds. Still, the basic underlying technology is the same between DPE and manufacturing; consistent dosing mechanisms, nozzles, and tubing are used, and the primary containers are identical. Nevertheless, even if the process impact on the drug product can be simulated in DPE's labs, the commercial and clinical manufacturing processes cannot. Furthermore, the clinical and commercial manufacturing filling equipment are not all consistent.

As such, clinical manufacturing filling experience cannot be used to predict commercial filling performance for all products. This situation, combined with Amgen's desire to reduce the risk of issues during commercial launch, means that additional work is required on the commercial equipment to ensure the filling process and its product impact are completely understood prior to process validation and commercialization.

5.2.1.3 Borrow, Rent, or Purchase Decision

Applying the Pilot Plant Cooperative framework to the filling equipment inefficiency problem, we see that four realistic options exist for obtaining filling equipment: (1) borrow existing equipment from within the DP Network, (2) "rent" equipment from a contract manufacturer or vendor, (3) purchase new equipment, or (4) continue to use the existing laboratory fillers. Each, of course, has a cost as well as potential benefits. A fully quantitative comparison of the three options is not realistic given the timeframe of this project, so we must use another method[6]. A semi-quantitative method commonly used for this purpose involves assigning weights and scores to a number of important variables and computing a total that can be used to compare one option to another. We use this method here but acknowledge that there are better semi-quantitative techniques available, such as Analytical Hierarchy Process, that we recommend applying to future decisions.

To keep our analysis simple, we select seven categories on which to base our comparison. Each option is assigned a score from 1-9, where a '1' equates to a filler inadequately meeting a specification (e.g. having a very high cost or poor comparability to manufacturing) and a '9' indicates a filler completely satisfying that specification. Each category is given a weight based on its perceived importance, such that the weights sum to 100%. The categories chosen are the following: lifetime cost; labor; mimicry of manufacturing process; mimicry of manufacturing product impact; accessibility for

[6] Appendix A includes a possible quantitative approach using NPV analysis. Should such an approach be used to compare the various filling options described here, the company would choose the option with the highest NPV, as long as that value was greater than zero.

studies; ability to produce non-clinical material; and flexibility. The analysis results are shown in Table 2.

Table 2: Rating summary comparing filling equipment options.

	Weight	Purchase New	Vendor / CMO	Clinical/Commercial Equipment	DPE Lab Equipment
Cost	0.25	3	5	5	9
Labor	0.05	5	9	7	3
Process Flow	0.10	3	7	9	1
Product Impact	0.30	9	7	9	5
Accessibility	0.15	9	5	1	9
Non-Clinical Production	0.05	9	9	9	1
Flexibility	0.10	7	3	1	5
Total Score		**6.5**	**6.0**	**5.9**	**5.9**

Our analysis shows that the "purchase new" option has the highest total score of the four options. Of course, this analysis is highly subjective, and the scores for all four options are within 10% of each other, so a more thorough analysis may be necessary if these results do not provide sufficient justification for pursuing a new machine purchase.

5.2.1.4 Case Study Evaluation

Based on the results of our initial filling equipment selection analysis in the previous section, our objective for this case study is to recommend new filling equipment to be used within the DP Network to better support commercialization activities. These activities can include filling evaluation studies from early- to late-stage process development, process characterization work, process troubleshooting, and other similar studies. In order to improve the likelihood of our recommendation being accepted at

Amgen, we must hold ourselves to the same standards as similar capital investment projects. Namely, the equipment chosen must be supported by a strong business case, and it must also meet the requirements of the groups that will use it. To help focus our recommendation development, we sought to answer the following three questions:

1. For which activities could new filling equipment represent an improvement over the current state?
2. What functionality and components must the filler have in order to perform the activities identified in question 1?
3. Can a defensible business case be made to demonstrate that the benefits of the new equipment outweigh the investment costs?

The following sections provide details of these user requirements, a description of our options and evaluation methodology, and the business case for our selected technology.

User requirements

We interviewed 18 representatives from the four groups within the DP Network to understand their requirements for filling equipment. Our questions focused on our two major areas of interest: (1) for which activities the equipment should be used, and (2) what the equipment should be (i.e. parts, scale, capabilities, etc.). We compiled the interview results and consolidated the findings into a set of common responses that best represent the DP Network's "requirements" (Tables 3 and 4). It should be noted that these requirements are not mutually exclusive, nor must they all be met. The lists presented here are simply a representation of the most important needs of the DP Network with regard to filling equipment used in development and commercialization work.

Table 3: User input on filling equipment requirements.

User Input – What the Filling Equipment Must Do	*Details*
Mimic stress on product of clinical and commercial filling. Must replicate shear, temperature and light conditions, product contact materials and air exposure.	Would allow for better fill evaluations and shear characterization, manufacturing issue replication, and NC investigations. Could enable process characterization work away from manufacturing site.
Mimic fill unit operation in clinical and commercial manufacturing. Must replicate process flow and reproduce product-specific observations (e.g. dripping, drying)	
Meet the needs of pipeline products. Should accommodate anticipated product characteristics and needs: high-viscosity, light/oxidation sensitivity, accurate small volume fills, cartridges.	Forward-looking equipment could reduce future uncertainty and expenditures, while anticipating equipment needs and procedural modifications.
Equipment should be flexible. Must accommodate vials, syringes and cartridges, both glass and plastic; should be able to easily switch out dosing mechanisms (e.g. T-P with Rotary Piston).	Reduces equipment investment (purchase one machine instead of two or more) while being adaptive to future changes.
Modular, easily accessible, and compatible with Amgen's Manufacturing of the Future initiative.	Consistent with the future direction of drug product manufacturing.
Act as a training facility for manufacturing staff.	Provides a space for new staff to train on manufacturing-like equipment without interfering with on-floor operations.

While the responses are generally consistent across the DP Network, we note a subtle difference in the focus of the development and manufacturing organizations. The development groups (DPD and DPE) seem to be mostly concerned with the product-process interaction and being able to use the filling equipment to better understand this dynamic. The manufacturing groups (both clinical and commercial), on the other hand, are more intent on the equipment being used to help understand manufacturing equipment settings and operating parameters. Perhaps this dichotomy is to be expected, given the areas of

expertise within these two parts of the DP Network. Still, the differences are interesting and may represent a remaining vestige of the pre-DP Network era.

Table 4: User input on what the filling equipment should include.

User Input – What should the Filling Equipment Include	***Details***
Match clinical and commercial manufacturing equipment as closely as possible. Should include an isolator, in-line vial washer and depyrogenation tunnel, robotic syringe tub preparation, automatic stoppering and capping with similar vacuum pump, etc.	Would allow for better fill evaluations and shear characterization, manufacturing issue replication, and NC investigations. Could enable process characterization work away from manufacturing site.
Meet Amgen's filling equipment standards. Filler should use Time-Pressure dosing, with Rotary Piston pump as a backup.	Complies with standards set by Amgen for all future clinical and commercial manufacturing filling equipment.
Equipment line speed should match that of clinical and commercial manufacturing. Must be capable of high-throughput, automatic filling. (Note: the actual fill rate may be lower than manufacturing's, but line speed can be the same by using fewer nozzles/pumps.)	Reduces time and manual labor for large studies, while better matching the manufacturing filling process.
Product storage tank (pre-fill) should be capable of controlling temperature.	Allows for evaluation of temperature impact on filling; can mimic a range of manufacturing conditions.

5.2.1.5 Evaluation of Options

The user requirements provide us with a context from which we can develop our filling equipment options. As mentioned earlier, we are not attempting to meet all user requirements, nor are we restricted to the input we received; we are trying to make the best recommendation possible, and the user requirements are merely a guide for doing so. Our filling equipment options can be divided into a number of categories. Each of these categories, along with a discussion of the options and our ultimate choice, are described in the following sections. Most of our decisions come down to a question of cost versus capability. We would like our new equipment to be of the highest quality and able to meet all our

existing and future needs, but the cost of such a machine would be prohibitive. Therefore, a balance must be struck and informed decision-making used to choose which features are absolutely necessary and which are not. It is also important to remember that other resources already exist within the network. There are bench top fillers in the DPE labs and larger scale machines on the manufacturing floor that are currently used and will be available for future use as well. These machines are not being replaced by the new equipment. Instead, they are complementary to it.

In making our decisions for each category, we apply a simple methodology. First, we ensure each of the options fits within the scope of the filling unit operation. We are concerned that including non-filling equipment (such as filtering equipment or vial cleaning) will weaken our request, regardless of the equipment's potential value to the DP Network. Second, we determine whether each option drives us toward our desired state of being able to mimic all filling process stresses on drug product quality, while producing a realistic facsimile of the filling unit operation. The former is quantifiable – the stresses must be the same – while the latter is open to interpretation. We want to processes to be similar but without restricting our options. Third, we consider the benefits of each option and compare these to the current state of laboratory equipment and other equipment available within the DP Network. Any option that does not provide a substantial upgrade to the existing practices should not be considered. Finally, we evaluate the financial costs of each option. Expensive, non-essential equipment is eliminated from consideration, but expensive, essential equipment is not. In the following sections, we discuss eleven categories and give our recommendations for each decision point.

Container Filling Capabilities

Amgen's current SKU portfolio includes both syringes and vials, so it is important for any new filling equipment to be able to fill these two types of primary containers. Syringes are typically 1 mL, though 2.25-mL syringes are also used, so both sizes should be accommodated. Syringes are filled in tubs, usually in 10x10 or 10x16 arrangements, but a machine should be flexible enough to handle these and a variety of other configurations. Amgen fills vials that are 3, 4, 5, 10, 20, and 50 cc, with 13 or 20

mm necks. As with the syringes, any filling equipment purchased must be able to fill all existing SKUs, at a minimum. The machines should also be configurable such that a new SKU of a different size could also be filled with the right change parts.

The filling equipment should also be able to meet Amgen's known future needs. This includes plastic containers (the currently used vials and syringes are all glass) and cartridges. Plastics should require little mechanical adjustment to the equipment, since the container sizes should be consistent with those that are currently used. However, plastics scratch more easily than glass, so there is a possibility that changes to the commercial and clinical filling equipment will be made to better handle these containers. If these changes are made, the new filling equipment should be adjusted in the same way. As for the cartridges, they are filled much in the same way as syringes – a tub of cartridges in some configuration is filled by a bank of needles. So, a syringe filler should theoretically be capable of filling cartridges, but this has yet to be fully tested at Amgen. As such, we recommend purchasing a filler with the flexibility to have its parts easily changed to meet the requirements for cartridges.

Dosing mechanism

As described in an earlier section, three major types of dosing mechanism are used at Amgen: Rolling Diaphragm Pump, Rotary Piston Pump, and Time-Pressure. Some of the key differentiators between these technologies include CIP/SIP suitability, shear stress, filling speed, and drip prevention. While we would like the new filling equipment to match all of Amgen's manufacturing filling machines, Time-Pressure dosing is officially Amgen's preferred technology, as it was named part of Amgen's filling equipment "standard." Similarly, the equipment standard named the Rotary Piston Pump as the backup to T-P. Meanwhile, the Rolling Diaphragm was left off the list, and will seemingly no longer be used at Amgen once the existing machines are taken out of service. For these reasons, we have decided that the new filling equipment should meet Amgen's filling equipment standards – T-P, with Rotary Piston as a backup – and should not support Rolling Diaphragm. We feel comfortable making this choice because of the costs we are avoiding associated with the diaphragm, as well as work required to clean the pump.

Additionally, we feel the existing DPE lab and manufacturing equipment can continue to support studies specifically related to the rolling diaphragm pump.

Fill Speed

Many of the DP Network members stated that the fill speed on the new equipment should match that of the manufacturing equipment. This does not mean that the machine should necessarily have the same throughput (or line speed) as the manufacturing equipment. This is an important distinction. Fill speed is the rate at which a single unit is filled, whereas throughput is the number of units the machine fills over a specific period of time. The difference between the two lies in the number of filling needles present in the machine. For a machine with one needle, the fill speed and throughput are the same. When more than one needle is present, the throughput increases proportionally. For instance, a machine that has a fill speed of 1 second per unit (or 60 units/minute/needle) has a throughput of 120 units/minute with two needles, 180 units/minute with three needles, and so on.

Fill speed is essentially the rate at which product is expelled by the filling needle. Since filling shear is in part dictated by the fluid velocity, mimicking manufacturing fill speed in laboratory filing equipment is critical to understanding the effect of filling shear on a product. Using comparable fill speeds to manufacturing also enables direct transfer of laboratory equipment settings to the manufacturing environment. This is critical when trying to minimize foaming and splashing or in predicting complications due to high viscosity or novel SKU dimensions.

We decided that any new equipment must be capable of running at manufacturing fill speeds, which can be as high as 50 units/minute/needle for 3 cc vials, and 30 units/minute/needle for 1 mL syringes. We chose not to attempt to match manufacturing throughput, as this would require either a machine with many filling needles (up to 16, in fact), or running at unrealistically high fill speeds. Not matching the manufacturing throughput limits Amgen's ability to predict operational issues, such as equipment failure points (e.g. jams, wear, vial scratch/breakage areas). However, we feel that the cost of

the needles and infrastructure to support manufacturing-level throughput outweighs the potential benefits, many of which can be prevented at the manufacturing site with careful monitoring and the preventive maintenance practices already employed by Amgen personnel.

Materials and Change Parts

As described earlier, the process materials (e.g. stainless steel, glass, Teflon, silicone) with which a product comes into contact during normal operation can sometimes impact product quality due to surface interactions or leaching. The relationship between process materials and the product is studied by DPE prior to a product entering a manufacturing site. Nevertheless, we believe that the materials in laboratory filling equipment should match those in the manufacturing equipment for a more representative environment. One reason for this is to reduce the number variables when troubleshooting a manufacturing process issue using laboratory filling equipment. If the lab and manufacturing equipment use the same materials, then conclusions can be drawn in troubleshooting (or other) studies without any caveats related to the materials.

In order to match Amgen's newest manufacturing equipment, all purchased filling equipment should include silicone and Teflon tubing, 316L stainless steel parts, a stainless steel surge vessel (Amgen's clinical equipment has a glass surge vessel, but we prefer to match the new commercial filling equipment), and a stainless steel product storage tank.

The machine parts dimensions dictate which container sizes and types can be filled and how closely the machine mimics the manufacturing equipment. We consider any dimensions related to product shear to be critical in that they must match manufacturing. This includes the T-P orifice, fill needle diameter, silicone tubing diameter, and Teflon hose diameter. The required dimensions are listed in Table 5. Additionally, the machine must be able to process 3" tubs, and the surge vessel should include pressure and level control, with a pressure range of 60 – 500 mbar.

Table 5: Filling equipment size requirements.

Part and Measurement	Size
T-P Orifice Diameter	0.4 – 0.7 mm
Fill needle internal diameter	1.1 – 3.4 mm
Silicone tubing internal diameter	1.6 – 5.0 mm
Teflon hose internal diameter	1.6 – 3.2 mm

Checkweighing

Amgen's new commercial filling equipment uses automated checkweighing, but this technology comes with a hefty price tag. While most members of the DP Network who were interviewed for this project agree that automated checkweighing capabilities would provide numerous benefits, but only a few thought that these benefits outweighed the costs. The argument against automated checkweighing typically focused on the fact that a laboratory filler would have a much lower throughput than a manufacturing filler and have none of the quality or IPC requirements. However, those who insisted that automated checkweighing is necessary did so with conviction and a strong rationale. Beyond the data collection benefits provided by automated checkweighing, it is imperative if T-P dosing is being used (recall that T-P dosing amounts tend to drift over time and depend on continuous feedback from the checkweigh machine to maintain dosing accuracy). Without automated checkweighing, the T-P filler would require manual data entry (based on manual offline weighing) at regular intervals, else the dosing accuracy would continue to drift unchecked.

We decided that, despite the costs, automated checkweighing is a necessary component of a new filler that depends on T-P technology. It completes the T-P feedback loop, generates a significant amount of fill weight data that might be used to better understand and control the commercial filling operation, reduces the amount of manual manipulation required (saving time and increasing the speed of operation),

and would better enable a laboratory filler to be used for non-clinical (toxicology and stability) production runs.

Temperature control

An often overlooked but critical factor in filling performance is the product temperature. Product is held in a cold room (at 2-8 C) prior to being filtered and filled at controlled room temperature. Without a temperature-controlled product tank, this means that the product in the tank warms over the course of a fill – the product filled at the end of a lot is warmer than the product filled at the start. Since temperature affects product viscosity and density, this means that the product fillability and volume is different between the beginning and end of a lot. Amgen's clinical filling equipment does not include temperature-controlled tanks, but its commercial equipment does. We do not feel that matching the commercial equipment is reason enough for investing in a temperature-controlling product vessel, since the lots run in the laboratory setting would be much shorter in duration and thus less prone to warming.

However, we still do feel that temperature control capabilities are required for the laboratory fill equipment. Having this equipment would enable DPE to fine-tune the filling temperature to achieve a lower viscosity (thus lower shear and improved fillability) while minimizing the product impact of exposure to higher temperature. This balance has not been fully explored in the past due to a lack of equipment for doing so, but it represents an area of potential breakthrough and increasing importance, as Amgen's drug products continue to push viscosity limits.

Environment (ISO X, GMP, etc.)

In drug product manufacturing facilities, the cleanliness of the filling environment is critical to meeting internal product quality standards and regulatory requirements. Accordingly, a significant amount of money is spent to ensure effective measures are in place to maintain an environment free of contaminants and other foreign particles. As described earlier, this is achieved through use of either an isolator (in newer fill lines), which maintains an ISO 5 state in an enclosed area directly around the filling

machine, or a clean room (in older fill lines), where the entire room is kept at ISO 5 levels. For laboratory filling equipment, there are no environmental regulatory guidelines that must be met, since material produced in these machines is not intended for human use. Still, there is some rationale in trying to mimic the setup of the manufacturing equipment, particularly for the isolator filling environment. The benefits of doing so are centered on optimizing the VHP cleaning cycle and understanding its product impact, while also providing an authentic manufacturing-like experience for training purposes. However, an isolator also inhibits access to the filling equipment. This is not as critical in the manufacturing environment, where mechanical manipulations are infrequently made. In the development environment, though, adjustments to the machine are common and are, in fact, a necessary part of many studies.

Another consideration is that non-manufacturing filling equipment can be used for pre-clinical drug product filling, as long as the filling environment is controlled and meets GLP (Good Laboratory Practices) requirements. Adding this capability to the new filling equipment is desirable to Clinical Manufacturing, as it would open up more time on their production schedule for clinical runs and reduce the amount of overtime required to meet clinical demand. (Under the current setup, Clinical Manufacturing occasionally runs at >100% capacity utilization). A GLP filler would also give Amgen the ability to manufacture pre-clinical drug products with characteristics not allowed in the Clinical Manufacturing plant, thus reducing costs of making these drugs externally. Both of these are examples of ways in which the cost of a new filler can be partially offset.

Our preference is for an ISO 5 filling environment without an isolator. This would allow GLP manufacturing but would not limit the accessibility of the equipment. DPE already possesses a test isolator on which the impact of the isolator cleaning cycle on a new product can be assessed, so there is little benefit to adding an isolator to the new filling equipment when an ISO 5 environment can be achieved in other ways.

Utilities and Cleaning

There are certain unavoidable accessories to the filling equipment; utilities and cleaning are two. Utilities include power supply, air, and nitrogen. A laboratory filler has the same requirements for each of these as a manufacturing filler: 480 volt AC, 3 phase, 60 Hz electric power; 80 psi clean air; and N_2 overlay capabilities. This means that any room in which the new filling equipment resides must be equipped with these. As for cleaning, a T-P filler can use CIP and SIP for most of its product contact parts, but this requires a set of CIP tanks, pipes, and automation, as well as clean steam. While these all add cost to the filling equipment investment, they are necessary to achieve a manufacturing-like filling operation. There is no way to have the desired filler without including these extras.

Process Steps and Flow

One topic on which we received a wide array of feedback from our DP Network interviewees is that of the process steps to be included in a new filling equipment setup. The minimalists argue that only a filler is needed. This is the least expensive option and still gives all the information needed to understand the filling process-product interaction. Others believe that automated stoppering and capping (and plunger-placement, for syringes) equipment is a necessary addition. Without it, any personnel time savings gained by using an automated filler is given back through manual stoppering and capping. There are also some who insist that a fully integrated filling process is the best option. This would include everything from component preparation, such as automated de-lid/de-lining (for syringes) and vial washing/depyrogenation, to product pre-processing (product hold tank, sterile filtration, surge vessel), to post-filling (stoppering and capping). Finally, one or two forward-thinking people want to invest in modular filling equipment, unlike anything Amgen currently uses. While this is a novel approach and matches what many believe is the future of drug product filling, it does not meet our criteria of investing in equipment that represents a reasonable approximation of the manufacturing filling equipment.

While we agree that a fully-integrated line most closely matches manufacturing and would allow for better process understanding and troubleshooting, we believe it comes at too steep a financial cost.

We propose cutting out the component preparation steps (vial preparation equipment would be hugely beneficial to DPE, but should be part of a separate capital project) and limiting the pre-processing equipment to a temperature-controlled product hold tank and surge vessel. Filtration – a capability already possessed within the development organization – requires expensive filters and can be performed separately. In summary, beyond the filling machine, we propose investing in a hold tank, surge vessel, and an automatic stoppering and capping machine and plunger-placement unit. Additionally, we prefer for the equipment to be adaptable to future changes, such as the attachment of a filtration unit or vial washing and depyrogenation line. The equipment should be like building blocks in that they can be connected and built upon when additional equipment becomes available.

Automated vs. Manual

DPE's existing filling machines are manual in that they require a staff member to physically place a container under the nozzle and then push a button to initiate filling. Each container is then manually stoppered and capped (or a plunger is inserted). This process is repeated for however many units are to be filled. Filling with these machines is a time consuming event, and the number of units filled is limited by these time requirements. Furthermore, the DPE personnel using the filling machine must sacrifice a significant amount of time to complete a fill. These staff members have other important work that is put off in order to dedicate enough to the manual filling process.

Our interviews revealed frustration among many DPE members over the burdensome manual filling equipment currently possessed by the group. Most staff members were adamant that a new filler must be automated. Naturally, there is a convenience cost associated here, so we need justification beyond frustration-avoidance in order to spend money on an automatic filler. One benefit of automatic fillers is that they enable relatively large fill lots compared to the existing equipment. But is there a need for filling larger lots in DPE? Not necessarily, but there are such needs across the rest of the DP Network. For example, toxicology and stability lots currently manufactured in the clinical manufacturing environment can be manufactured elsewhere – if the right equipment is available. An automated filler

would make a laboratory setting a much more desirable location for filling these non-clinical lots. Another example is DPD's Design of Experiment (DOE) studies, which require a large number of filled units using a variety of different formulation parameters. An automated filler would allow for larger DOEs with more factors explored without increasing the fill time required.

In our opinion, these examples, plus the DPE staff time potentially saved, are rationale enough to support investing in an automated filler. In fact, if we had decided that a manual filler would suffice for the network's needs, then no new investment would be necessary at all. The true benefit of a new filler is in its automation.

Number of Machines

Amgen fills both vials and syringes in its manufacturing plants. Each container type uses a different filling machine, mainly because of the way the containers are packaged and their cleaning requirements. Vials must first be washed and sterilized, and so they are separated into individual units prior to entering the filling line, and they remain separate until they are packaged for shipment. Syringes arrive pre-cleaned in nests, and so they move through the filling process in these nests. Amgen's filling equipment is designed to handle either individual units, or nests, and not both. (Amgen will fill cartridges in the future, which, like syringes, are nested. Thus, cartridges will likely be filled on the syringe filling lines.)

This difference between syringe and vial filling equipment complicates our investment decision. Do we invest in two machines, at twice the cost of one machine, in order to fill both syringes and vials in the same way they are filled in manufacturing? Or do we invest in a single machine capable of filling both but does not match the manufacturing equipment? Our preference is for one machine, for financial reasons, but we do not want to render irrelevant the information produced with this equipment. To make an informed decision, we must first understand the differences between a multi-container filler and a single-container filler.

According to Amgen's internal filling experts, there are two basic ways to use one filler for both vials and syringes. The first is to change the vial cleaning and packaging design. If Amgen were to order pre-cleaned and pre-sterilized vials that are contained in nests, these could easily be filled with the same filler as the syringes. However, in ordering these types of vials, Amgen would be eliminating the opportunity to perform equipment-container compatibility studies for traditional vials. Additionally, the vial line operation could not be mimicked for operational troubleshooting or other such purposes.

The second approach is to have a flexible fill line with the change parts required to transform a vial line into a syringe line, and vice versa, with little effort. This is a more expensive option than the one previously described, but it would allow use of manufacturing-like primary containers and maintain a manufacturing-like process flow. As such, this filler setup would be better suited than the other to anyone interested in investigating the impact of the filling equipment on the primary containers themselves – a major concern for some container types (e.g. plastics).

Our preference comes down to the relative importance of cost versus comparability to manufacturing process flow. The cost difference is potentially significant – possibly more so than any other factor we are investigating – while the process flow comparability may still not be guaranteed, even if the more expensive option is chosen. Accordingly, we believe a single filling machine capable of filling all primary containers is the better choice.

5.2.1.6 Summary of Filler Decisions

As described earlier, our filling machine specifications are based on input from subject matter experts and other members of the DP Network, as well as our own considerations of cost and functionality. These specifications, summarized in Table 6, are nothing more than recommendations and can be modified based on information not currently available to us or adjusted to reflect changing requirements. The filler described by our recommendations is one that is capable of mimicking manufacturing product impact, our highest priority when making decisions on each of the characteristics

under consideration. It also minimizes cost in a few important areas – number of fillers and change parts, floor space, process steps included – while using higher cost options in other areas where the added functionality was deemed necessary – automation of filling, weighing, and stoppering/capping, ISO 5 environment, CIP/SIP. The filler described would reduce study time, while providing more relevant data to manufacturing. It does not fully replicate process flow, but this was a necessary concession, giving the price increase that would have been required to completely match manufacturing. Besides, process flow is already well understood for existing SKUs on Amgen's manufacturing equipment. New SKUs are seldom introduced, and studies on these can be conducted using manufacturing or vendor equipment when needed (as is currently done).

Table 6: Summary of filling equpmenet recommendations.

Category	Recommendation	Notes
# of Fillers	One filler, capable of filling all primary containers. Container flow will be in tubs, using a nested configuration	Lower cost Smaller footprint Does not simulate vial flow
Automation vs. Manual	Automated	Matches manufacturing Saves time Higher cost
Process Steps / Flow	Filling, stoppering/plungering, capping	Lower cost than including all affiliated steps Smaller footprint Reduces container closure time
Utilities / Cleaning	Utilities: 480 volt AC, 3 phase, 60 Hz electric power; 80 psi clean air; and N_2 overlay capabilities. Cleaning: CIP and SIP capabilities and equipment	Matches commercial filling equipment and cleaning
Environment	ISO 5 clean room, no isolator	Equipment more accessible/configurable than with isolator Lower upfront cost; higher operating cost
Temperature Control	Yes, jacketed product transfer tank for temperature-control	Mimics commercial filling Better understanding of temperature impact Higher cost
Checkweighing	Automatic weighing	Generates useful data Non-destructive Higher cost than manual
Fill Speed	30-50 units/minute/needle	Matches manufacturing fill speed (product impact) Does not match throughput

Product Contact Materials	316L stainless steel machine parts, surge vessel, and product transfer tank; silicone and Teflon tubing	Matches Amgen's new commercial filling equipment
Dosing	Time-Pressure as primary dosing mechanism; Rotary Piston as backup.	Matches Amgen filling standards Mimics shear of all new filling machines.
Containers	Vials and syringes, plus adaptability to new container types, such as cartridges and plastics.	Matches manufacturing

5.2.1.7 Business Case

With the specifications defined for our desired new filling equipment, we must create a business case to justify Amgen's investment. The case is relatively straightforward, as we believe that many advantages can be realized by purchasing the new filling equipment. In particular, we focus on the capital investment's impact on five categories considered critically important by Amgen: economics, speed, risk/quality, supply, and alignment. Each is discussed separately in the following sections.

Economics

New filling equipment has a clear and quantifiable cost to Amgen. This includes the fixed equipment purchase cost – typically upwards of $10 million -- as well as recurring operating, maintenance, and labor costs, and the cost of the floor space required. While these costs are not insignificant, they can be offset by some of the benefits gained through use of the new equipment. Unfortunately, the magnitude of these gains is difficult to estimate, as the financial value may be spread over many years, only occasionally realized, or, most likely, not obvious. Regardless, assigning even a rough value can help us understand whether the financial benefits might outweigh the costs, thus helping justify the business case for a new filler. In Appendix A, we provide a sample Net Present Value calculation that can be customized for Amgen's purposes once the appropriate data are available.

Here, we qualitatively discuss several potentially non-trivial financial benefits to purchasing and using the new laboratory filling equipment specified in the previous sections. The first two are by increasing utilization of the commercial and clinical manufacturing facilities. The others are by reducing reliance on contract sites, diminishing the likelihood of discarded commercial product, requiring less bulk

drug substance for large scale engineering and characterization runs, more quickly commercializing new products, and mitigating the risk of not meeting patient demand. Each of these is discussed below, but more in-depth analysis will be required if a decision is to be based on these benefits.

Commercial Utilization

Prior to manufacturing a new drug product at a commercial site, or prior to introducing a new SKU or similar product or process change, Amgen typically requires studies to ensure manufacturability of the new or modified product. Today, these studies are commonly performed on the commercial site equipment, and thus the commercial site is unable to make actual drug product while the studies are in progress. If the commercial sites are running at capacity, there would be an opportunity cost associated with these studies. For example, if the studies required use of commercial filling equipment for one day, the opportunity cost is the cost of the product that would otherwise have been produced that day. (There are other ways of calculating opportunity cost, as well. It could, for instance, be the facility operating costs. We chose to use product cost because it represents Amgen's philosophy of always ensuring that its patients are supplied with product.) Biologics are of high value, so the opportunity cost would be quite high in this example. However, Amgen's commercial sites do not typically run at capacity. In fact, the planning group budgets ~10% of equipment time for non-production activities, such as these studies. As such, unless the studies need >10% (24 days) plant time in a given year, there is no opportunity cost of using the commercial equipment.

There are, however, two caveats to the "no-cost" scenario described in the previous paragraph. First, Amgen's pipeline is growing, which means that there is a chance of additional commercial products in the portfolio in the foreseeable future. The implications of this are twofold: more manufacturability studies will be required, and the commercial production volume will be higher. Both of these outcomes increase the probability of conflict between the studies and production runs on the commercial equipment, which in turn increases the likelihood of study-induced opportunity cost.

The second caveat is the impact of Amgen's changing manufacturing landscape. Two new commercial sites are being brought online in the next few years – one in Puerto Rico and one in Ireland. Once the new Puerto Rico site is running, there is a chance that the old Puerto Rico site (currently, Amgen's only in-house commercial drug product manufacturing facility) will be shutdown. The capacity of the new plants should at least equal the capacity of the existing facility but with one major difference: changeover time. The new fill lines will be equipped with isolator technology, which, as described earlier, requires a long (~12-hour) cleaning cycle between different product fills to avoid cross-contamination. This means that every time a study is run on the manufacturing fill line, the total line time required is equal to the study duration plus up to 24 hours for changeover (depending on whether the study is for the same or a different product than is being manufactured). This is not insignificant and represents a dramatic shift from the current state, in which changeover can be completed in a matter of hours. The increase in changeover time has one clear consequence: a greater probability of a study affecting commercial production, and therefore generating an opportunity cost.

Clinical Utilization

Performing studies using the clinical manufacturing filling equipment at Amgen's facility in California can have a similar opportunity cost to the one described above for the commercial sites. Of course, the opportunity cost is lower in the clinical environment than in the commercial environment, since the clinical product has no market value. Instead, the opportunity cost is the value of a "fill slot," which is essentially a working day in the plant. At Amgen, a fill slot includes the variable filling operational costs, along with quality support and overhead.

As in the commercial utilization discussion, the existence of an opportunity cost in the clinical plant depends on whether or not equipment time is available. Here, too, non-production time is built into the schedule for maintenance and studies. In 2011, out of 270 available fill slots, only 190 were scheduled for clinical material production, a 70% utilization rate. While it would appear that sufficient time was available during the year for DPE and other groups to access the equipment, in reality the plant

utilization was significantly higher, particularly at the end of the year. Specifically, November and December utilization were each >100% (overtime was required to fill all clinical lots). As such, using the machines for studies at this time would have had an associated opportunity cost. Purchasing a filling machine for the DP Network would help avoid these costs.

One final note on both commercial and clinical utilization: regardless of the amount of non-production time built into the production plan, there is still a convenience cost of using the manufacturing equipment for filling studies. In other words, one must schedule around the manufacturing production plan. For example, if the clinical plant had its equipment available for all of October 2011 but a researcher did not need to perform a study until November (when the plant was already overbooked), then the built-in non-production time was not useful.

Contract Site and Vendor Reliance

When time on the commercial or clinical equipment is not available for studies, Amgen often asks its vendors for help with the tests. For instance, there may be concern that a highly viscous new product could encounter filling issues on the syringe filling machine in Puerto Rico. Since that machine is in use, Amgen sends a sample of the drug product to Cozzoli (the manufacturer of the syringe filling machine) for investigation. Similarly, any contract manufacturers of Amgen's products may be relied upon to run studies on their equipment, requiring Amgen to pay for their line time at some quoted rate. If Amgen had a suitable representative filling machine available in a lab, the cost of using a vendor for the study could have been avoided.

Drug Product Discarding

A filled and finished drug product has a considerable cost associated with it. Thus, discarding a filled unit for any reason comes at a steep price, both in terms of actual cost to Amgen and the market value of the product. Product can be discarded for a variety of reasons, including product quality test failures (due to changes in protein structure, potency, or appearance, for example), out-of-specification

fill weight, visual inspection failures (of either the product or the container), broken containers or damaged packaging, prolonged exposure to unacceptable temperatures, and other such issues. Many of these are unavoidable, but the risk of occurrence of some can be reduced if the product-process interaction is better understood prior to manufacturing. For example, if a manufacturing-like filling machine is used for filling studies, undesirable product quality impacts or likely sources of fill weight errors can be identified early, and process changes can be made to eliminate these effects.

Bulk Drug Substance

As described in the preceding paragraphs, operational and other costs of biologics are substantial. Much of this cost comes from the drug substance manufacturing portion of the process, which consumes the majority of the overall resources and time allocated to biologics production. The cost is great even when the drug substance is produced in smaller amounts in a pilot plant, as much of the material used in commercialization studies is. A reduction in the amount of material required for these studies could both save Amgen the cost of manufacturing the drug substance and enable the pilot plant staff to focus their efforts on more value-added activities. A new filling machine in a DP Network laboratory could create such an outcome, as its smaller scale would enable use of less drug substance material while still representing the manufacturing environment. This result is not a certainty, however, and so we add the caveat that our claim can only be true if accompanying changes that call for less drug substance are made to the filling study protocols.

Commercialization Speed / Time-to-Market

To generalize, a company that enters a market first can capture more of the market share than a competitor whose market entry lags behind. Of course, if the first company rushes to market at the expense of quality, or if the second competitor has a clearly superior product, the market share can shift if favor of the second. Notwithstanding these exceptions, there is an advantage to being the first to enter a market, and efficient operations that are designed to shorten a product commercialization cycle can make this a reality.

In biotechnology, there are many obstacles a new product faces before commercial launch. From an operational perspective, this includes demonstrating process understanding and control and passing validation runs. Additionally, a company must also successfully manufacture a product, both to supply clinical trials and, after regulatory approval, to supply the commercial market. The new filling machine we propose purchasing could potentially speed up commercialization time and reduce the likelihood of delays. The filling machine can shorten the commercialization cycle by eliminating the bottleneck the commercial filling equipment creates by being the sole internal asset on which representative filling studies can be performed. Similarly, it can help avoid commercialization delays by allowing earlier detection of potential fillability issues that could otherwise have resulted in validation run failures or product quality issues.

Patient Supply

Intimately tied to increased commercial utilization and reduced risk of product quality failure is the ability of Amgen to supply patients with the drugs they need. A failure to do so could result in a loss of goodwill that impacts sales and stock price, in addition to the obvious missed sales due to unavailable product. In the same ways that our proposed new filler could shepherd financial gains by alleviating commercial site utilization issues and avoiding discarded product, it could likewise do so by maintaining the ability to meet patient demand.

Speed

DPE members can sometime spend a substantial amount of time performing filling studies on the manual fillers in DPE's labs. These highly educated staffers (many with PhDs) can spend multiple days per study filling, stoppering, and capping thousands of individual units, when there is other important pipeline-related work awaiting them. A new automated fill line on which these studies could be performed would generate significant time savings when the studies are large. It is important to note that setup time on the new equipment would likely be longer than the setup on the existing equipment. Thus, if study time is more important than other equipment characteristics, the DPE staff could choose which

equipment to use based on which would allow the shortest overall study duration. Specifically, they would use the new equipment when the following holds true:

$$\textit{\# of units to be filled in study} > \frac{setup\ time_{new} - setup\ time_{old}}{fill\ time\ per\ unit_{old} - fill\ time\ per\ unit_{new}}$$

Risk

As an industry, biotechnology companies tend to be risk averse. While this cultural trait might originate from patient safety concerns, it has carried over into companies' operations, as well. A relevant example might be a company going to great lengths – multiple internal and external studies, test protocols, excessive process monitoring, etc. – to ensure that a new product can be filled at a manufacturing site, rather than using past experience or theoretical approaches. As such, any measure that reduces systemic operational risk can potentially save a company like Amgen substantial time and money. Our assertion is that a new filler would accomplish this by providing a better, more germane dataset to support transfer of a product to the commercial site. This would reduce the risk of validation run failure, as well as non-conformances (process excursions) during manufacturing.

Quality

Amgen is required to test its products to ensure the safety and efficacy is within a prescribed range. As described earlier, the filling unit operation can potentially change some of the product characteristics through shear and other effects. It is critical that this impact is understood prior to commercial manufacturing. Otherwise, there exists a risk that product will fail the quality tests, necessitating product discarding. This has both economic and supply implications, as discussed previously in each of the corresponding sections.

Product quality also plays into the filling unit operation in another way: fill weight. Each unit must be filled to a level within a specified tolerance. Any unit filled outside this range is discarded, even if the product within meets all other specifications. For example, some products have a tendency to drip, which might mean that product intended for one unit accidentally drips into another unit. Such behavior

can be observed and understood earlier if manufacturing-like equipment is available. The filler we recommend purchasing would provide such early detection capabilities, thereby reducing the likelihood of manufacturing product quality issues.

Supply

In considering the effect on supply, we apply the same logic as in the 'Economics' section. Using new filling equipment that is representative of manufacturing allows us to relocate some studies from the manufacturing equipment to the new equipment. This means that more time on the manufacturing equipment can be dedicated to meeting commercial and clinical demand. Amgen has made a commitment to its patients that it will never fall short of supplying a patient with medicine – "Every patient every time" is the guiding principle. Any measure that helps Amgen maintain this commitment should be desirable, and this filling equipment investment is no exception. Additionally, as noted in the 'Quality' section, the new equipment would generate a greater assurance of commercial product quality, which in turn should reduce the likelihood of discarded product due to quality failures. This means production targets can be met with higher probability and patient supply can be maintained.

Alignment

Amgen has made a concerted effort to align across functions, geographies, and products. (In fact, this project is evidence of the company's commitment to achieving alignment.) By purchasing the filling equipment we recommend here, better alignment would be achieved between DPE/DPD and Amgen's clinical and commercial manufacturing sites. This would be a much needed step in "walking the talk." In addition to the other benefits outlined above, this purchase would also represent something less concrete but more meaningful. It would prove, more so than anything done so far, that Amgen believes in the importance of alignment to the company's future.

Summary

We use the Pilot Plant Cooperative framework to choose from among multiple options for closing a Filling unit operation gap in the DP Network. Based on stakeholder feedback and our own analysis, we recommend that Amgen purchases a new pilot-scale filling machine for use in process scale-up and evaluation activities. There are many potential benefits to Amgen of making this investment, including financial and time savings, quality improvement, risk reduction, supply maintenance, and alignment promotion.

5.2.2 Case Study #2: Clinical Support of Commercial MFG

The Pilot Plant Cooperative's utility is in making evident existing opportunities that could create a more efficient commercialization process. As it turns out, many of these opportunities reside in the Clinical Manufacturing organization. To reiterate the point made earlier, transferring a product and process to a commercial site requires complete understanding of important process parameters and equipment settings. All of Amgen's internally developed commercial products were once manufactured in the clinical plant, and the unit operations in both plants are identical. Thus, this manufacturing experience could provide a relevant commercialization dataset in a more efficient way. In some cases, however, equipment and procedural differences preclude transfer of clinical data.

In this section, we present a case study that investigates how Clinical Manufacturing can facilitate the commercialization process, focusing specifically on the data needed for process characterization. We also discuss the changes necessary, if any, to generate more pertinent data. We divide the discussion by unit operation, as each has a unique role in the generation of data.

5.2.2.1 Bulk Drug Substance Freeze and Thaw

Drug substance freezing and subsequent thawing is a passive and straightforward unit operation, usually performed in two different locations – the liquid is frozen in the drug substance manufacturing facility and thawed in the drug product manufacturing facility. The product is transported in a frozen

state between the two facilities by truck or plane, depending on the relative locations. The most critical aspects of this operation are the rates of freezing and thawing, which depend on the heat transfer between the environment and the product. The heat transfer, in turn, depends on a number of factors, including the room temperature, the container type, the liquid volume relative to the container size, and the location of the container relative to other containers. Additionally, exposure to light and the vigor of agitation (when used) are also important during this step.

Currently, the clinical and commercial sites do not always use the same size containers. Commercial manufacturing almost always freezes drug substance in 10 L polycarbonate containers, while clinical manufacturing may use 2 L containers instead. Even when the same size containers are used, the conditions of the freeze and thaw may differ in terms of the light exposure, distance between carboys, and fill volume. If procedural changes are made to ensure these conditions are the same, then clinical manufacturing data about freeze and thaw times and the impact on product quality can easily be used to support commercialization, possibly eliminating the need for additional freeze/thaw studies.

Table 7: Freeze-thaw characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Type of bulk container and fill volume • Freeze and thaw temperatures • Freeze and thaw time range • Freeze/Thaw cycle limit • Distance between carboys • Light exposure • Agitation speed (for dynamic thaw)	• Logistics of storage • Handling • Transportation	• DPE F/T study • Monitoring of B20 lots • Monitoring of commercial eng run • Mimic solution F/T

5.2.2.2 Formulation and Mixing

Drug product formulation and mixing is a relatively simple unit operation with generally little product impact. Nonetheless, full-scale characterization studies are performed to understand the time required to achieve homogeneity, as well as acceptable time, temperature, and speed ranges (

Table 8). Since the mixing operation exists at the clinical and commercial sites, there is an opportunity to use the clinical data in place of, or to support, commercial mixing characterization. For instance, time to achieve homogeneity, or the ideal mixing parameters, may already be known for a given product and can simply be transferred. Unfortunately, the mix tank dimensions and impeller locations differ between the scales, greatly reducing the relevance of the clinical data. Improving the situation would require clinical investment in new mix tanks with identical geometries and impellers to the commercial sites (e.g. 45, 115, and 500 L stainless steel tanks with bottom-mounted, stainless steel, non-Teflon impellers, and a 0.2 – 0.35 impeller:tank diameter ratio).

Table 8: Formulation characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Mix speed range • Mix time range • Mix temperature range • Batch size range	• Mix tank and impeller geometry • Impeller mounting location	• DPE shear study • Stability profiles • Full-scale mimic solution mixing • Full-scale homogeneity study

5.2.2.3 Filtration

The two filtration steps – bioburden and sterile – are performed in a consistent manner on similar equipment at the clinical and commercial sites. Of all the unit operations, the opportunity to use clinical data in support of commercial characterization without procedural or equipment changes is probably greatest for the filtration operation. For instance, Vmax can be measured during clinical drug product manufacturing by simply recording the volume filtered over time. This calculation can be used in place of the separate Vmax study performed by DPE prior to commercialization. Additionally, the compatibility of the drug product with the filter type used in clinical manufacturing provides information normally collected during a separate study. Finally, data on polysorbate homogeneity and binding can be easily captured during clinical runs. In short, much of the data required from characterization studies is

already available in clinical manufacturing. The data would be even more relevant if clinical manufacturing invests in a jacketed stainless steel hold tank for temperature control of the drug product. With this, there would be further assurance that the drug product is filtered under identical conditions at the clinical and commercial sites.

Table 9: Filtration characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Target pressure and limits (based on Vmax, flux, and filtration time from DPE and B20)	• Filtration apparatus (tubing size/length, fitting, connection) • Filter membrane area and filter geometry • Single vs. dual filtration • Filter preparation (flush, bubble point)	• Vmax, flux, filtration time from DPE study • DPE filter compatibility study • DPE pressure impact study • Monitoring Vmax/Pmax and PS20 homogeneity and binding at Commercial

5.2.2.4 Bulk Drug Product Hold

Bulk drug product hold in a stainless steel tank exposes the drug product liquid to the tank surface and the air overlay for an extended period of time. Depending on the product's sensitivity to the stainless steel or to oxidation, this hold duration may need to be shortened to avoid adverse product quality impact. These steps are performed in consistent environments in the clinical and commercial settings, but the tank sizes and fill volumes can differ, which means that product exposure to the tank and air can vary depending on the site. If these differences are measured for each product and used to develop an exposure conversion factor, then the longest hold duration during clinical manufacturing can serve as the starting point for commercial site hold studies.

Table 10: Stainless steel tank hold characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Hold duration • Hold temperature	• Hold tank (material, size, fill volume) • Tank location (temperature, light)	• DPE hold time evaluation • On-site engineering runs

5.2.2.5 Filling

The filling equipment differs somewhat between the commercial and clinical sites, as described in detail in the previous case study. To summarize, the clinical filling machines use the same dosing technology as the older commercial equipment but differ greatly from the new commercial equipment in both Puerto Rico and Ireland. Since Puerto Rico will likely transition fully to the new equipment over the next few years, we focus our recommendations on that future state. There is some information that can be transferred from clinical to commercial regardless of equipment differences. This includes filling challenges (e.g. drug product with a propensity for dripping or sticking) experience during clinical runs and certain equipment settings, such as nozzle size. Still, with this knowledge, characterization work on the commercial site will be needed. Avoiding this work is only possible if clinical manufacturing invests in new filling equipment that meets Amgen's filling standards: time-pressure dosing with an isolator barrier. Consistent filling technology could then enable sharing of many settings, including speed, overfill volume, vacuum, T-P parameters, and surge tank volume control.

Table 11: Filling characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Pump size (for Rolling Diaphragm and Rotary Piston), nozzle size, cam drawback (vials) • Line speed range • Fill weight alert and action limits (w/ overfill volume/weight) • Plunger placement/vacuum settings (syringes) • Level control in surge vessel (for sterile filtration/filling) • Future: Pressure and time settings for T/P filler	• Filler type and change parts • Surge vessel size	• Bench-top fill evaluate in DPE • DPE shear study • B20 fill monitoring • Commercial site fill characterization

5.2.2.6 Lyophilization

Only some of Amgen's drug products require a solid dosage form, necessitating a lyophilization process step. In fact, Amgen's Puerto Rico manufacturing site does not even run this unit operation, leaving all lyophilized products to contract manufacturers (and, eventually, to the new Ireland site). The unit operation is complex, involving a number of controlled temperature and pressure changes. The clinical and commercial lyophilizers have similar capabilities but are of different makes and models, and therefore there is no easy way to transfer recipes from one to the other. Hence, the machines' comparability (e.g. effect of shelf number, duct dimensions, surface areas, heat and mass transfer) must be characterized to enable transfer of settings and recipes. Additionally, with known comparability between the sites, clinical manufacturing might be able to perform worst-case challenges to set an upper boundary for the commercial site runs.

Table 12: Lyophilization characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Lyophilization cycle parameters (shelf temperature, pressure, ramp rates, time) • Batch size / shelf load	• Shelf temperature mapping • Pressure control precision • Radiation of heat • Sublimation rate / condenser capacity	• DPE lyo cycle development • Pilot plant characterization • B20 lyo monitoring • Full scale runs under target and worst case conditions

5.2.2.7 Inspection

Drug product is inspected either manually or automatically, depending on product characteristics and inspection machine capabilities. Amgen's clinical manufacturing facility currently has a vial inspection machine, but no syringe inspection machine. Furthermore, the vial machine is relatively old and lacks many of the capabilities of the commercial vial inspection machine. Further clouding the picture, the clinical site recently decided to purchase a new vial inspection machine, but this one also differs from the existing vial machines at the commercial site. In short, the lack of comparability between the clinical and commercial inspection equipment means that very little data can be transferred between the two, unless a comparability study is performed to determine appropriate conversion factors for various equipment settings. Without this information, the best information available for transfer is the existence of potential inspection challenges. For instance, a drug product may have a combination of moderate viscosity and particle load that, on their own would not present an issue, but in concert caused the inspection machine to miss identify 'passing' and 'failing' units. This knowledge might lead the commercial site to take extra precaution during inspection, or possibly to switch to manual inspection.

Table 13: Inspection characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Automatic: spin, break, light strength, view setting, sensitivity setting • Manual: inspection procedure	• Equipment type • Manual inspection station	• DPE inspection evaluation and particle studies • On-site qualification and validation of equipment settings

5.2.2.8 Light and Temperature Exposure

Drug product exposure to environmental factors – light and elevated temperature, in particular – is of great concern, as long exposure duration can lead to product degradation. Characterization work is performed to understand at what point product quality is affected by exposure and to ensure the commercial manufacturing process does include such conditions (Table 14). Having some separate studies at the commercial site makes sense in this case, since the facility layout, and thus the lighting and temperature conditions, are different than at the clinical site. However, there are opportunities to better use the clinical data. One such opportunity is to leverage the exposure times of drug product during clinical manufacturing and use these times to set commercial process limits rather than perform a new set of exposure studies (or, alternatively, to use these times as a baseline for the experimental design). Another option is to use the exposure study data generated by DPE before clinical manufacturing and adapt it to the commercial site. If this option is to be considered, the lighting conditions must first be mapped at both the clinical and commercial manufacturing sites. This will allow a better comparison of lighting intensities between the sites, which can be used to understand how light exposure at the clinical site can give meaningful information about exposure at the commercial site.

Table 14: Light and temperature exposure characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Light intensities in cold room, mfg floor, inspection station • Physical location of product • Duration of light exposure • Operation temperature and duration	• Site lighting conditions (light map) • Temperature monitoring	• Formulation stability tests • DPE photoexposure study w/commercial site light mapping

5.2.2.9 Component Preparation

Component preparation, while not itself a manufacturing unit operation, affects container and product quality and must run synchronously with the manufacturing process. Our definition of component preparation includes container (e.g. vial) cleaning and sanitization, as well as process equipment washing, autoclaving, and CIP/SIP. Commercial component preparation includes tests to assess product cleanability and determine ideal cleaning routines (Table 15). These tests are performed for each new product transferred to the commercial site. Meanwhile, Clinical Manufacturing runs a consistent "worst-case" cleaning procedure for all products demonstrated to be easier to clean than a historical worst-case product. The clinical routine could be used as a starting point for commercial method development, thereby capping the upper limit of the experimental design. Product specific information from DPE's clinical cleaning studies could augment the dataset to a greater extent, further narrowing the characterization experimental range.

Table 15: Component preparation characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Dirty equipment load, staging time, dirty hold time • Cleaning cycle (steps, concentration and volume of solutions, time, temperature)	• Type of rinse and washing equipment • Maximum allowable product carryover	• DPE coupon cleaning evaluation • Monitoring of B20 cleaning • Evaluate max allowed carryover • Perform cleaning monitoring and/or validation at commercial site

5.2.2.10 Transportation

We define transportation as all of the activities involved in moving filled drug product from Amgen's manufacturing facilities to its warehouses, distribution centers, and customers, including the labeling and packaging processes. Transportation is not a drug product manufacturing unit operation, but it is nonetheless an important step in the drug product value chain and has implications for the quality of drug product ultimately received by customers. The process of characterizing and qualifying transportation, labeling, and packaging involves a number of tests that are used to ultimately set commercial parameters (Table 16). Few of these tests are performed on the commercial site equipment, but one that is has room for improvement. Without a packaging pilot plant, commercial line development is often performed on the commercial line itself – an inefficient and potentially costly practice. There is an opportunity to instead test new configurations on the clinical line to generate data that could enable more efficient introduction of configurations to the commercial site.

Table 16: Labeling, packaging, and transportation characterization attributes

Operating Parameters for Commercial Site Transfer	Equipment Considerations	Current method for setting ranges
• Packaging configuration and procedure • Vibration, pressure, temperature of transportation lane • Transportation route and carriers	• Packaging qualification • Label and Pack line setup • Transportation carrier	• DPE transportation simulation • Transport OQ • Real-world transport/performance qualification • Packaging drop test

Summary

In this case study, we employ the Pilot Plant Cooperative as the basis for recommending improved data transfer from Clinical to Commercial Manufacturing. Our suggestions include purchasing new equipment, modifying procedures, and collecting additional data to better align the unit operations performed by the two manufacturing groups. The expected result is a more robust and efficient commercialization process.

5.2.3 Case Study #3: First-in-Human Process Evaluations

The Pre-Commercial DPE group initiates First-in-Human (FIH) process evaluation studies to prepare for the introduction of new drug products to the clinical manufacturing facility. Since these new products have never before been processed on manufacturing-scale equipment, it is important that the process-product interaction be determined and the procedures and equipment adjusted accordingly to minimize preventable manufacturing and quality issues. DPE's studies are designed to do just this; each study reveals important information about product physical properties, manufacturability, or product quality impact. Our objective in this case study is to improve the efficiency of these FIH process evaluation studies by employing elements of the Pilot Plant Cooperative.

DPE's FIH studies can be time-consuming, and, along with other FIH activities (including writing technical reports, attending meetings, and supporting manufacturing), can require a significant time commitment. Since the DPE staff is already time-constrained due to other pipeline commitments, improving the efficiency of the FIH studies could have a meaningful impact on the group's productivity in other areas.

In this case study, we examine efficiency improvement opportunities in DPE's FIH studies. In particular, we aim to uncover the purpose of each study and, using the Pilot Plant Cooperative concept, determine whether the intended outcome can be achieved through other, more efficient, means. This might involve modifying a study to reduce the time or material requirements, generating data with different equipment or by partnering with other groups, using a model as a study replacement/supplement or as a screening tool, or eliminating a study altogether with support from historical data and process understanding. When multiple options are available for a study, we use a rating system to rank the options based on how well each maximizes efficiency without compromising product transfer to the clinical manufacturing site.

5.2.3.1 Scope

In looking at improving process development efficiency, we chose to refine our scope in two ways. First, we selected FIH over other phases of development (e.g CPD, PC) because its studies are typically consistent from one product to the next, because there are fewer studies than in other stages, and because the historical dataset from past products is relatively large. Second, we decided to evaluate study efficiency improvements only for those FIH products that use Amgen's platform formulation. Amgen has had extensive experience with this formulation, and so its interaction with the manufacturing process is relatively well understood. In short, the subset of products in the platform formulation provides us with a starting point for recommending FIH studies changes. Once these recommendations are accepted and proven for these products, they can potentially be expanded to include non-platform products, and then to other stages of development.

5.2.3.2 Defining Efficiency

We define FIH study efficiency as the cost of generating the data required for introduction of a new product to the clinical manufacturing environment. Colloquially, it is a 'bang-for-buck' measurement; efficiency it is maximized when the required information is created at the lowest possible cost. According to DPE personnel, there are three components of a study that contribute to the study's cost. First is the labor hours required; this is the amount of time spent by DPE staff actively performing the study. The more time spent on a study, the less time the staff has for other work. Second is the total duration of the study. This differs from the labor hours by the amount of time the study runs without active human participation. For example, a staff member may set up and initiate a study and then let it run without intervention for weeks. The study duration is important because it affects the overall development and manufacturing FIH timeline. A particularly long study may represent a process bottleneck, delaying the start of clinical manufacturing. The third component is the amount of drug substance material used for a study. This material is expensive to make and is often in short supply (material shortages sometimes preclude performance of certain studies). Much of the material is

produced by a drug substance pilot plant, which must dedicate some of its time to supply this material rather than performing other value-added work.

5.2.3.3 FIH Platform Formulation

Amgen's FIH Phase I and II clinical trials have included an increasing number of monoclonal antibody (mAb) drug candidates in recent years. In order to reduce time and resources required for mAb FIH development activities, a platform strategy was created, generating a consistent set of studies and development guidelines. A significant part of the strategy is to use a platform formulation based on a generalized set of components and storage conditions that have been shown to be suitable for clinical testing of over twenty mAb drug candidates.

Roughly half of new FIH molecules use the platform formulation. Since the platform has been used for a large number of historical products, and thus is relatively well understood, it provides an excellent opportunity for studying the applicability of predictive modeling for FIH manufacturability studies.

5.2.3.4 FIH Studies

Physical Properties Determination

Drug Product physical properties are intrinsic attributes that define a product's behavior at typical manufacturing environmental conditions. Since a product's measurable properties are good predictors of its manufacturability, they are routinely determined during the DPE FIH evaluations. In particular, DPE measures density, viscosity, and surface tension, as described in the following sections.

Density

Drug Product density is important for its role as an input to the filling unit operation. Density is used to convert volume to mass, and so an accurate measurement of density is required for setting appropriate fill weight targets and dispensing the correct amount of product. During FIH, DPE measures density (in triplicate) at 25º C using a densitometer. This measurement is later confirmed by Amgen's

Quality group, using material from the Lead Lot fill. This second measurement is used as the official density measurement for all future purposes.

Viscosity

Drug Product viscosity – the resistance of a fluid to deformation under shear stress – is influenced by the formulation buffer, concentration of excipients, and concentration and structure of the active molecule. The viscosity is also inversely correlated to temperature and can therefore vary during manufacturing depending on the surrounding temperature. From the manufacturing perspective, viscosity has an impact on filtration, filling, inspection, and cleaning; high viscosity products tend to cause more difficulty for these unit operations. For example, high viscosity products may cause hanging droplets on filling nozzles, which could affect fill weight. Measurement of each Drug Product's viscosity is therefore necessary in order to make manufacturing recommendations for FIH manufacturing. DPE takes two measurements each at 25º C and 5º C using a rheometer across a range of shear rates. The results are compared to previous successfully manufactured FIH drug products to predict manufacturability.

Surface Tension

Surface tension is the property of the surface of a liquid that allows it to resist an external force. Historically, it has not been measured for all FIH products, but its status as an important physical property has become more widely accepted in recent years. Its relevance to the manufacturing process lies in its impact on dripping during the fill unit operation. Products with high surface tension are more likely to form the hanging droplets that often create fill weight challenges.

Drug Substance Freeze-Thaw Evaluation

Drug substance is typically more stable when frozen than in a liquid state. To take advantage of this property, Amgen freezes all FIH drug substance and only thaws the material when drug product processing is imminent. However, the liquid-solid-liquid transformation (the "freeze-thaw cycle") itself places stress on the product, potentially affecting protein integrity and product quality. According to

process experts in DPE, most product damage occurring during the freeze-thaw process is caused by cryo-concentration. Cryo-concentration can be influenced by the freezing rate (slower freezing results in increased gradient formation within the solution), the protein concentration (higher concentration increases the likelihood of cryo-concentration), and viscosity (more viscous solutions are less apt to self-mix, thus creating greater cryo-concentration potential). Furthermore, the number of freeze-thaw cycles a product undergoes is directly correlated to product quality impact. To test the product quality impact of freeze-thaw, DPE puts an FIH drug product candidate through three small-scale freeze-thaw cycles (a "worst-case" scenario).

The DPE study is performed in two stages. First, the formulation buffer (without the product) is frozen and thawed in a 10 L polycarbonate container inside a controlled-rate freezer. The temperature profile of the buffer is monitored and recorded. For drug products in the platform formulation, this first step is excluded, as the freeze-thaw profile of the platform formulation has already been recorded. In the second stage, this profile is programmed into a controlled-rate freezer, and three freeze-thaw cycles following the profile are performed on 50 mL of product inside 250 mL polycarbonate bottles. Samples are taken before the first freeze and then after each cycle and are submitted for analysis to determine product quality impact. If the test results show no product degradation over the course of the three cycles, Clinical Manufacturing is able to freeze and thaw the material up to three times without concern for product quality issues. If the data indicate product quality concerns, DPE and Clinical Manufacturing will develop a revised freeze-thaw procedure to limit the product quality impact.

Filtration Evaluation

In the filtration evaluation, DPE uses a small-scale filtration apparatus to assess product filterability. Based on the study results, DPE makes recommendations to manufacturing regarding filter size, capacity, scalability, processing times, and membrane compatibility for low protein binding. The filtration evaluation results apply to both of the filtration unit operations (bioburden and sterile filtration).

The small-scale filtration run by DPE is based on the gradual pore-plugging model, which is based on the premise that the blocking of filter pores is a function of the volume of product that passes through the filter. The result of the plugging is a non-linear decline in flow rate. A plot of filtrate volume/time (at a constant pressure) versus time creates a filtration "fingerprint" specific to a particular drug product. The maximum filter throughput, V_{max} can be derived from this plot by estimating the inverse of the slope. The V_{max} value is then used along with Amgen's filter recommendation guidelines to choose an appropriately sized filter for manufacturing of the drug product. Analytical tests on the pre- and post-filtered drug product give information on product and polysorbate retention by the filter, as well as product changes as a result of the filtration operation. One other relevant point is that the filtration evaluation is typically performed using cold (~5° C) drug product, as this represents a worst-case scenario from a viscosity perspective (filtration is more difficult for high viscosity products).

Shear Evaluation

Shear, the force per area acting on a fluid due to the presence of a velocity field, is generated during drug product processing due to velocity gradients produced by the manufacturing equipment. There are two major sources of shear in drug product manufacturing: mixing and filling. Mixing shear is of low intensity (rate) and long duration, while filling shear is of high intensity and short duration. Both types of shear could, separately and cumulatively, adversely impact product quality. DPE's FIH shear study uses a rheometer to evaluate each type of shear independently, as well as in tandem, to understand their effect on formulation stability and particle generation. Samples are taken and analyzed to test whether the product will show shear-induced degradation during manufacturing, allowing DPE and Clinical Manufacturing to make process adjustments if necessary.

Cleanability Evaluation

Cleanability is a measure of the relative ease with which drug product residue can be removed from manufacturing equipment using normal cleaning procedures. DPE performs this assessment by tracking the amount of time required for a drop of drug product to be completely cleaned from a piece of

stainless steel in a water bath and comparing it to the time required to clean a worst-case product. If the time required for the new drug product is shorter than for the worst-case product, then Clinical Manufacturing's validated cleaning procedures can be used. Otherwise, a new, more stringent, cleaning procedure must be developed.

Stainless Steel Hold Evaluation

Drug product is held at 5° C in a stainless steel vessel between the two filtration steps. Depending on the drug product's susceptibility to oxidative stress and sensitivity to stainless steel, this hold step could lead to product quality degradation. In order to understand the hold duration a product can withstand, DPE typically performs a simple hold test. In this test, product is held in a stainless steel vessel for up to a week, and samples are removed at regular intervals to test product quality. The amount of time before product quality is impacted is set as the maximum hold duration in manufacturing.

Fill Evaluation

During FIH manufacturing, drug product is filled into vials (syringes are not used at this stage). The ease of filling and the accuracy of the fill depend on the product's inherent physical properties, such as viscosity and surface tension. DPE's fill evaluation is designed to test a drug product's behavior during a small-scale fill. In particular, DPE seeks to identify any filling challenges that may be present in manufacturing and to select ideal equipment settings to minimize these challenges. Additionally, DPE determines whether the filling operation has an impact on product quality due to the high shear rates or any other processing conditions. Observations, such as dripping, stickiness, or foaming are recorded and reported to Clinical Manufacturing. Process settings, such as fill speed and nozzle size, are also sent as recommendations to Clinical Manufacturing.

Inspection Evaluation

The FIH inspection process can involve either automated or manual inspection, and both are used to detect particles and other visible and sub-visible materials in the liquid drug product. The purpose of

the step is to catch and reject all vials with undesirable visible attributes prior to packaging and shipment. During inspection, the product is exposed to light, room temperature conditions, and the physical stress of product handling during transport and inspection. DPE's inspection evaluation is not designed to catch product sensitivity to any of these conditions. Instead, DPE records observations during inspection and delivers this information to Clinical Manufacturing, along with a recommended inspection method (manual vs. automatic).

5.2.3.5 Approach

Our path in this case study involved three steps. First, we sought to understand the current state. This included defining FIH studies in terms of their purpose and procedures, determining the costs (labor, duration, and materials) of each study, and identifying all other DPE FIH tasks. Second, for each study, we developed a set of alternative approaches, each generating the same output as the current study but using different methods. Finally, we used KT analysis to compare all study options and make a recommendation for the most efficient option.

5.2.3.6 Results

Step 1: Current State

The DPE FIH process evaluation studies, described above, all have a specific purpose, whether to determine the impact of the manufacturing process on product quality, or to recommend procedural or equipment settings. Combined, they form a data package that enables transfer of an FIH drug product candidate into the clinical manufacturing environment. The current state of each of these studies, along with their purpose, inputs, and outputs are summarized in Table 17.

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Table 17: Summary of DPE FIH studies

Study	Purpose	Critical Inputs	Output
Physical Properties Measurement	Determine key physical properties of drug product.	N/A	Density at 25C; Viscosity at 25C and 5C; Surface Tension
Freeze-Thaw Evaluation	Study impact of multiple freeze-thaw cycles on DS. Selection of parameters to minimize occurrences of NCs during freeze, storage, and thaw.	Freezing rate (influences degree of supercooling and ice front velocity) Freeze temperature and time Thaw temperature and time Thaw agitation DS volume and container type/geometry	Max number of freeze-thaw cycles (based on PQ impact)
Filtration Evaluation	Determine membrane compatibility for low protein binding and polysorbate loss; capacity, scalability, processing times, mfg site needs.	Fluid characteristics (density, viscosity), filter type, particle size, loading on filter surface, concentration, filtration mechanism, temperature	V_{max}, V_{50}: used to select filter guideline (size, capacity). Flow rate; filtration time.
Shear Evaluation	Ensure formulation (mixing) and filling operations do not damage the protein.	Shear rates (mix speed, fill speed, geometries) and durations for filling and mixing. Protein concentration Viscosity Temperature	Shear sensitivity of the formulation (mixing, filling, and combined) based on PQ impact.
Cleanability Evaluation	Determine whether worst-case B20 cleaning sequence is acceptable.	Density, viscosity, concentration, etc. Qualitative (stickiness, dryability).	Clean time on stainless steel coupon relative to worst-case product. Yes/No decision on validated cleaning procedure.
Stainless Steel Hold Evaluation	Evaluate product contact with stainless steel; prolonged exposure to 5C.	Container type, hold duration, formulation components.	PQ impact of in-process hold in mfg-like containers. Acceptable hold duration.

Fill Evaluation	Evaluate formulation for potential filling issues.	Container size, type, density, viscosity, volume, shear sensitivity, surface tension, particle/foaming tendencies	Fill speed Nozzle size Potential challenges (Look for dripping, foaming, product adhesion, speed limitations, fill weight check)
Inspection Evaluation	Evaluate formulation for potential inspection issues.	Fill volume, vial size/type Agitation, light exposure, temperature, particle/foaming tendencies	Inspectability - foaming, microbubbles, homogeneity, aggregates, particulates. Manual vs. Automatic recommendation

The three attributes comprising our definition of efficiency – DPE labor (resource time), study duration, and drug substance volume required – can be combined to generate an overall "Efficiency Score" for each study. We calculate this score based on each study's relative contribution to the total efficiency of DPE's FIH evaluations (Table 18). Specifically, we use the following equation:

$$\frac{\frac{x_i}{\sum_{i=1}^{10} x_i} + \frac{y_i}{\sum_{i=1}^{10} y_i} + \frac{z_i}{\sum_{i=1}^{10} z_i}}{3}$$

where
x_i = DPE Labor Hours for study i
y = Study Duration for study i
z = Drug Substance volume required for study i

Each of the three components is given equal weight because we have no compelling reason to do otherwise; the majority of DPE staff members we surveyed consider each to be as important as the others.

Table 18: Efficiency scores of each DPE FIH study with a heat map identifying efficiency 'hot spots'[7]

DPE FIH Studies	DPE Resource Time Required (hrs)	Study Duration (hrs)	Drug Substance Material Required (mL)	Score (low)	Score (high)
Density	1-2	2-8	10-50	0.11	0.14
Viscosity	2-8	8-16	10-50	0.20	0.43
Surface Tension	2	2-16	10-50	0.18	0.19
Freeze-Thaw	5-8	1000	50-100	3.45	3.07
Filtration	2-3	3-8	500-600	1.60	1.09
Shear Evaluation for mixing and filling	6-32	6-32	10-175	0.48	1.51
Cleanability Assessment	6-8	6-8	10	0.48	0.32
Stainless Steel Hold	4-6	96-168	50	0.72	0.74
Fill evaluation	14-16	7-8	250-500	1.76	1.40
Inspection Evaluation	4-8	4-8	250-500	1.03	1.11

In essence, this score allows us to compare the efficiency of different studies, generating a rank order of the potential for efficiency gains from overhauling each study. The resulting score should be high for relatively inefficient studies (one or more variables contribute substantially to the overall average of that variable). For instance, the Freeze-Thaw study clearly has the highest score, and therefore the lowest efficiency. This is a result of its long duration and moderate labor and material requirements. A high score does not necessarily imply that the study is poorly designed; it does, however, indicate that the study is less efficient in its use of resources and time than are the other studies. More colloquially, high-score studies represent the low-hanging fruit. A moderate improvement in these studies can have a dramatic impact on the overall FIH efficiency. Similarly, the relative efficiency of the FIH studies can be visualized in a bubble chart (Figure 10). The chart is simply a tool for identifying studies with the greatest potential for improving the overall FIH study efficiency.

[7] Data source: Estimates from three recent projects given by DPE lab analysts

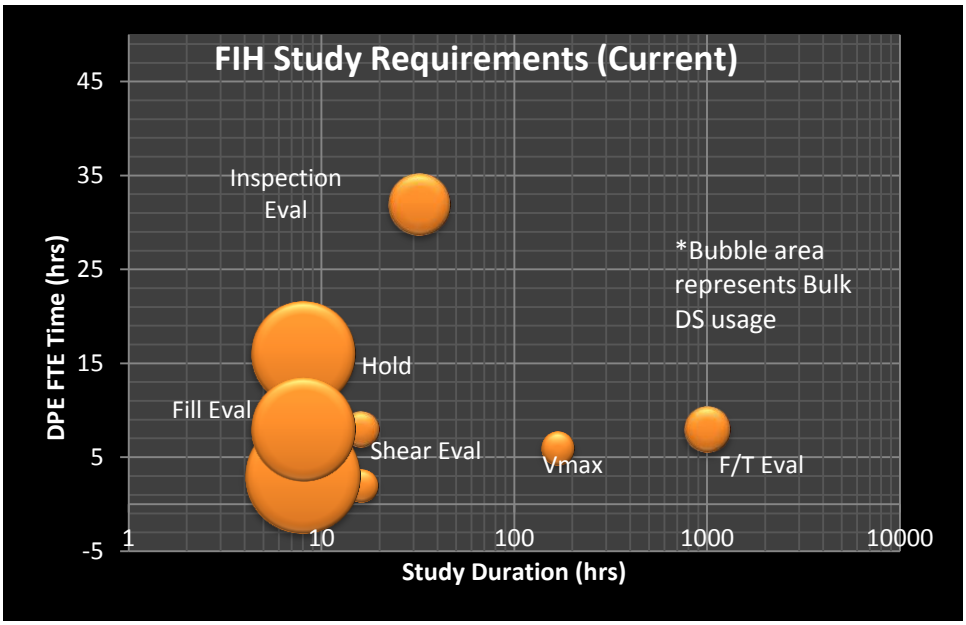

Figure 10: Bubble chart showing relative efficiency of the DPE FIH studies

One important note regarding these efficiency metrics is the interrelatedness of some of the data, which has important implications for improvement potential. The Fill Evaluation, for example, has a high drug substance material requirement (~500 mL). When viewing this study in isolation, it should stand to reason that reducing by half the material used would cut 250 mL from the overall DPE FIH material usage. When viewed as part of the entire suite of studies, though, it turns out that the material used in the Fill Evaluation is recycled from the Filtration Evaluation. Therefore, only after cutting the material usage of both studies can an actual improvement be made. The effects of shared material and overlapping timelines are discussed further in the section below on the evaluation of FIH study options.

Step 2: Alternative Options

To have the most profound impact on FIH study efficiency, we must ensure we are making the best recommendation possible for each study. Our approach was to develop a set of possible improvement options and then compare those options to the current practice. In general, our options are of four types: (1) Change the study protocol to take advantage of data measured elsewhere, (2) Replace part or all of a study with a model based on historical or small-scale data, (3) Eliminate part or all of a study, or (4) Some combination of these approaches. In comparing the options, we take into account the

change in efficiency (material, labor, and duration), the risks and challenges involved in implementing and running the study, and the potential benefits to the network. Appendix B contains a summary of these attributes for various alternatives identified for each study, alongside those of the incumbent practice. An evaluation of these options is presented in the following section.

Step 3: Evaluation of Options and Recommendations

For each study, we collected information through DPE staff interviews on the current practice and then estimated the same information for our alternative options. This information includes savings in material and time relative to the existing method ('Efficiency Benefit'), as well as qualitative measures of challenge and risk (described in the previous section). In the 'Efficiency Benefit' category, we rate each of the three components – material usage, labor hours, and study duration – on a scale of 1-5 based on the rubric in Table 19. A score of 'one' corresponds to a substantial efficiency improvement, while a 'five' represents little or no improvement. An overall 'Efficiency Benefit' can then be calculated from the product of the three categories. Similarly, scores of one through five are assigned to the 'Risk' and 'Challenge' of each option based on DPE staff input. These qualitative metrics also range from 'one' ("very low") to a 'five' ("very high").

Table 19: Scoring rubric for study efficiency metrics. Amounts and durations indicate savings relative to the current practice. [8]

	Rating				
Category	1	2	3	4	5
Bulk DS	>100 mL	51-100 mL	26-50 mL	1-25 mL	0 mL
DPE FTE Time	>6 hrs	5-6 hrs	3-4 hrs	1-2 hrs	0 hrs
FIH Timeline	>7 days		4-7 days		0-3 days

[8] For simplification purposes, savings for each study were calculated as if the study was performed in isolation (i.e. no other studies exist). For example, eliminating a study with a 100-mL material requirement would generate a 100 mL savings in our analysis, even if that material were still used for another study.

A combined score is generated for each option from the product of the three component scores. Furthermore, we multiply, rather than add, the three scores, as this gives more influence to the extreme scores – an effect we consider realistic from a decision-making perspective (a 'five' in any category can be a red flag, while a 'one' can be a green light). Based on these combined scores, we can create a hierarchy of options for each study, allowing a direct and objective comparison. Still, just because one option is better than all others does not mean it should necessarily be recommended as a replacement for the existing study. We account for this by grouping the combined scores into three classes: favorable (score < 20), moderately favorable (20-30), and unfavorable (> 30). In general, when one or more options for a given study fall into the 'favorable' class, we recommend the best for implementation. When the top option is only 'moderately favorable,' we may recommend a partial implementation. Finally, when the top option is unfavorable, we recommend no change to the current practice. Below, the scores for all options and the resulting recommendations are listed for each FIH study.

Physical Properties Determination

We evaluated two alternative approaches to determining a drug product's physical properties – using already available data from the Molecule Assessment (MA) group, and transferring the studies from DPE to DPD (Table 20). Based on our analysis, both options fall into the 'unfavorable' class, meaning that neither is particularly desirable. In the case of using the MA data, there is a high risk, since the formulation analyzed at that early stage of development is made using different procedures at a smaller scale and, according to DPE staff, is often not representative of the formulation used by DPE. Thus, the MA viscosity measurements may not be comparable to those made by DPE, especially for high concentration products. Transferring the studies to DPD, on the other hand, is considered a significant challenge because it involves convincing DPD to take on more work.

Table 20: Ratings of alternative study options for Physical Properties Determination

	Option	Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Use available MA viscosity data	4 (high)	3 (moderate)	3.3 (med-low)	40
2	Transfer studies to DPD	2 (low)	5 (very high)	3.7 (med-low)	37

As such, our primary recommendation is to leave the Physical Properties Determination unchanged. We also suggest doing a statistical comparison of the MA and DPE viscosity data to confirm the suspicion that they do not match. If this suspicion is proved to be unfounded in the actual data, we recommend using the MA viscosity data in place of the DPE data.

Drug Substance Freeze-Thaw Evaluation

We evaluated five options for replacing or modifying the Freeze-Thaw study, including a screening model, using DPD data, alternative study methods and equipment, reducing sampling requirements, and a combination of the model and DPD data (Table 21). Our analysis shows that three of those options are 'favorable'; the lowest score belongs to the reduced sampling option due to its limited risk and challenge. The other two – using DPD data and combining DPD data and a screening model – both scored low primarily due to their substantial efficiency benefit. Generally speaking, a modified Freeze-Thaw approach has little risk or challenge, since most DPE process experts express only minor concern for Freeze-Thaw sensitivity of platform molecules. In fact, evaluation of historical data of fifteen platform molecules confirms this assertion; not one of the fifteen products showed signs of impact after three Freeze-Thaw cycles.

Table 21: Ratings of alternative study options for Freeze-Thaw Evaluation

Option		Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Model to determine if F/T req.	3 (moderate)	4 (high)	2 (high)	24
2	DPD-generated F/T data	5 (very high)	2 (low)	1.7 (high)	17
3	Options 1 + 2 combined	2 (low)	4 (high)	2 (high)	16
4	Alternative methods (e.g. Cryowedge, Celsius Pak)	Moderate	Med-high	Med-low	30-45
5	Sample after 3rd cycle only	2 (low)	1 (very low)	4.7 (very low)	9

In accordance with these results, we recommend using a screening model (based on previously built DPE Freeze-Thaw models) in conjunction with existing DPD Freeze-Thaw data to determine the necessity of a separate DPE Freeze-Thaw study. If the model and DPD data show there to be little Freeze-Thaw risk, then DPE would not be required to run its own study. If, however, the model and DPD

data flag the new drug product as being at risk, DPE would run the traditional study. In the case that the study is run, we further recommend collecting samples only after the third cycle to minimize DPE and DPD time requirements while still generating pertinent information regarding the product's Freeze-Thaw behavior.

Filtration Evaluation

We compared four options for the Filtration Evaluation: predicting Vmax from Small Volume Filtration (SVF)[9], from viscosity measurements, from a combination of the two, or from a comprehensive prediction model. Based on the results, two of those options – using SVF alone and combined with viscosity – are considered 'favorable.'

Table 22: Ratings of alternative study options for Filtration Evaluation

	Option	Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Correlate SVF to Vmax	3 (moderate)	2 (low)	3.3 (moderate)	20
2	Predict Vmax from SVF + viscosity	2 (low)	2 (low)	3.3 (moderate)	13
3	Use predictive model w/o SVF	4 (high)	4 (high)	3.3 (moderate)	53
4	Predict Vmax from viscosity	4 (high)	2 (low)	3.3 (moderate)	27

There are three reasons for this, each of which reduces the expected risk and challenge of implementation. First, while more testing is needed, early SVF results show the promise of this technique for estimating Vmax. Second, a viscosity model is used today to estimate Vmax when the traditional pore-plugging model does not fit a drug product, despite a weak correlation (Figure 11). Given that a model using SVF should improve Vmax estimation relative to the viscosity model, little resistance to such an approach is expected. Finally, Vmax studies are typically performed *after* pre-clinical runs. As such, the opportunity exists to measure Vmax during the pre-clinical filtration operation and use this information to make adjustments for later clinical runs. This on-floor data analysis can act as a safeguard

[9] SVF is a new experimental approach in which less than 10 mL of drug product is filtered from a syringe to understand the filtration implications of the particle load.

against improper filter selection during clinical manufacturing, meaning that the accuracy of the SVF or SVF + viscosity models is less critical to the unit operation's success.

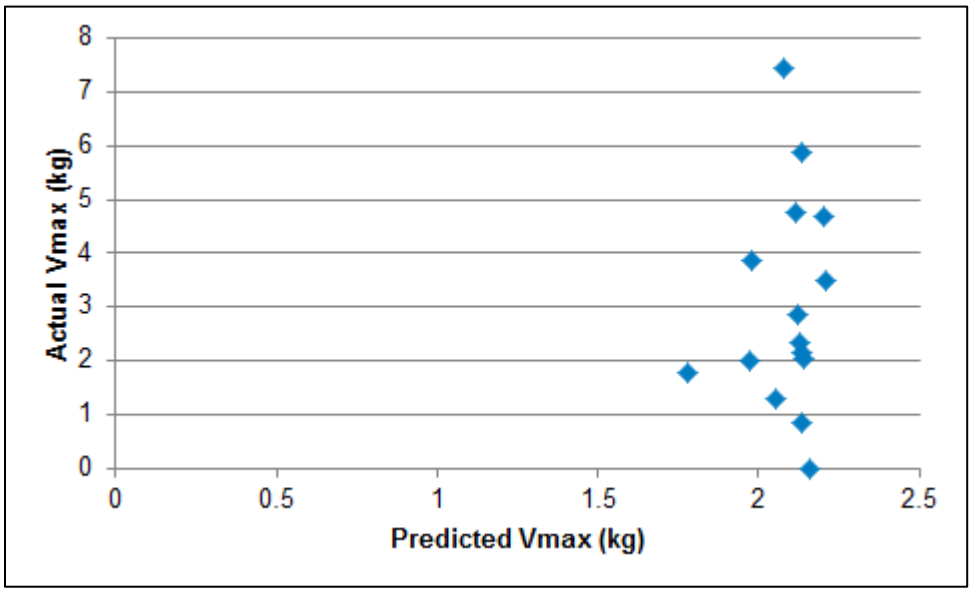

Figure 11: Plot of Actual Vmax vs. Predicted Vmax for 15 historical platform mAbs based on Amgen's viscosity model

Therefore, we recommend using a model that combines SVF and viscosity to estimate Vmax, allowing selection of a corresponding filter guideline for pre-clinical runs by Clinical Manufacturing. During these initial runs, we suggest that Vmax is measured on the manufacturing floor to confirm the predicted value. Adjustments to the filter guideline can then be made if necessary.

Shear Evaluation

We analyzed three options for the Shear Evaluation study: using a screening model, modifying the study to reduce time and material requirements, and eliminating the study altogether (Table 23). All three options fit into the 'favorable' class due to their high efficiency benefit and low risk (the FIH platform formulation is historically robust to shear effects – none of the thirteen historical platform molecules tested for shear sensitivity exhibited signs of quality defects – so there is little chance any evaluation would reveal unexpected adverse results). Additionally, the modified approach and study

elimination have low expected challenge, since DPE has for years been considering changes to the Shear Evaluation are therefore likely to support these actions.

Table 23: Ratings of alternative study options for Shear Evaluation

Option		Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Screening Model	2 (low)	4 (high)	2.3 (high)	19
2	Modified study approach	2 (low)	2 (low)	2.3 (high)	9
3	Eliminate study	2 (low)	2 (low)	2.3 (high)	9

Based on these results, we recommend eliminating the Shear Evaluation study completely, but only after confirming the low risk of FIH platform shear sensitivity based on historical data. If the study cannot be eliminated, we propose modifying the study approach such that it is comprised of worst-case mix and fill shear sampling, or, alternatively of only combined mix and fill shear, thereby significantly reducing the labor and material required.

Cleanability Assessment

We chose to evaluate only one option for the Cleanability Assessment. Specifically, we looked at using a screening model to assess the necessity of the Cleanability Study (Table 24). The combined score for this option is well above the 'favorable' threshold due to high risk and challenge and limited efficiency benefit. Interviews with DPE staff revealed that no model would be acceptable in this situation, due to quality and safety risk. Additionally, the existing method works well and is already relatively resource efficient, so the need for improvement is insubstantial. Therefore, we recommend making no changes to the Cleanability Assessment.

Table 24: Ratings of alternative study option for Cleanability Assessment

Option		Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Model to assess need for study	4 (high)	4 (high)	3.7 (med-low)	59

Stainless Steel Hold Evaluation

We assessed two alternative options to the current Stainless Steel Hold Evaluation. The first is to use a screening model to assess the need for a study, and the second is to eliminate the study (Table 27). Our analysis shows that eliminating the study is 'moderately favorable,' while the screening model is not due to its limited benefit over the existing method and the anticipated difficulty of constructing such a model. Study elimination is considered only moderately risky and challenging because of the robustness of the mAb platform formulation (due in part to insensitivity to oxidative degradation) to stability issues during typical hold times. Additionally, Clinical Manufacturing can already hold product for up to seven days based on other data, so the hold study is not needed for this purpose. Based on this analysis, we recommend eliminating the Hold Evaluation. If this is ruled infeasible due to a lack of supporting data, we alternatively recommend limiting the study hold duration to 96 hours – the maximum time required by Clinical Manufacturing during FIH – in order to shorten the FIH timeline as much as possible.

Table 25: Ratings of alternative study options for Stainless Steel Hold Evaluation

	Option	Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Model to assess need for study	3 (moderate)	3 (moderate)	3.7 (med-low)	33
2	Eliminate study	3 (moderate)	3 (moderate)	2.7 (moderate)	24

Fill Evaluation

We compared three Fill Evaluation options, including a screening model, a study modification to increase efficiency, and eliminating the study altogether (Table 26). While none of the options is 'unfavorable,' the options of eliminating the study and modifying the methodology both score in the 'favorable' range due to low anticipated challenge. This is because there is little historical evidence of adverse findings during Fill Evaluation for mAbs in the platform formulation (all twelve historical platform molecules for which the Fill Evaluation was performed passed post-fill analytical tests), so any change, or even total elimination, is unlikely to warrant objection. In fact, many of the DPE staff members we interviewed agreed that the Fill Evaluation requires too much time for the minimal benefit it provides. Their reasoning for the impression that the benefit is small include the irrelevance of the study

data due to differences between the DPE and Clinical Manufacturing equipment, the timing of the study (the DPE work is performed *after* pre-clinical fills have already occurred), and the lack of adverse findings noted above.

Table 26: Ratings of alternative study options for Fill Evaluation

Option		Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Model to assess need for study	3 (moderate)	4 (high)	2.3 (high)	28
2	Modified study approach (fill fewer vials)	3 (moderate)	2 (low)	3 (moderate)	18
3	Eliminate study	3 (moderate)	2 (low)	2.3 (high)	14

We therefore recommend eliminating the Fill Evaluation and using conservative fill equipment and process settings for pre-clinical runs in Clinical Manufacturing based on knowledge of the drug product physical properties. Adjustments can be made prior to clinical fills based on this experience. If this recommendation is not accepted, we alternatively propose using a modified Fill Evaluation, in which no more than thirty vials are filled for all required SKUs, thus saving time and material.

Inspection Evaluation

We analyzed two Inspection Evaluation options: using a screening model to determine the necessity of a full evaluation and eliminating the study altogether (Table 27). Our analysis shows that the study elimination option is clearly favored over the screening model. Both its risk and challenge scores are low, since the study is thought be of little value in its current form and rarely yields information relevant to Clinical Manufacturing's inspection procedures. Based on this assessment, we recommend eliminating the Inspection Evaluation.

Table 27: Ratings of alternative study options for Inspection Evaluation

Option		Risk Rating	Challenge Rating	Benefit Rating	Overall Rating
1	Screening Model	3 (moderate)	4 (high)	3.3 (moderate)	40
2	Eliminate study	2 (low)	2 (low)	3.7 (med-low)	15

FIH Summary

As described in the previous sections, our final recommendations for the eight DPE FIH studies include eliminating the study completely, modifying the existing study, using a screening or predictive model, and making no changes to the study whatsoever. Should Amgen choose to follow these proposals, substantial efficiency gains can be achieved, as shown in Table 29. Per product, the potential improvements are shown below in Table 28.

Table 28: Potential efficiency improvements resulting from FIH recommendations

	Current State	Estimated Future State
FIH Timeline	Six weeks	One week
DS Material Required	600 mL	100 mL
DPE Labor Hours	60 hours	20 hours
Analytical Tests	50 tests	16 tests

The last of these four categories – 'Analytical Tests' – was not one of our initial DPE efficiency components, but it constitutes a huge time drain on DPD resources, so we consider it an important factor in demonstrating the overall impact of our recommendations. Visually, one can see a clear efficiency improvement across the FIH eight studies (Figure 12). We should note that we refrain from assigning a financial value to these improvements due to the many uncertainties and assumptions that would be involved in developing such a figure. However, we can say with confidence – after consulting staff members across the DP Network – that the economic benefit would not be insignificant.

Table 29: Summary of FIH study recommendations and the resulting savings[10]

FIH Study	Recommended Action				Estimated Savings Relative to Current State			
	Eliminate	Modify	Use Model	No change	Material	Manpower	FIH Timeline	Analytical testing
Physical Properties				X	N/A	N/A	N/A	N/A
Freeze-Thaw		X	X		0-100 mL	0-6 hrs	0-6 weeks	8-16 tests
Shear	X				50-175 mL	6-32 hrs	1-3 days	20 tests
Hold	X				50 mL	4-6 hrs	4-7 days	8 tests
Filtration		X	X		450-500 mL	1 hr	N/A	0-8 tests
Fill	X				250-500 mL	14-16 hrs	1 day	4 tests
Inspection		X			250 mL	4 hrs	N/A	N/A
Cleanability				X	N/A	N/A	N/A	N/A
Total Savings per product*					400-600 mL	29-65 hrs	1-5 weeks	40-56 tests

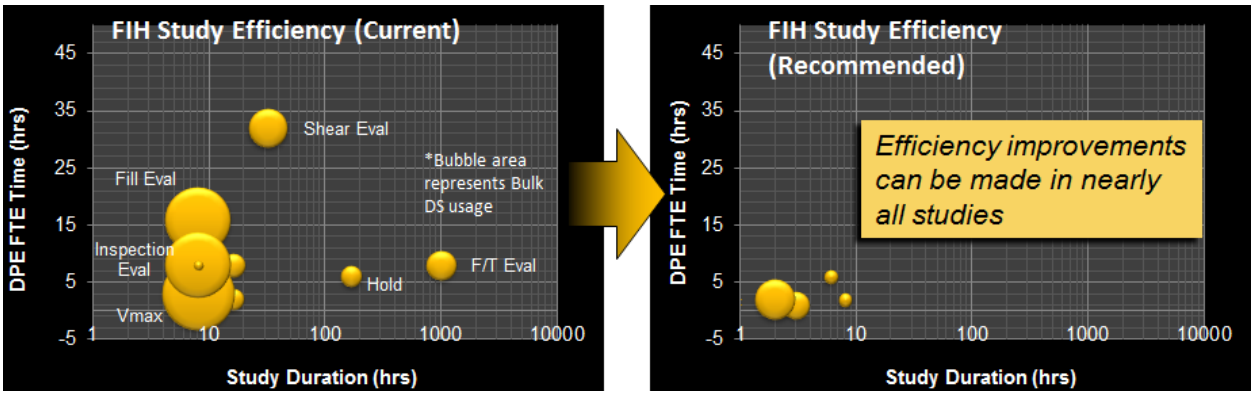

Figure 12: Bubble charts of study efficiency showing potential improvements from the current state (left) to the future state (right), assuming all recommendations are implemented.

Summary

We can draw from these recommendations several general suggestions. First, efforts should be made across all studies to reduce sampling and analytical testing as much as possible. The current set of FIH roles and responsibilities does not provide DPE with disincentives to submit samples for testing only when absolutely necessary. As a result, samples are sent to DPD in abundance, sometimes overwhelming

[10] "Total Savings" do not equal the sum of each study's savings, since material is reused for multiple studies and studies overlap in the timeline

the DPD analysts and preventing them from completing other important work. DPE should be made aware of these consequences of oversampling and procedural adjustments should be made.

Second, as much information as possible should be gathered from Clinical Manufacturing's pre-clinical runs. The knowledge gained during these runs is more relevant than most data collected in DPE's studies, and it can be used to improve process understanding and to make process adjustments prior to the clinical runs.

Third, historical FIH evaluation and Clinical Manufacturing data should be used to build models or support study elimination when necessary. To reach this point, however, a system must first be implemented to collect and store this information in a location accessible to all of the DP Network.

Finally, the real value of this analysis of DPE's FIH studies is its implications for DPE studies during later development stages (e.g. CPD, PC), when the time and resource requirements are more significant and the timelines more critical. By implementing some of our FIH recommendations, Amgen can prove the Pilot Plant Cooperative concept on a small scale with limited risk. If successful, there should be little resistance to rolling out similar measures in the other stages, where the gains can be more substantial.

6 Recommendations and Conclusions

The previous sections show how the Pilot Plant Cooperative concept can be applied to specific cases at Amgen and the potential benefits that may be realized as a result. While these examples are useful in their demonstration of our strategy's utility, they are limited in their scope. In other words, if Amgen were to employ the Pilot Plant Cooperative for only these cases, the overall benefit would be minimal and short-lived. The goal of this project is to induce meaningful, widespread, and long-lasting commercialization efficiency improvements at Amgen. In this section, we list a set of actionable steps that, if followed, will help ensure alignment and efficiency is achieved and maintained.

6.1 Procedural Recommendations

Amgen, like most biotechnology companies, is procedurally driven. From the perspective of the change agent, this has both benefits and drawbacks. On the positive side, it means that Amgen employees will follow the instructions laid out for them in a procedure; thus simply modifying a procedure to promote desired behaviors can quickly incite widespread change. On the negative side, changing a procedure can be time-consuming and requires multiple cross-functional reviews and approvals. Still, procedural-based integration is particularly effective in highly codified environments (Kim, Park, & Prescott, 2003), so making the effort to modify procedures can be a useful and necessary method for driving alignment and efficiency at Amgen.

Our first recommendation is to update the manufacturing and development SOPs and guidelines to better align practices across all groups. Our gap analysis revealed myriad procedural inconsistencies and omissions, a problem that could easily be remedied by ensuring uniformity in these procedures. Specifically, representatives from each group should convene, review our gap analysis, decide on best practices to be employed by all groups, and update the procedures accordingly. The result would be a better and more relevant operational understanding earlier in the development cycle.

Our second recommendation is to collect relevant data in DPD, DPE, and Clinical Manufacturing, and transfer this information to Commercial Manufacturing. Of course, this recommendation cannot be fully enacted until the first recommendation is implemented. The concept here is simple and is based upon our second case study: Commercial Manufacturing requires specific data about the manufacturability of a drug product prior to producing that product on its equipment. Currently, much of this information is gathered through on-site characterization and engineering studies. If some of this information can instead be collected by other groups, Commercial Manufacturing's effective capacity would increase, allowing use of the plant for higher-value activities. Acting on this recommendation requires formal communication between Commercial Manufacturing and the other groups in regard to the information required for drug product commercialization. Once the requirements are understood, the

other groups should modify their processes, equipment, and data collection practices to ensure they are able to measure and record the information requested. The line of communication should remain open so that feedback can be continuously given, resulting a constantly improving commercialization dataset.

Our final procedural recommendation is also perhaps the most contentious and may therefore be difficult to implement. We advise Amgen to rework its capital investment process to reflect the true cost and benefit to the *entire DP network* of an equipment investment. This recommendation stems from our observation that one of the primary sources of misalignment in the DP network is an asymmetrical distribution of financial resources, which results in lopsided equipment investment. More specifically, the Commercial Manufacturing groups are considered profit centers, while the Clinical Manufacturing, DPE, and DPD groups are considered cost centers. When viewed as separate entities, one can understand how Commercial Manufacturing may be able to present a more straightforward NPV argument in favor of purchasing a new piece of equipment, while the other groups may struggle to show a positive financial benefit of such an investment. Ideally, analyzing the NPV of an investment in any group at Amgen should consider the incremental costs associated with all groups *throughout the entire company* (Higgins, 2007).

Still, even if all groups are considered when calculating NPV, this does not preclude misaligned investment. As such, we further recommend that any equipment investment in one group is matched by investments in similar equipment in the other groups (where applicable). For instance, if Commercial Manufacturing invests in new filling technology, an investment should be made in the same technology for Clinical Manufacturing and DPE to ensure alignment is maintained. The apparent cost of such an investment might seem unreasonably high (and the corresponding NPV low), but we believe this represents the true cost of the investment in the aligned world to which Amgen has committed itself. Surely, the overall cost of this one-time, aligned investment is lower than that of the current practice, in which an isolated investment results in misalignment and subsequent "catch-up" investments at the other sites.

This recommendation necessitates a change to Amgen's capital investment business process. One supporting modification is to require approval from all DP Network groups whenever one group requests funding for new equipment. This would ensure that the entire network is aware of any potential change that would result in misalignment. Furthermore, in the same request, the other groups would have the right to ask for alignment-maintaining funding for their own investment, and all groups would sign-off on the final proposal. While this may add time upfront to the capital investment process, it should save time in the long run, as lengthy catch-up investment proposals would be avoided.

6.2 Cultural Recommendations

While the procedural recommendations can impose on Amgen employees a set of rules that should result in desired behavior changes, they do not, on their own, create a culture of alignment. This may seem like a minor concern, but a desired transformation will be long-lasting only if cultural change accompanies procedural change. Put another way, commitments that produce "inner change" are most likely to stick (Cialdini, 1993). To lead to successful cross-functional integration, this commitment should be focused on a common and readily understandable goal of alignment (Allport & Cooke-Davies, 2010). With this in mind, we have developed a few specific cultural recommendations to help ensure alignment is maintained once it has been achieved.

Our first recommendation is to use incentives and rewards to reinforce alignment-promoting behavior. A strong incentive system is one in which performance is clearly connected to specific objectives (Ancona, Kochan, Scully, Van Maanen, & Westney, 1999). One simple way to do this is to take advantage of Amgen's existing internal award program. The program allows any employee to nominate any other deserving employee for an award. The award recipient is generally given a prize that, while small, carries with it recognition by management, and, according to some employees, generates pride in their work. Additionally, managers can give their employees alignment-oriented goals on which year-end reviews and bonuses are based. Both of these approaches require top-down emphasis on alignment so that it becomes integrated into the incentive system. However, incentives alone are not

sufficient to induce widespread cultural changes. Like procedural changes, incentives do not necessarily create sustained commitment because they do not always alter the attitudes that underlie our behavior (Pfeffer, 1998). Our other cultural recommendations are intended to complement a strong incentive program and overcome these limitations.

The second recommendation is to use focused hiring practices to identify candidates who fit well within, and would strengthen, an aligned culture. The responsibility for this recommendation falls on the shoulders of Human Resources. Ideally, HR would give hiring managers a set of questions to ask and traits to look for in potential candidates to understand how each candidate might contribute to the alignment effort. Examples of desirable traits include extroversion, sociability, curiosity, a collegial mindset, strong communication skills, internally uncompetitive, and respectful. Similarly, Clark and Fujimoto suggest that a climate of communication between Development and Manufacturing requires mutual trust, as well as shared attitudes and responsibilities (Clark & Fujimoto, 1991). Additionally, candidate attraction and selection can be complemented by the incentive system in place. This was done with great success at Duke Power, where the company created rewards for the express purpose of attracting, retaining, and developing the right people (Williams, 1996). With the right people and personalities in place, a culture of alignment can more readily be achieved and sustained.

The final cultural recommendation is to create, in Jack Welch's words, a "Boundaryless Organization." At General Electric, this meant breaking down the cultural, geographical, and organizational boundaries by sharing information across groups, distributing decision making power throughout the organization, and giving employees incentives to achieve shared goals (Allport & Cooke-Davies, 2010). Kim et al. further assert that Development and Manufacturing are well-suited for people- and information-based integration (Kim, Park, & Prescott, 2003). The former includes the use of cross-functional teams, meetings, and management, while the latter emphasizes implementation of shared databases and other communication systems. These are not foreign concepts to Amgen, as the company has for years made an effort to "encourage different departments to learn about one another and try to

understand how their actions would affect other parts of the organization (Binder, 2008)." Still, many in the DP Network acknowledge a need for further cross-functional integration. In response, we have identified the following underutilized approaches through which Amgen could reduce organizational boundaries in the DP Network.

1. **Create a virtual hub for sharing information**. By creating an intranet site that serves as a common location for sharing data, equipment lists, procedures, etc., Amgen would be bringing the DP Network virtually closer without requiring physical proximity. This hub could also serve as a "Pilot Plant Cooperative" toolbox, showing all resources available for generating data.
2. **Implement a cross-training program**. Allowing employees from one group to work temporarily in another would serve multiple purposes. It could result in a greater degree of mutual understanding and respect, better sharing of information, relationship-building, and implementation of Network-wide best practices. More simply, it would help eradicate the "us-them" problem that Amgen, like most large, global companies, faces.
3. **Promote site visits and facility tours**. Due to budgetary vigilance, many Amgen employees do not have the opportunity to visit other sites. While this appears to make clear financial sense, it does not come without cost. For example, members of DPE who support product transfer to the commercial site may have never seen the equipment on which the product will be run or met the employees who will be receiving the product. This creates a culture of distrust and misunderstanding that is difficult to overcome without a face-to-face meeting or site visit. Furthermore, even when two groups are co-located (e.g. DPE and Clinical Manufacturing in ATO), there is limited inter-group interaction, and visits to the other group's facilities occur infrequently if at all. This can be easily ameliorated but requires a commitment from DP Network management to create the opportunity for inter-group mixing and to arrange regular facility visits.

6.3 Conclusions

Through implementation of our Pilot Plant Cooperative alignment strategy, we believe Amgen can quickly realize significant efficiency improvements in drug product process development, technology transfer, and commercialization. The results of these improvements include reduced development and manufacturing costs, lower production and quality risk, and faster and more robust evolution of drug products from early stage development through commercial manufacturing. However, these gains can be sustained only if long-term alignment strategies are put in place. We emphasize the use of both procedural and cultural strategies and recommend specific approaches for each.

This paper merely serves as the starting point of a long journey. By following our recommendations, remaining committed to the project's goals, and maintaining the flexibility to change the approach if necessary, Amgen should propel itself down the path toward real and permanent alignment.

7 Glossary

CPD	**Commercial Process Development.** An intermediate process development stage, during which the commercial manufacturing process and formulation are defined and tested.
DP	**Drug Product**. The drug dosage form in the final packaging intended for use in the clinical and commercial environment.
DP Network	**Drug Product Process Development and Manufacturing Network.** The set of groups (DPD, DPE, Clinical Manufacturing, and Commercial Manufacturing) working together to develop and commercialize a drug product manufacturing process.
DPD	**Drug Product Development.** The group involved in formulation and assay development for drug products.
DPE	**Drug Product Engineering.** The group charged with developing a consistent and robust clinical and commercial manufacturing product.
DS	**Drug Substance.** An intermediate form of the product, prior to final formulation and filling.
FDA	**U.S. Food and Drug Administration**. The regulatory agency that governs biotechnology companies that manufacturing and/or sell products in the United States.
FFF	**Formulation, Fill, and Finish**. The activities comprising the drug product manufacturing process.
FIH	**First-in-Human**. An early stage of process development during which a process is first set for manufacturing drugs used in Phase 1 clinical trials.
mAb	**Monoclonal Antibody**. The basis for therapeutic drugs typically produced in mammalian tissue culture cells through recombinant DNA technology.
NPV	**Net Present Value**. A calculation in which future cash flows are discounted to determine the present value of a project or investment.
QbD	**Quality by Design**. A paradigm under which pre-determined product specifications define the manuafacturing process; quality is built in to the process.
PAT	**Process Analytical Technology.** A system for designing, analyzing, and controlling manufacturing through in-process quality and performance measurements.
PC	**Process Characterization**. The final stage of development prior to validation, during which process parameter ranges are defined and tested.
SOP	**Standard Operating Procedure**. A document detailing the steps of a procedure.
VHP	**Vaporized Hydrogen Peroxide.** A gaseous form of hydrogen peroxide used to sterilize the interior of isolators in drug product filling suites.

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9 Appendix A: Sample NPV Calculation for Filling Equipment

Our recommendation to purchase filling equipment for use during process development is based primarily on qualitative metrics, including risk reduction and quality improvement. However, our argument for purchasing the filler could be strengthened with a supporting quantitative analysis. Net Present Value (NPV) is widely regarded as the preferred approach for such an analysis. NPV considers all cash flows associated with a project and discounts the future cash flows according to the cost of capital of the project. In this appendix, we perform a sample NPV calculation for the filling equipment purchase described earlier in this paper. **For proprietary reasons, all data used here – unless otherwise noted – are fictional and for illustrative purposes only.** Nonetheless, we suggest that Amgen employs a similar methodology for future equipment investment decisions.

The NPV formula is as follows:

$$NPV = \sum_{i=1}^{n} \frac{CF_i}{1 + WACC}$$

Where CF_i = Incremental Cash Flows from the project in year 'i'

WACC = Weighted Average Cost of Capital, which is given by the equation:

$$WACC = k_D (1\text{-}t) \frac{D}{D+E} + k_E \frac{E}{D+E}$$

Where k_d = Cost of debt capital

k_E = Cost of equity capital

t = Marginal tax rate of the project

$\frac{D}{D+E}$ = Leverage of the target capital structure

Determining WACC is relatively straightforward compared to determining many of the cash flows associated with a given project. Here, we first discuss these cash flows and then estimate WACC from its components.

Cash Flows

The most obvious cash flows associated with the purchase of a piece of filling equipment are the initial outlay of cash and the future tax savings due to depreciation expenses. In our filling equipment example, we can assume that the equipment, lab space, and utility infrastructure would cost $10 million upfront. It is also reasonable to assume that the filling equipment has a 10-year useful life and that Amgen would employ a straight-line depreciation over those ten years. As such, there would be an annual tax savings of $10,000,000/10 * t, where 't' is the tax rate. Additionally, there would be some recurring costs, such as maintenance, utilities, and parts replacement, that should also be considered. We estimate these costs to total $10,000 per year.

Assigning a value to the benefits resulting from the filler purchase is more complicated, which, as described earlier, is one of the reasons investments like this are difficult to justify. Referring back to Section 5, there are several areas in which Amgen can financially benefit through purchase of a new laboratory filler: commercial and clinical site utilization, contractor/vendor reliance, product discarding, bulk drug substance requirements, time-to-market, and patient supply. Here we assign artificial values to each, where possible, to demonstrate their potential effect on NPV.

Commercial and Clinical Utilization

A representative laboratory filler would allow Amgen to fully utilize its Commercial and Clinical site capacity for actual production, since process characterization and other studies could be performed in the lab. We arbitrarily assume that a day of production is worth $100,000 and that five days per year would be gained by moving characterization work to the laboratory filler (5 x $100,000 = $500,000 saved per year). It should be noted that this amount represents the accounting cost of operating the plant and is *not* related to the value of the product.

Contractor and Vendor Reliance

As noted earlier, Amgen sometimes relies on vendors and contract sites to perform filling studies when their commercial or clinical sites are unavailable. A typical vendor, whose services might be required ten days per year, could conceivably charge $5,000 per day to perform these studies. Avoiding this cost would amount to savings of $50,000 per year.

Product Discarding

For the purposes of this exercise, we assume Amgen discards 500 filled units per year due to quality defects that could have been prevented if the process had been better understood (i.e. a laboratory filler would have improved process understanding in advance of commercial manufacturing). In reality, such an estimate would be nearly impossible to make, since one would be hard-pressed to prove that a defect could have been prevented with the proposed filling equipment. Still, if we assume a filled unit has a cost to Amgen of $1,000, then the cost per year prevented through use of a laboratory filler would be $500,000.

Bulk Drug Substance Use

We assume that a laboratory filler has roughly one-quarter of the drug substance material requirements of a full-scale filler during a fill assessment (based on the reduced number of filler heads at the lab scale). If we estimate that 20 liters are typically used in these assessments in a given year, then 15 of those liters would be saved with the new equipment. Assuming that drug substance material costs $10,000/liter to produce in the pilot plant, then the new equipment would save $150,000 per year.

Time-to-Market

Earlier, we discussed how a new laboratory filler should result in shorter commercialization timelines, allowing Amgen products to potentially reach the market more quickly. There are two financial implications of this result: Amgen could sell its product sooner, thereby making money before it

otherwise would have, and, by beating competitors to the marketplace, Amgen could consequently capturing a larger portion of the market. While the financial impact of either of these is potentially significant, the specific amount saved is difficult to estimate. As such, we do not include them in our calculation but urge Amgen to attempt to quantify these amounts in the future, as the company may pass up NPV-positive projects by failing to include these benefits in its analysis.

Patient Supply

Two substantial costs of poor quality are production delays and product recall, both potentially resulting in product shortages in the market. The likelihood of these events is already low, but we contend that new laboratory filling equipment would further reduce this risk. However, as before, the amounts saved by maintaining consistent patient supply are difficult to estimate, so we do not include this in our analysis.

WACC

As shown above, WACC depends on estimates of a project's target capital structure, cost of debt, cost of equity, and the company's marginal tax rate. To determine the target capital structure, we can look at the capital structure of firms whose core businesses are similar to the proposed project. In the case of filling equipment investment, we would typically look at contract aseptic fill companies as ideal comparables. Unfortunately, firms that derive the majority of their business from these activities are, without exception, privately held, so their financial statements are not publicly available. Instead, we use Amgen's financial data to estimate the components of WACC.

First, we can capture Amgen's leverage ratio (Debt/Assets) from its balance sheet. In 2011, Amgen's leverage was \$19.5B/\$43.5B = 0.45. Second, without data from comparable firms, we estimate Amgen's cost of debt to equal 5.0%, or roughly the rate Amgen's creditors would demand in funding this project. Third, we estimate the cost of equity using Amgen's equity beta and the CAPM equation:

$$k_E = r_f + \beta_E * (r_m - r_f)$$

We estimate the risk free rate of return (r_f) to equal 3.0% (based on the long-term treasury bond rate), the market return to equal 7.0%. Combining these with Amgen's β_E of ~0.44 and plugging them all into CAPM, we see that k_E is equal to 4.8%. We can now return to the WACC formula ($WACC = k_D (1\text{-}t) \frac{D}{D+E} + k_E \frac{E}{D+E}$) and determine Amgen's weighted average cost of capital based on the estimates we made in the preceding paragraphs. Using this information, we see that WACC is equal to 4.4%.

Finally, the NPV of the project can be calculated by discounting the cash flows described above with the WACC. In the invented scenario described here, the project NPV is $1.05 million (Table 30). Since this value is greater than $0, we would recommend the investment is made. Again, this result is based almost entirely on data invented for the purposes of demonstrating the NPV calculation and does not in any way reflect the actual NPV of Amgen's filling equipment investment.

Table 30: NPV inputs and calculation for invented scenario described in Appendix A.

Year	Purchase	Facilities	Depreciation tax savings	Plant Utilization	Contractor/ Vendor	Product Discarding	BDS Use	Yearly total	Present Value
0	(10,000,000)							(10,000,000)	(10,000,000)
1		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,331,418
2		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,275,304
3		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,221,556
4		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,170,073
5		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,120,759
6		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,073,524
7		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	1,028,280
8		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	984,942
9		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	943,431
10		(10,000)	200,000	500,000	50,000	500,000	150,000	1,390,000	903,670
								Total NPV	**1,052,957**

10 Appendix B: FIH Process Evaluation Option Analysis

The following are tables showing FIH studies and alternative options identified in this project. All options in the tables are described from the perspective of DPE, so a labor requirement of "0 hours" does not mean that no labor is required across all of Amgen but that DPE staff time is not needed.

Physical Properties	Current Practice	Alternative Option 1	Alternative Option 2
Brief Description	Density, Viscosity, and Surface Tension are measured	Use available MA viscosity data	Transfer studies to DPD
Material Required	Density: 10-30 mL Viscosity: 10-60 mL Surface Tension: 10-50 mL	Viscosity: 0 mL (others same as before)	0 mL
Study Duration	Density: 2-8 hrs Viscosity: 8-16 hrs Surface Tension: 2-16 hrs	Viscosity: 0 hrs (others same as before)	0 hrs
Resource Time Required	Density: 1-2 hrs Viscosity: 2-8 hrs Surface Tension: 2 hrs	Viscosity: 0 hrs (others same as before)	0 hrs
Risks	None	Using non-representative viscosity data could adversly affect mfg decisions. (May be overly or underly cautious.)	None
Challenges	Studies can require significant staff time; viscosity is measured elsewhere	Acquiring viscosity data from MA group.	Gaining buy-in
Benefits	Can use measurements to set process parameters and predict mfg challenges	Reduce DPE physical properties testing by 1/3	Potentially save time (and material?) by realizing efficiencies due to relative capabilities
Potential Savings	N/A	0-60 mL Bulk DS 0-16 hrs FIH timeline 2-8 hrs DPE staff time	0 mL Bulk DS (?) 1-2 hrs resource time (total)

Freeze-Thaw	*Current Practice*	*Alternative Option 1*	*Alternative Option 2*	*Combination of 1 and 2*	*Alternative Option 3*	*Alternative Option 4*	*Alternative Option 6*
Brief Description	3 Freeze-Thaw cycles using large scale profile. Test PQ after each cycle.	Model to determine necessity of F/T study	F/T data generated by DPD	Use model + DPD F/T data to mitigate risk	Cryowedge	Celsius Pak	Sample only after 3rd cycle
Material Required	50-500 mL	0 mL	0 mL	0 mL	50-500 mL (est.)	< 100 mL	50-500 mL
Study Duration	1000 hrs (6 weeks)	< 1 week	N/A	~2 hrs	1000 hrs (6 weeks)	30-1000 hrs (6 weeks)	1000 hrs (6 weeks)
Resource Time Required	5-8 hrs	~ 2 hrs	N/A	~2 hrs	5-8 hrs (est.)	5-8 hrs (est.)	3-6 hrs
Risks	Small scale does not replicate large scale cryoconcentration --> may not predict product quality impact.	Model may fail to indicate F/T study req'd --> unpredicted PQ issues in B20	Conditions/ container/ formulation not representative of mfg --> unpredicted PQ issues in B20	Minimal risk of failure to predict F/T issues	Initial study results are inconclusive w.r.t comparability to large scale carboy --> may not predict PQ in B20	Fast F/T cycle does not represent mfg conditions --> may not predict PQ in B20	Cannot determine at which cycle PQ issues arise, nor see a trend --> no cycle-specific info delivered to B20
Challenges	Long duration; excessive analytical testing	Model must be built; correlation of process and formulation parameters to F/T PQ is currently unknown; gaining buy-in; additional testing to obtain model inputs may be required	Obtaining data from DPD (minor)	Building model; gaining buy-in (reduced relative to 1); obtaining data (see 1 & 2)	Unfamilar technology.	Requires skilled personnel and can be costly. Unfamiliar technology.	None
Benefits	Uses mfg container type and F/T profile	Significant FIH study time reduction, material savings	Understand F/T impact on PQ without performing study in DPE	Significant FIH study time reduction, material savings	Reduced risk of uncertainty: should better simulates mfg F/T conditions (cryoconcentration)	Fast (10-11 hrs per cycle); can be scaled linearly	Eliminates unnecessary testing by DPD.
Potential Savings	N/A	0-100 mL Bulk DS 4-6 weeks total time 3-6 hrs resource time	0-100 mL Bulk DS 4-6 weeks total time 4-7 hrs resource time	0-100 mL Bulk DS 4-6 weeks total time 3-6 hrs resource time	N/A	up to 100 mL Bulk DS 0-5 weeks total time	~2 hrs resource time (plus significantly more in DPD)

Filtration (Vmax)	Current Practice	Alternative Option 1	Alternative Option 2	Alternative Option 3	Alternative Option 4
Brief Description	Vmax test on bench-top filter setup to select filter guideline	Use SVF and correlate to Vmax	Use SVF + Viscosity to predict Vmax	Use predictive model	Viscosity
Material Required	500+ mL	10-20 mL	10-20 mL	0 mL (unless add'l tests req'd)	0 mL
Study Duration	3-8 hrs	2-4 hrs	2-6 hrs	~2 hrs	~1 hr
Resource Time Required	2-3 hrs	1-2 hrs	1-4 hrs	~2 hrs	1-2 hrs
Risks	Poor data quality could indicate incorrect filter guideline --> over- or undersized in B20	Vmax prediction is incorrect; Filter is over- or undersized in B20	Vmax prediction is incorrect; Filter is over- or undersized in B20	Vmax prediction is incorrect; Filter is over- or undersized in B20	Viscosity-based guideline is over- or undersized for B20 pre-clinical run
Challenges	Significant material requirements; filter guideline selection not always appropriate for MFG	Gaining buy-in; collecting SVF data for correlation	Gaining buy-in; collecting SVF data for correlation	Gaining buy-in; additional testing for model inputs may be required	Gaining buy-in; checking correlation.
Benefits	Provides reliable filter recommendation w/o requiring mfg-scale testing	Minimal time savings; significant material savings; can perform multiple runs	Minimal time savings; significant material savings; can perform multiple runs	Minimal time savings; significant material savings; can perform multiple runs	Significant in all three categories
Potential Savings	N/A	200-450+ mL Bulk DS (depends on elimination of other studies) 1-4 hrs FIH timeline ~1 hr resource time	200-450+ mL Bulk DS (depends on elimination of other studies) 1-2 hrs FIH timeline ~1 hr resource time	250-500+ mL Bulk DS (depends on elimination of other studies) 1-6 hrs FIH timeline ~1 hr resource time	250-500+ mL Bulk DS (depends on elimination of other studies) 1-6 hrs FIH timeline ~1 hr resource time

Shear	Current Practice	Alternative Option 1	Alternative Option 2	Alternative Option 3
Brief Description	Use benchtop rheometer to test mix, fill, and mix+fill shear	Model correlating shear sensitivity to product characteristics to assess whether study is required	Modify study approach	Risk-based elimination of study for all platform formulation molecules
Material Required	10-175 mL	0 mL	Mix only: 10-65 mL Fill only: 2-65 mL Mix+Fill only: 10-45 mL Reduced sampling (worst-case only): 10-30 mL	0 mL
Study Duration	6-32 hrs	< 1 week	Mix only: 1-4 hrs Fill only: 1-4 hrs Mix+Fill only: 2-8 hrs Reduced sampling (worst-case only): 2-6 hrs	N/A
Resource Time Required	6-32 hrs	~2 hrs	Mix only: 1-4 hrs Fill only: 1-4 hrs Mix+Fill only: 2-8 hrs Reduced sampling (worst-case only): 2-6 hrs	N/A
Risks	None (currently); rheometer cannot test fill shear of T-P pump (future)	Model may fail to predict shear sensitivity --> unforeseen PQ issues in B20	May fail to identify shear stress in mix/fill or lack clarity on point at which shear-induced degredation occurs	Shear sensitive product will not be identified before B20 mfg --> PQ issues in B20
Challenges	Testing of all shear conditions requires many tests/samples; rheometer cup/bob can only handle small amounts relative to sample requirements.	Creating predictive model (determining important parameters and correlating to shear); gaining buy-in	Gaining buy-in; enforcing the approach	Gaining buy-in; collecting enough data to justify elimination
Benefits	Use small scale equipment and relatively little material to understand impact of two critical unit ops	Significantly reduces staff time (DPE & DPD) and material requirements (depending on material use strategy)	Significant time reduction (DPE & DPD); minor material reduction	Significantly reduces staff time (DPE & DPD) and material requirements (depending on material use strategy)
Potential Savings	N/A	0-175 mL Bulk DS 0-1 weeks FIH timeline 4-30 hrs DPE resource	0-100 mL Bulk DS 0-1 weeks FIH timeline 4-24 hrs DPE resource	0-175 mL Bulk DS 0-1 weeks FIH timeline 6-32 hrs DPE resource

Cleanability	Current Practice	Alternative Option 1
Brief Description	Spot product on SS, soak in solution, watch until product is removed	Use model (based on old matrix?) to determine necessity of cleaning evaluation
Material Required	10 mL	0 mL
Study Duration	6-8 hrs	~2 hrs
Resource Time Required	6-8 hrs	~2 hrs
Risks	Measurement is qualitative - based on visual assessment --> accuracy of result could be affected	Possible that screening model misidentifies a tough-to-clean product as an easy one --> B20 cleaning procedure would not be sufficient; product carryover possible
Challenges	Maintaining focus throughout test duration	Gaining buy-in (esp. since matrix use was discontinued); determining cut-off point for study vs. no study
Benefits	Simple test; Head-to-head comparison against worst-case allows for straightforward conclusion	Saves time for ~1/2 the products
Potential Savings	N/A	0-10 mL Bulk DS 2-6 hrs FIH timeline 2-6 hrs DPE staff

Hold	Current Practice	Alternative Option 1	Alternative Option 2
Brief Description	Hold product in SS vessel for 4 days	Use model to determine necessity of hold study	Risk-based elimination of study with DPD stability data
Material Required	50 mL	0 mL	0 mL
Study Duration	96-168 hrs	~2 hrs	0 hrs
Resource Time Required	4-6 hrs	~2 hrs	0 hrs
Risks	None	Model fails to detect potential hold-induced stability issues --> PQ issues in B20	No detection of potential hold-induced stability issues (mitigated by DPD stability data?)
Challenges	Requires moderate material and time	Collecting required data; gaining buy-in	Gaining buy-in (esp. since study was just introduced)
Benefits	Test worst-case hold/SS contact conditions (?)	Cut time off FIH timeline; no container cleaning required	Cut time off FIH timeline; no container cleaning required
Potential Savings	N/A	0-50 mL Bulk DS 0-168 hrs FIH timeline 4-6 hrs DPE staff time	0-50 mL Bulk DS 0-168 hrs FIH timeline 4-6 hrs DPE staff time

Filling	Current Practice	Alternative Option 1	Alternative Option 2	Alternative Option 3
Brief Description	Fill vials on B30 Bosch filler to check for potential fill issues	Use model to determine whether fill evaluation is necessary	Modify study procedure (e.g. fill fewer vials)	Eliminate study
Material Required	250-500 mL	0 mL	50-100 mL (est.)	0 mL
Study Duration	7-8 hrs	~2 hrs	2-4 hrs	0 hrs
Resource Time Required	14-16 hrs	~2 hrs	4-8 hrs	0 hrs
Risks	Equipment not entirely representative of B20 --> Unforeseen fill issues could arise	Model may indicate that study is not necessary but fill issues occur in B20	Fill issues not observed due to small sample size	Potential fill issues not detected until B20 fill.
Challenges	time consuming; requires 2 people; manual process	Gaining buy-in; determining data required for model; possibly conducting other studies to obtain model inputs	Getting approval to modify guideline	Buy-in.
Benefits	Can use relative inexpensive, small-footprint filler to mimic (to an extent) B20 process	Significantly reduce staff time (DPE & DPD); vial prep needs from B20; material	Moderate material and time savings; "leaner" process	Significantly reduce staff time (DPE & DPD); vial prep needs from B20; material
Potential Savings	N/A	0-250 mL Bulk DS 0-5 hrs FIH timeline 12-14 hrs resource time	0 - 250 mL Bulk DS 0-3 hrs FIH timeline 8-10 hrs resource time	250 mL Bulk DS 7-8 hrs FIH timeline 14-16 hrs resource time

Inspection	Current Practice	Alternative Option 1	Alternative Option 2
Brief Description	Use camera and manual inspection to look for particles, bubbles, and other factors that could affect B20 inspection	Use model to determine necessity of inspection evaluation	Modify study to use minimum # of required vials
Material Required	250-500 mL	0 mL	30 mL
Study Duration	4-8 hrs	~2 hrs	4-8 hrs
Resource Time Required	4-8 hrs	~2 hrs	4-8 hrs
Risks	No upper viscosity limit for manual inspectin; evaluation is subjective, leaving room for interpretation	Model fails to identify potential inspection issues --> B20 auto inspection rejects "good" vials or fails to reject "bad" vials; no risk(?) to manual inspection	Hand-filled vials not representative of B20.
Challenges	Identifying potential issues (subjectivity)	Gaining buy-in; selecting appropriate model parameters	Gaining buy-in.
Benefits	Pictures can be taken and used for many purposes; straightforward go/no-go decision on Automatic inspection	Significant reduction of resource time	Significant reduction of material.
Potential Savings	N/A	0-250 mL (if fill & Vmax also eliminated) 0-6 hrs FIH timeline 2-6 hrs DPE staff time	0-250 mL (if fill & Vmax also eliminated) 0-6 hrs FIH timeline 2-6 hrs DPE staff time