Improving Supply Chain Resiliency through Aseptic Connector Alignment and Standardization

by

Toni Guiriba

B.S. Materials Science and Engineering,
Johns Hopkins University, 2015

Submitted to the

MIT Sloan School of Management and
Department of Mechanical Engineering

in partial fulfillment of the requirements for the degrees of

Master of Business Administration
and
Master of Science in Mechanical Engineering

in conjunction with the Leaders for Global Operations program at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
June 2023

Authored by: Toni Guiriba
MIT Sloan School of Management
MIT Department of Mechanical Engineering
May 12, 2023

Certified by: Dr. Stephen Graves, Thesis Supervisor
Abraham J. Siegel Professor of Management
Professor Post Tenure in Operations Management

Certified by: Dr. Daniel Frey, Thesis Supervisor
Professor of Mechanical Engineering
MIT D-Lab Faculty Research Director

Accepted by: Maura Herson, Assistant Dean, MBA Program
MIT Sloan School of Management

Accepted by: Nicolas Hadjiconstantinou, Chair
Mechanical Engineering Committee on Graduate Students

This page is intentionally left blank

Improving Supply Chain Resiliency through Aseptic Connector Alignment and Standardization

by

Toni Guiriba

Submitted to the

MIT Sloan School of Management and
Department of Mechanical Engineering
on May 12, 2023
in partial fulfillment of the requirements for the degrees of

Master of Business Administration
and
Master of Science in Mechanical Engineering

in conjunction with the Leaders for Global Operations program

Abstract

Single-use technologies (SUT) for biomanufacturing have been gaining wide adoption over the last ten years. This was even more accelerated during the COVID-19 pandemic when vaccine developers utilized the technology, having priority access to manufacturing capacity and material inventory through Operation Warp Speed. This was a testament to the manufacturing and development efficiencies enabled by SUT compared to traditional stainless-steel manufacturing, but also a bane to the rest of the pharmaceutical industry from a supply chain perspective.

To persist in the short-term, Amgen continued their operations through a dedicated task force that collaborated closely with internal plants and external suppliers to anticipate shortages and mitigate them. To build supply resiliency in their single-use assemblies for the long-term, Amgen sought to standardize aseptic connectors, enabling greater collaboration and network transferability of parts within plants that are currently standardized to different connector preferences.

Here we show a detailed assessment of the various aseptic connector options at Amgen, along with a cost-benefit-risk evaluation of standardization, and an implementation plan supported by an external benchmarking of a few of Amgen's peer companies. Our analyses and recommendations were informed by internal stakeholder interviews, peer company and subject matter expert interviews, supplier outreach, internal data analysis, and a manufacturing associate survey. We evaluated the connectors based on technical design specifications, supply robustness, defect risk, and user experience.

Due to cost constraints to undertake standardization comprehensively all at once, we recommend selecting a single candidate connector for standardization with a phased approach for implementation upon new site builds and technology introduction. This allows Amgen to deploy standardization as part of other value-adding improvements to their operations, such as their new site build in Amgen North Carolina. With introduction of a standard aseptic connector in this new site, over 60% of existing connectors from two other plants are covered by the revision, lowering the barrier for those plants to move to the standard in the future. This approach to evaluating the impact of process component standardization across a network of manufacturing sites is useful for other technology standardization that companies are evaluating.

Thesis Supervisor: Dr. Stephen Graves
Title: Abraham J. Siegel Professor of Management, Professor Post-Tenure in Operations Management

Thesis Supervisor: Dr. Daniel Frey
Title: Professor of Mechanical Engineering, MIT D-Lab Faculty Research Director

This page is intentionally left blank

Acknowledgments

This project would not be possible without Amgen's commitment to the MIT Leaders for Global Operations (LGO) program. Thank you for providing us the opportunity to learn from your world-class biomanufacturing operations while applying our knowledge and experience to deliver value to your company. Special thanks to my Amgen managers, Sowmya Selvanathan and Dr. Jeff Raney; my Amgen mentor, Hillary Costa; and the rest of the Amgen team for answering my questions, helping me navigate the company, and playing a crucial role in the success of my project.

I would also like to express my sincerest gratitude to my thesis advisors, Prof. Steve Graves and Prof. Dan Frey, for their mentorship, guidance, and support throughout my project. Thank you for your time, patience, and willingness to help as I progressed through my internship and sought your input. Your expertise and dedication have been invaluable to my growth and development as a student and an operations professional.

I would also like to extend my heartfelt thanks to my family, especially my Mom, for her hard work, moving to this country more than a decade ago to provide a better future for me and my brothers. You are my inspiration. I would not be standing here doing this work, if not for your sacrifices. Thank you for believing in me and helping me thrive.

Finally, I would like to thank my partner, Michael, for his unwavering support and encouragement, especially during the many challenging times I have been pushed out of my comfort zone during this program. Your love and support have been a constant source of strength and motivation. Thank you for cheering me on and supporting my dreams.

This page is intentionally left blank

Contents

This page is intentionally left blank

List of Figures

This page is intentionally left blank

List of Tables

This page is intentionally left blank

Acronyms

ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Material
BiTE ® molecule	Bispecific T cell engager molecules
BPI	BioProcess International
BPOG	BioPhorum Operations Group
BPSA	Bio-Process System Alliance
CAGR	Compound Annual Growth Rate
CAR	Chimeric Antigen Receptor T-cells
COVID-19	Coronavirus disease 2019, also known as SARS-CoV-2
DP	Drug Product
DS	Drug Substance
EE	Early Engagement
ESQ	External Supply Quality
ETA	Engineering Technical Authority
HDMI	High-Definition Multimedia Interface
ISO	International Organization for Standardization
LGO	Leaders for Global Operations
mAb	Monoclonal Antibody
NPS	Net Promoter Score
P&ID	Process and Instrument Drawing
R&D	Research and Development
SDD	Standard Disposable Design
SDO	Standard Development Organizations
SKU	Stock-Keeping Unit
SOP	Standard Operating Procedure

SUS	Single-Use System
SUT	Single-Use Technology
USB	Universal Serial Bus

This page is intentionally left blank

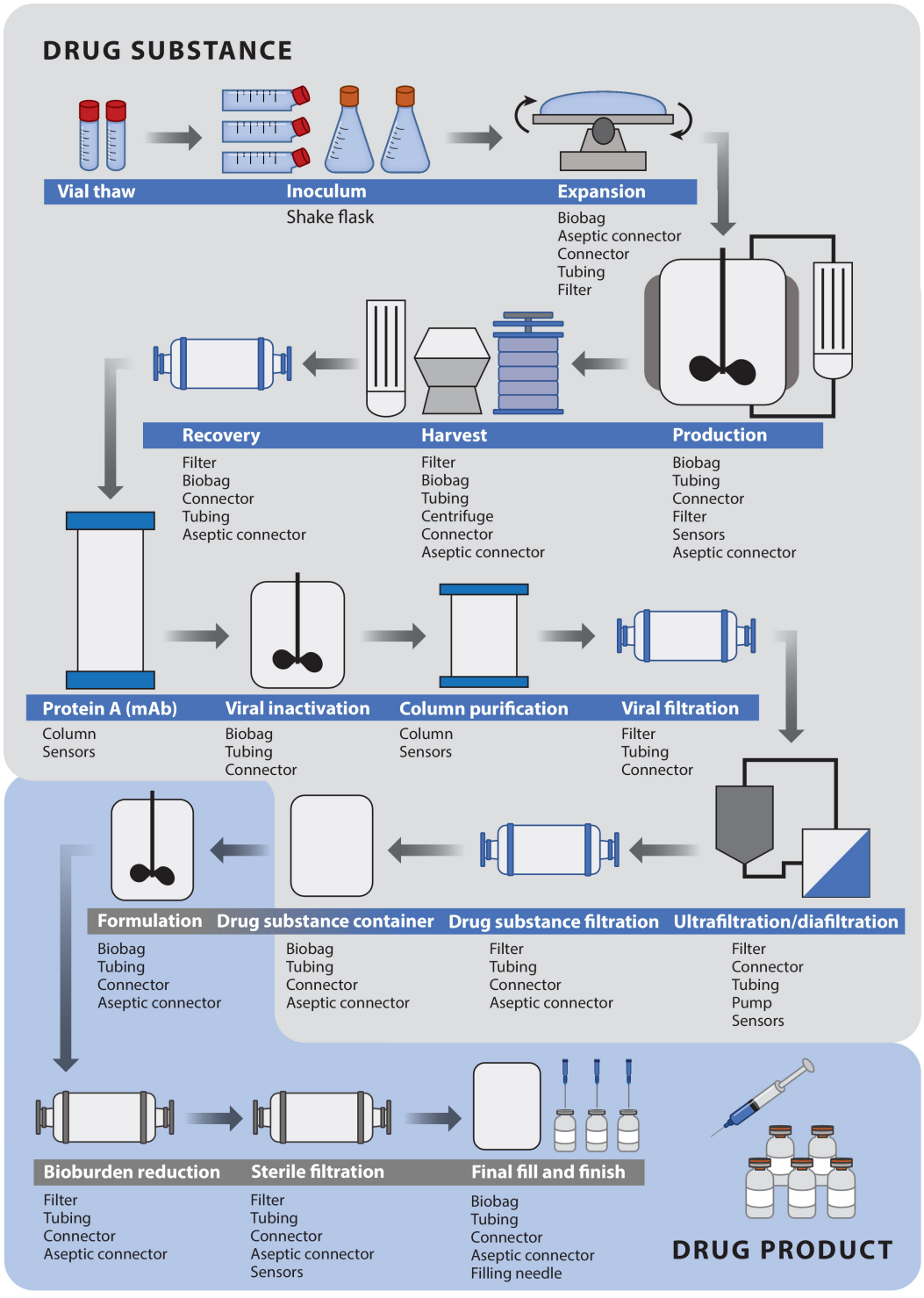
Chapter 1. Background

1.1. Biologics manufacturing

Biologic drugs, such as monoclonal antibodies, differ from traditional small molecule drugs as they are produced by living cells rather than a chemical synthesis process. Biologics begin with an engineered cell line designed in the laboratory to produce certain therapeutic proteins. Once the cell line is developed, the cells are allowed to proliferate to establish a Master Cell Bank, from which vials of cells are later thawed for continued production of the product. [1]

Figure 1 below shows a generalized monoclonal antibody manufacturing process. [2] The process involves two phases: drug substance (DS) and drug product (DP) manufacturing. Drug substance manufacturing is composed of upstream (cell proliferation) and downstream (protein capture) processes where the cells are thawed from the master cell bank vials, expanded to a certain density, and the protein of interest expressed by the cells is harvested and purified. After the drug substance is collected, drug product manufacturing occurs. In this phase of the process, the final drug product is formulated to the right composition for patient dosing and filled into an appropriate container.

Traditional manufacturing technology for biologics involve stainless steel formulation tanks and pipes for material and product transfers. As will be discussed further in the following sections, the biopharmaceutical industry is beginning to move toward single-use components due to the operational efficiencies enabled by this technology. As seen in **Figure 1**, there are various single-use components used in each step of the process. For example, in production stage of the cells, the process utilizes a biobag (also called a bioreactor) that houses the cells as they continue to proliferate. Various flexible tubings are connected to the bag to enable feeding of raw materials, sample collection, and product transfer in and out of the bag. Filters are attached to the bag to allow filtration of materials being added. Sensors are used to monitor the cell environment, such as pH, temperature, oxygen levels, and pressure. Lastly, tubing lines are connected via aseptic connectors or tube welding to establish a fluid path from one assembly to the next.



Samaras JJ, et al. 2022
Annu. Rev. Chem. Biomol. Eng. 13:73–97

Figure 1. Single-use components used in various unit operations for a monoclonal antibody manufacturing process [2]

1.2. Amgen as a biopharmaceutical company

Established in 1980, Applied Molecular Genetics Inc., now referred to as Amgen, is one of the world's leading biopharmaceutical companies. Amgen focuses on discovery, development, manufacturing, and commercialization of innovative therapies in disease areas with high unmet need such as oncology, nephrology, bone health, neuroscience, inflammation, and cardiovascular disease. The company started by harnessing the power of living cells to make biologics such as monoclonal antibodies (mAbs). Today, their diverse portfolio includes not only mAbs and other biosimilars, but also small molecules and other innovative modalities such as Bispecific T cell engager molecules (BiTE ® molecule), fusion proteins, siRNA, chimeric antigen receptor T-cells (CAR-T), and many others. Some of Amgen's successful products in the market include Enbrel, Neulasta, and Epogen. [3]

Apart from their successful science, Amgen is also a world leader in biomanufacturing. From process development, engineering innovation, site design and build, and adoption of new technologies, Amgen is at the forefront of advancing the biotechnology industry. [4] One of Amgen's major breakthroughs in manufacturing technology is their adoption of single-use technologies for biomanufacturing to improve efficiency and productivity, eliminating the need to sterilize equipment and speeding up changeover times. It has led to greater process flexibility as the modalities, manufacturing processes, volumes, and dosing regimens of their medicines changed over the years. [5]

Operations is a competitive advantage for Amgen and the company is committed to strengthen this position every day. They know that a successful biotechnology company starts with a productive research and development (R&D) pipeline and thrives when complemented by robust operations that turn discoveries into tangible products. Innovation spans Amgen's operations with the goal of reducing cost while improving the safety, quality, and reliability of their medicines. They have an unrelenting focus on **READ** – reliability, efficiency, agility, and differentiation. At the heart of their operations strategy is reliable service to patients, efficient manufacturing of medicines, agile delivery of products to market, and differentiated manufacturing technologies and product capabilities.

All of these are realized and made possible through a culture of innovation built by mission-driven and talented people in the areas of process development, quality, engineering, manufacturing, and supply chain. [6]

Delivering on their promise of "Every Patient, Every Time", Amgen is one of only two companies to have never shorted the market in terms of drug supply. This is a remarkable accomplishment and one that has involved four key operational elements to achieve – **prevention** of unforeseen supply and manufacturing issues through robust operations, risk management, and business continuity planning; **technology** investments to improve process efficiency and product quality; **inventory management** to guarantee availability of raw materials and products at various points in the supply chain along with well-maintained relationships with a diversified supplier base; and **redundant manufacturing** across eight manufacturing sites and other contract manufacturing capabilities across the globe. [7] Amgen is continuously expanding their biomanufacturing footprint and have started breaking ground at two new locations – Amgen North Carolina and Amgen Ohio. [6] [7]

1.3. Single-use systems (SUS) in the biopharma industry

Adoption of single-use components and assemblies across the biopharmaceutical industry has grown consistently over the last 10 years. Initially, this next-generation technology gained wide applicability in pre-commercial/clinical production given their flexibility and customizability while the manufacturing process is still under development. Today, applications in commercial operations have been on the rise with the potential to soon surpass traditional stainless-steel technology. [10] Figure 2 shows data gathered by BioPlan Associates demonstrating the increasing trend of single-use technology adoption across upstream and downstream manufacturing processes for both clinical and commercial operations over the years. [11]

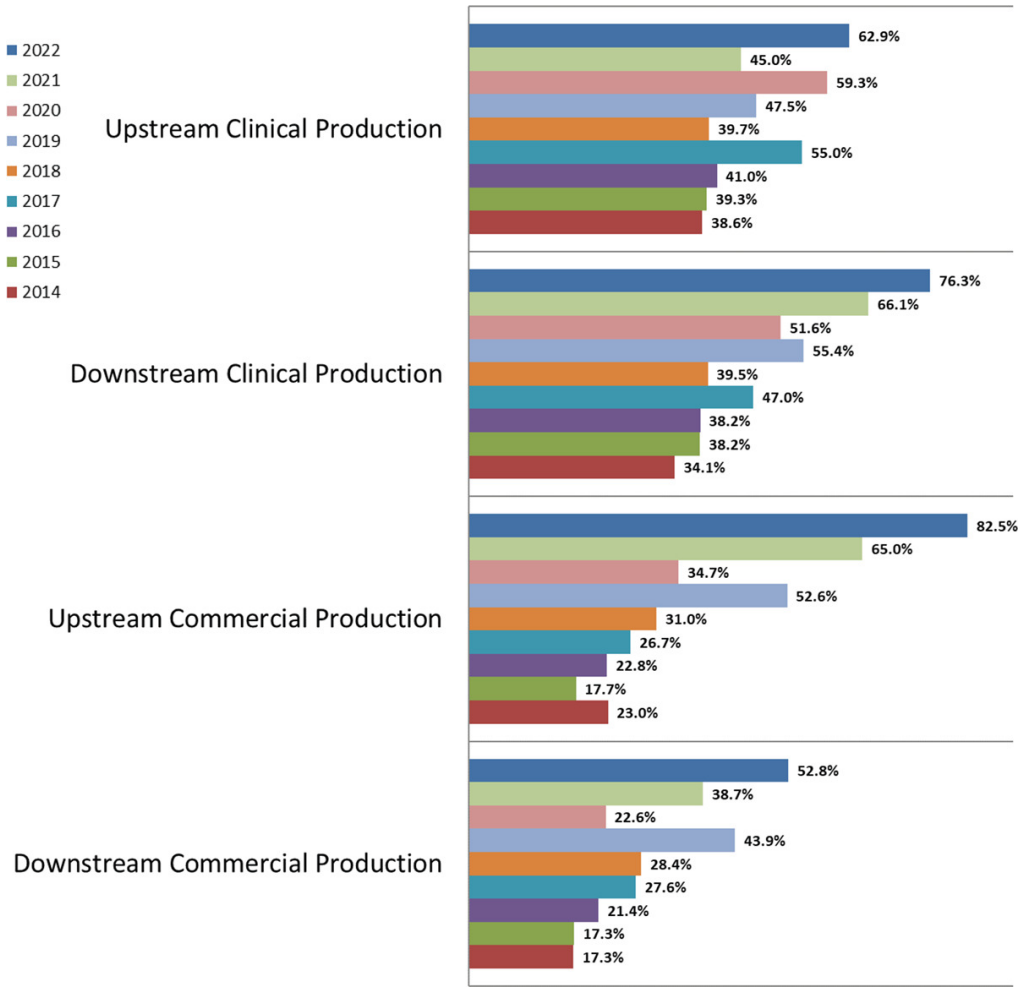


Figure 2. Adoption of single-use technology across biopharmaceutical operations

As the name implies, single-use technologies are used once and discarded. Figure 3 shows a few examples of single-use assemblies. These assemblies are comprised of components such as tubings, filters, bioreactors, storage containers, and connectors. The individual components are supplied by certain vendors in the industry and integrated into custom systems by integrators. Once designed and sourced by customers, these single-use systems often come sterile and ready-to-use, alleviating time and effort associated with traditional cleaning and sterilization methods as well as process validations necessary for stainless steel equipment. The main benefits of single-use technology can be broken down to four themes: 1) higher productivity and efficiency, 2) better quality and contamination controls, 3) increased process flexibility, and 4) smaller facility footprint.

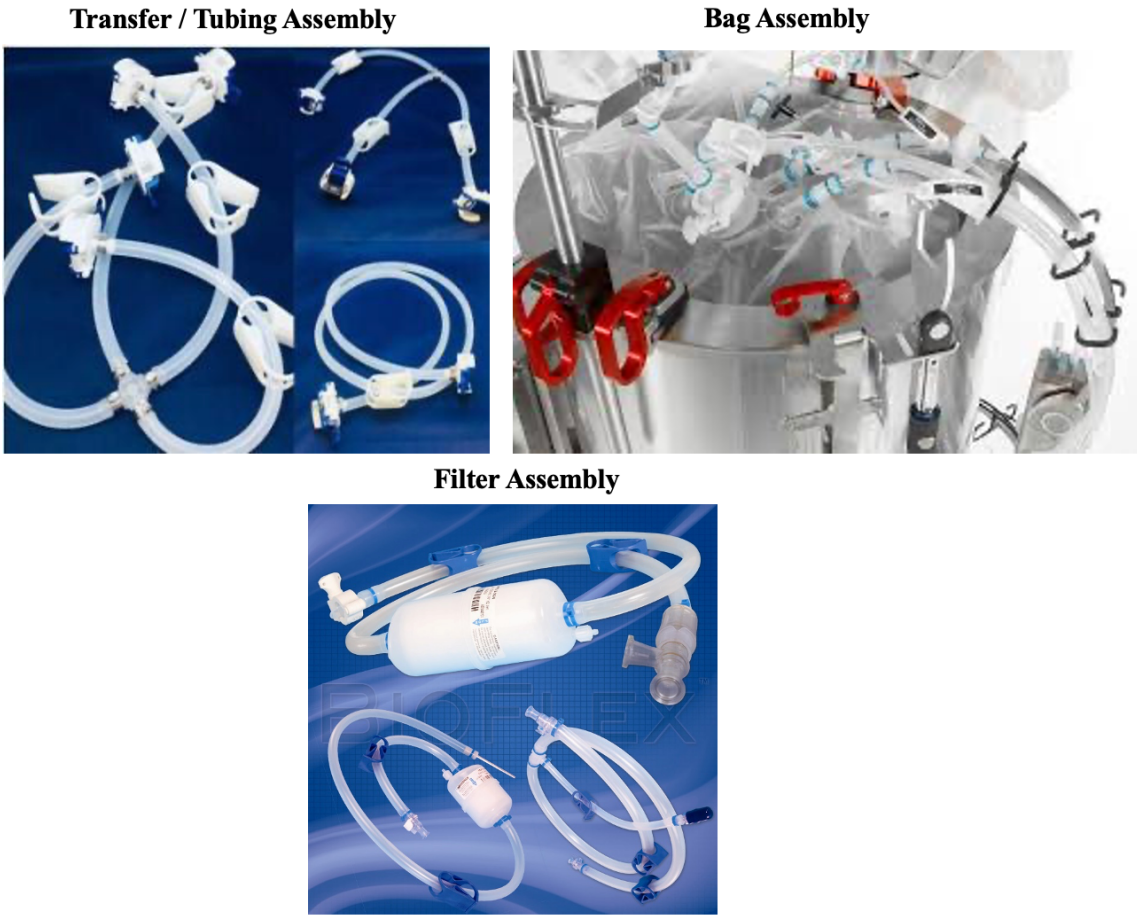


Figure 3. Examples of various single-use assemblies – transfer/tubing assembly [12], bag assembly [13], and filter assembly [14]

Higher productivity and efficiency are brought on by quicker changeovers since the single-use components are discarded after use and the process of cleaning and sterilizing reusable equipment is eliminated. By eliminating the need for cleaning validations, which can take weeks or months to complete, companies are able to speed up the product development process. While these assemblies are disposable, there are environmental benefits harnessed by the technology such as lower water and chemical consumption, less energy from steam generation, and reduced liquid waste from cleaning. [15]

Better quality and contamination controls are achieved by eliminating the risk of cross-contamination as every new batch of product manufactured uses brand-new assemblies. Options are also available to pre-sterilize assemblies with x-ray or gamma irradiation.

Process flexibility is harnessed as the design of the process and the assemblies for manufacturing can be modified at any time as opposed to permanent stainless steel equipment installations. Adoption of new technologies to increase the yield of the manufacturing process are more achievable and less time- and cost-intensive to implement. This also enables quicker product development cycles. In contract manufacturing and small-scale development settings, the manufacturer can have an empty room that is highly customizable according to the needs of the product and the manufacturing process.

Smaller facility footprint is realized through flexible and modular process components such as flexible tubing and bioprocessing tanks that are mobile and can be rolled into place as seen in Figure 4. These bioprocessing tanks are fitted with single-use bioreactor bags and connected to other process components via flexible tubing and aseptic connectors. A real-world example of an efficient facility, Amgen's Singapore manufacturing facility, was built in half the time with a quarter of the cost and is 75% smaller than the footprint of a traditional biomanufacturing plant with only a third of the operating cost. [11] [12]

Figure 4. A look inside a single-use biomanufacturing facility (image from Integrated Project Services) [18]

The adoption of single-use technology has been driven by several factors, including the increasing demand for biologic medicines and new modalities; the need for faster drug development cycles and more efficient manufacturing processes as biosimilars enter the market; and the risks of cross-contamination. Single-use technology has also improved and matured, with expanded product selections and better chemical compatibility than ever before. As an example, for aseptic connectors which is the subject of this thesis, improved designs with chemically resistant materials of construction have become available. However, there are still drawbacks and challenges looming over the industry such as the lack of guidance on standardization, the need for leak-proof systems, and challenges with leachables which are chemical byproducts extracted from single-use parts under normal process conditions and are considered a contamination risk for the product. [19].

1.4. Literature review

Standardization has enabled us to travel to a new country and know exactly the electrical requirements and travel adapters we need so that we can safely power and connect our devices. In the US, for instance, the power supply for common everyday use is standardized to 120 V, 60 Hz with Type A or B electrical plugs. Wherever we travel in the country, regardless of the state, we can expect to be able to connect our device as long as it is compatible with the power supply, and we have the right plug or adapter. This is an example of standardization for interoperability. Without a common standard, it would be cumbersome to predict the appropriate plug to use for different locations and could even be unsafe should one mistakenly connect an incompatible device.

In a review article published by Allen and Sriram on the role of standards in innovation[20], they define standards as “documented agreements containing technical guidelines to ensure that materials, products, processes, representations, and services are fit for their purpose.” From this definition falls four broad types that we encounter in industry. One that most will recognize are measurement standards such as the metric system where we use kilograms for mass, meter for length, and liters for volume. The second type are process-oriented standards which outline a specific process for completing a task so that it is done consistently. Standard Development Organizations (SDOs) such as the International Organization for Standardization (ISO) and American Society for Testing and Material

(ASTM) publishes common process standards for industry. Certain companies may also publish their own Standard Operating Procedures (SOPs) for this purpose. The third type are performance-based standards where the final product is subjected to a certain rating to meet safety and regulatory requirements. For example, the American Society of Mechanical Engineers (ASME) publishes standards for pressure ratings, dimensions, and tolerances of mechanical parts to meet performance for various industries. Lastly, and as mentioned in the example above, the fourth type of standard is an interoperability-based standard. These standards enable equipment and systems to interconnect and function smoothly. Standardization of aseptic connectors at Amgen fall under this category as it is meant to enable interconnectivity of various single-use assemblies across the manufacturing network.

Other common examples of standardization for interoperability in various industries include electronic devices that utilize Universal Serial Bus (USB) connectors, enabling computers and other electronic devices to interconnect. For audio and video connections, we also have High-Definition Multimedia Interface (HDMI) which connect televisions, computers, and multimedia players. These connectors were adopted over time through industry consensus. [21] With single-use technology for biopharmaceutical manufacturing being relatively new and still evolving, standardization of components and assemblies are still largely company-dependent. [22]

In a recent paper, A Strategic Approach to Management of Single-Use Technology [23], Schmidhalter et al., discuss single-use assemblies and the variables that become multipliers of design variants shown in Figure 5. For example, in transfer or tubing assemblies, these variables include tubing material, diameter, length, connector type, and geometry. As a simple illustrative example, the paper discusses connectors as one of these components to standardize as sites that have similar assemblies with different connectors will inevitably have to maintain separate stock-keeping units (SKUs) and cannot share parts. That is, a straight transfer assembly with the same tubing material, diameter, and length but different aseptic connector will require two separate part designs and cannot be interchanged. This leads to distinct inventory levels of the two parts, duplicating the work required to manage supplies and documentation, while also precluding sharing of supplies in the event of a

shortage. With flexibility in the design of single-use assemblies, customization of variables can result in thousands of assemblies that a company must manage and source continually. To achieve long-term operational sustainability and supply robustness, standardization of these variables must be undertaken.

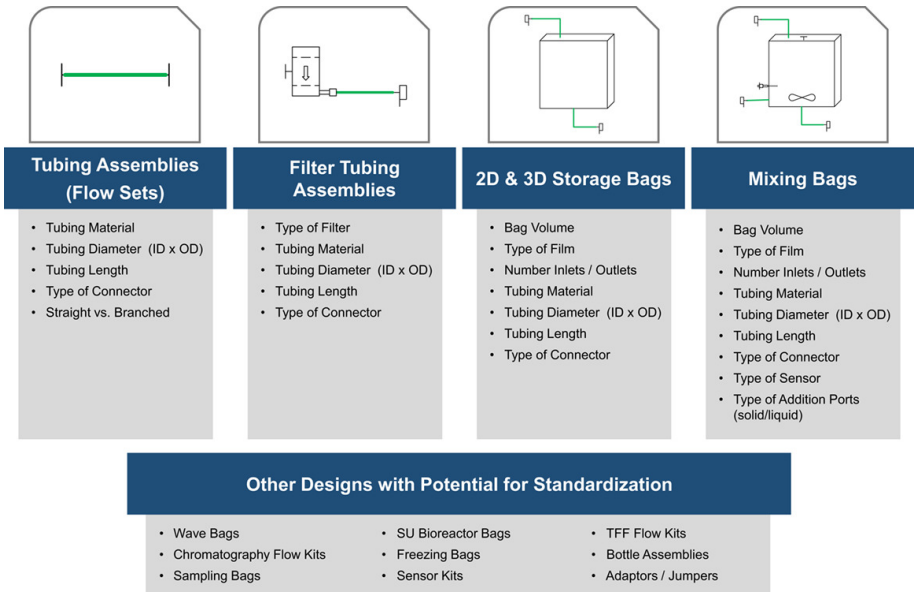


Figure 5. Design variables for various types of single-use assemblies

In Clinton Rendall's LGO thesis from 2018 [24], they evaluated modularity of single-use systems (SUS) to enhance design and procurement of assemblies at Amgen. As one of the recommendations for future work, they identified standardization of components, primarily of aseptic connectors as "the single most important enabler of greater SUS modularity". Modularization of assemblies addresses the problem of highly customized assemblies, since a particular application can combine modular components to build their assembly instead of designing a unique assembly. One important consideration for this is that modular assemblies will not be able to interconnect and will instead yield an extensive array of components without a standard connector as illustrated by the design variables in Figure 5.

An article published by BioProcess International (BPI) [22] discusses some of the hurdles that have hindered industry-wide standardization efforts, including enormous switching costs associated with modifying validated processes required for the biopharmaceutical industry, company differences in design preferences and procurement approaches, and

suppliers' unwillingness to adopt industry-wide standards as they are benefitted by differentiating their own products. However, as experienced by both companies and suppliers during the COVID-19 pandemic, the lack of standards have resulted in a complex supply chain requiring high inventory levels of many custom parts. Not only was the industry capacity constrained, these parts also required more effort to oversee as the shortages occurred and suppliers had to manage customer demand.

A current industry-wide initiative called the Standard Disposable Design (SDD) was started by the PM Group five years ago. [22] Their standard designs and design tools, combining supplier drawings and process and instrument drawings (P&IDs), are informed by suppliers, end-users, and engineering firms. To-date, it is unclear how widely adopted the SDD approach is among biopharmaceutical manufacturers. In Moon and Lee's paper, The Primary Actors of Technology Standardization in the Manufacturing Industry [25], they describe the role that primary actors such as technology producers (complementary products companies), technology users (core companies, and following companies), and regulators play in establishing standards. They propose the conceptual framework shown in Figure 6.

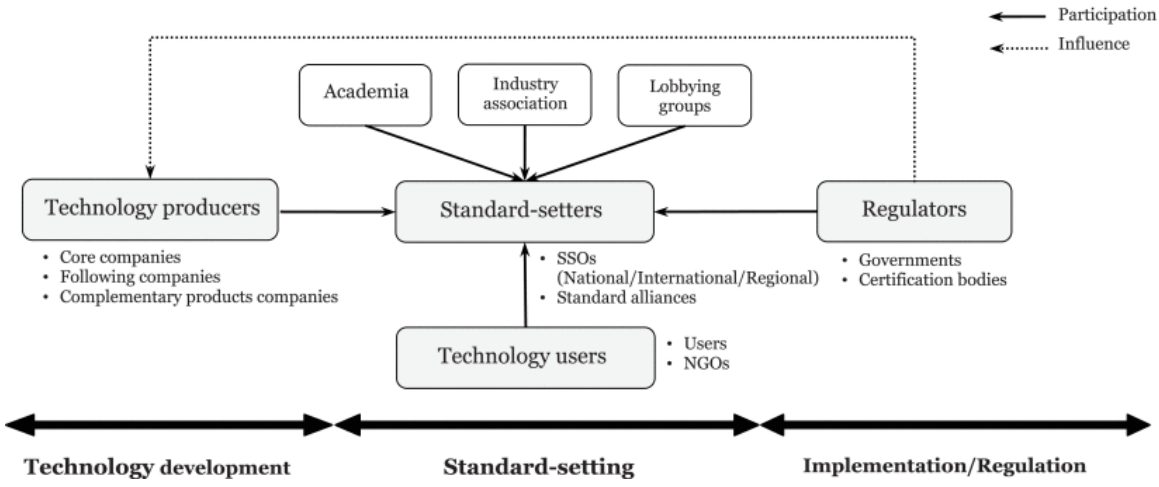


Figure 6. The primary actors in standardization and their involvement across the phases of development and adoption of a technology [25]

Applying this framework to SDD implies that wide acceptability across the industry will require buy-in from core companies who can help shape the standards, provide feedback,

and serve as agents for change. Core companies are those who have the resources and credentials to influence the standard as well as the views of their peer companies. As shown in Figure 6, to attain standardization across the industry, companies, suppliers, academic institutions, and existing industry groups such as Bio-Process System Alliance (BPSA) and BioPhorum Operations Group (BPOG) will have to collaborate. [26]

The other aspect of this project is improving supply resiliency of single-use assemblies. In the book Supply Chain Risk Management, Radhakrishnan et al. provides a broad overview of the concept of Supply Chain Resiliency. [27] As cited in the review chapter, Peck et al. previously defined resilience as "supply chain's ability to cope with the consequences of unavoidable risk events in order to return to its original operational state or to move to a new, more desirable state after being disturbed". Resilience is influenced by two other factors – supply chain risk management and supply chain vulnerability. As shown in Figure 7, we can see that risk management improves resilience, while vulnerability decreases resilience.

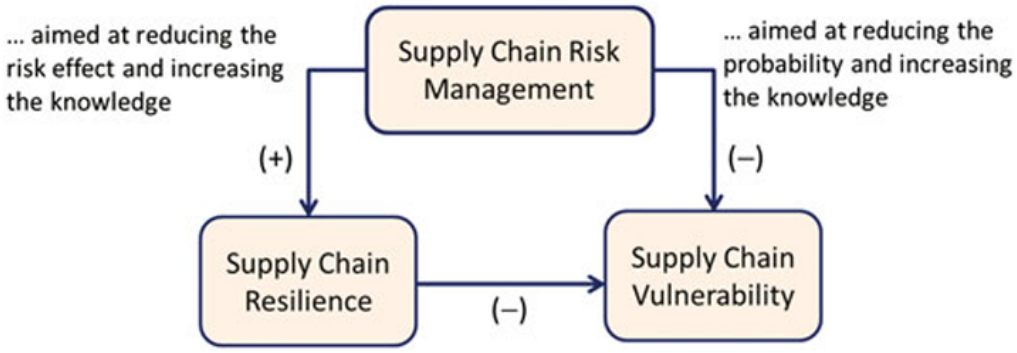


Figure 7. Factors influencing supply chain resilience from Juttner and Maklan, 2011

Furthermore, they also discussed the components of resiliency as described in the literature. It includes flexibility, velocity, visibility, and collaboration. In the following Chapters, we explore how standardization influences supply chain risk management and vulnerability, and how we strengthen flexibility, velocity, visibility, and collaboration to overall improve supply chain resilience.

Chapter 2. Project introduction

2.1. Problem statement

Prior to the COVID-19 pandemic, Amgen established a Supplier Relationship Excellence program to build robust relationships with their top suppliers in the industry. However, as the world closed and the race for a vaccine ensued, even the strong relationships that Amgen built succumbed to the pressures and challenges faced by the global supply chain. Manufacturing capacity and individual component supplies dwindled. While vaccine manufacturers were prioritized through Operation Warp Speed, longer lead times and supply shortages plagued the rest of the pharmaceutical industry. As a result, single-use systems were deemed high-risk for Amgen, prompting the company to find alternate, long-term actions to further strengthen the resiliency of their supplies.

In the short term, during the height of the pandemic, Amgen started a task force responsible for closely monitoring their single-use supplies and mitigating risks for stockouts. Internally, this task force comprised of the single-use system network team, engineering technical authority, and site technical leads. Externally, they also maintained frequent and open communication with suppliers. Altogether, these stakeholders spent many hours fighting fires related to inventory stockouts and component substitutions.

To secure the future of their supplies, Amgen concurrently searched for ways to further enable network-wide supply coordination and collaboration. One problem that Amgen encountered is the limited opportunity to transfer parts between sites due to aseptic connector differences. Those missed opportunities to share supplies across the internal manufacturing network became a strong driver towards more standard components and assemblies, starting with aseptic connectors.

2.2. The hypothesis: Standardize to improve supply resiliency

Separate single-use assemblies are joined through aseptic connectors, creating a sterile fluid pathway when connected. As mentioned, this is an area of standardization that can unlock great potential as companies evaluate modularity and network transferability of supplies across sites. Standardizing connectors enable interconnectivity of various

assemblies and would otherwise, hinder transfer of supplies between sites that use one connector versus another. At present, almost every connector in the market is deployed at Amgen with varying degrees of adoption and usage. Differing aseptic connector designs contribute to proliferation of assembly designs, each of which need to be maintained and sourced.

There are ~600 SUS assemblies routinely sourced for Amgen's continued production. Our hypothesis is that with aseptic connectors standardization, we will standardize to the best connector option, reducing the number of assemblies with critical supply while enabling further transferability of parts across Amgen's internal manufacturing network. A thorough assessment of the current state will improve supply chain risk management and reduce vulnerabilities by eliminating connectors with poor supply or performance. Consistent with Amgen's goals, improving supply chain resiliency through standardization will simplify processes and ensure continued delivery of products to every patient, every time.

2.3. Approach and methodology

With the eight connectors currently deployed at Amgen, we needed to determine the best connector option for standardization and how to effectively implement the change.

The approach was broken down to three parts:

1) Assess the current state and diversity of connectors within Amgen's internal manufacturing sites in Rhode Island, Thousand Oaks, Puerto Rico, Singapore, Ireland, and North Carolina (currently under construction). This includes an analysis of the usage, defects, and supply robustness associated with the various connectors as well as a summary of insights gathered from relevant stakeholders and manufacturing associates.

2) Understand industry trends on standardization through external benchmarking of Amgen's industry peers. This includes a study of the various considerations for assessing a standard connector.

3) Present options for standardization and evaluate the costs, benefits, and risks of each option. This includes identifying a proposed action for implementation, along with risk mitigation and change management plans.

Chapter 3. External benchmarking

The external benchmarking informed our assessment of the current state of aseptic connectors at Amgen in the following chapter.

3.1. Standardization journey

The biopharmaceutical industry is shifting from introduction and adoption of single-use systems to highlighting the importance of standardization of designs. [16] [19] [21] [2] Single-use technology has enabled flexibility and many other great advantages but when care is not exercised in managing and controlling designs, the technology can lead to inefficiencies and waste – higher levels of SUS inventory due to highly customized assemblies with limited applications; underutilized talent focused on managing an extensive design library; excess waiting from long lead times of a wide selection of supplies; and extra processing later on to simplify designs and select standards.

As part of Amgen's efforts to define their long-term sourcing strategy around single-use systems and to understand how others in the industry are approaching standardization, we reached out to a few of their peer companies and single-use subject matter experts to learn about their experience and gain additional insights. From our interviews, we learned that companies are in different stages of their standardization journey. There are early adopters of single-use technology who considered standardization early on in their journey, aspirants who realize the value of standardization and are actively working towards achieving it, and contemplators who are reflecting on the idea and if or how it will fit their operation.

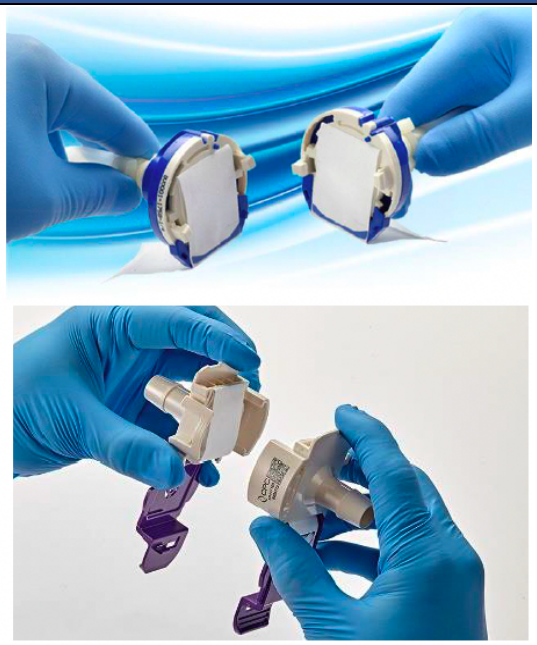
Early adopters have been on their journey for close to a decade with standard connectors, tubings, filters and bag films implemented. Aspirants have completed studies to justify the change and understand how to standardize their components and are actively testing the idea or building a strategy to roll out the initiative. On the other end, contemplators are still considering standardization but have decided to not pursue it today as it does not fit their current organization and strategy. While most have echoed the benefits of standardization in their operation, they also highlighted that there are many considerations to deliberate before taking on this journey.

3.2. Considerations for companies

Based on internal research at Amgen and external benchmarking of our peers in the industry, there are four main considerations in selecting a standard connector. These include 1) technical design specifications, 2) supply robustness, 3) reliability, and 4) user experience.

Technical design specifications include the material of construction and chemical compatibility of the connector with a diverse range of chemicals used in the manufacturing process. Materials of construction that are deemed highly resistant to harsh chemicals are typically made of polysulfone, polyethersulfone, or polyvinylidene fluoride. Utilizing the appropriate material of construction for the application is important as incompatible materials can lead to catastrophic failure as well as contamination of the product by impurities such as extractables and leachables from the polymer materials. We also consider whether the connector is gendered vs genderless as shown in Table 1.

Table 1. Examples of genderless and gendered aseptic connectors

Gendered Connectors [29], [30] (Male and Female)	Genderless Connectors [31], [32] (Neutral)
	

Genderless connectors require less variations in design since all connectors are connectible without considering the gender and orientation of the assemblies. For example, a straight filter assembly with gendered connectors may need two different variations – male to female and female to male – to allow it to connect to different process setups, whereas a genderless connector will only need one version. Another factor we consider is the level of technical support provided by the original equipment manufacturer. Manufacturers who fully support their product and are proactively collecting data to validate its use and solve technical issues have been valuable to Amgen in the past.

Supply robustness refers to the vendor's ability to supply the connector consistently and reliably for years to come. We reached out to all the manufacturers of the various aseptic connectors at Amgen and inquired about their current manufacturing capacity utilization, redundancies and business continuity plans, lead times, and future plans to expand capacity, if needed. The responses provided by suppliers, while qualitative, provides a level of confidence given the strong partnership between Amgen and their suppliers. The goal here is to ensure that the supplier can not only supply Amgen's current demand but also any other future growth should the connector be chosen as the standard and its usage increases. We also asked the vendors regarding the overall percentage of their total demand that is attributable to Amgen and overall acceptance of their product among integrators to ensure that there is a diverse user base and market neutrality.

Under reliability, we consider the risk for defects associated with the connector. Leaks are the most common defect associated with single-use connector which can stem from a defective part or a technique error such as bad connection or a bad pull. A bad connection refers to any error with the assembly of the connector such as mating the two different sides and twisting or clicking of the connection together to seal it. A bad pull specifically refers to an error associated with pulling the sterile membrane of the connector such as tearing or disentanglement of the pull tabs shown in Figure 8. In selecting a standard connector, we want to ensure that these issues are not recurring inherently due to a flawed design of the connector.

Figure 8. A genderless aseptic connector showing the sterile membrane to be pulled [32]

Lastly, we evaluate the user experience, considering ergonomics, safety, and the experience of the manufacturing associates who assemble these connectors during production. It is important to inform the changes under consideration with input from those who are directly involved in the manufacturing process since they have the most knowledge and experience, and these changes will impact them directly. This not only supplements our assessment, but also shows respect to one of Amgen's most valuable assets – its people.

These considerations are meant to reveal potential risks and vulnerabilities associated with the current aseptic connectors, enabling us to manage and alleviate these to improve supply chain resiliency. Aside from these four considerations, the company must determine how standardization fits into their operational strategy. While most companies would benefit from having a standard, there are instances where the changes can be cumbersome and limiting. For example, a company that has multiple sites they acquired over time may have completely different process, equipment, and site design, where standardization becomes an expensive investment requiring not only harmonization of the components, but also the overall manufacturing process and plant design. Meanwhile, for other companies, standardization can be crucial especially if they view their manufacturing sites as a cohesive network that can work together and pool their capacity to realize economies of scale and meet market demands. Each company must weigh this decision for their organization before committing to standardization, as we do for Amgen in this project.

Chapter 4. Current state of aseptic connectors at Amgen

4.1. History and Evolution of SUS at Amgen

4.1.1. Adoption and development across the manufacturing network

Amgen is a pioneer in the adoption of single-use biomanufacturing technology. [33] In 2014, they opened Amgen Singapore (ASM), one of the first biomanufacturing facilities in the world utilizing entirely single-use components including bioreactors, filtration assemblies, transfer assemblies, and storage bags. The facility is a realization of the benefits of switching to single-use technology mentioned in Chapter 1, specifically, the site is built in half the time, 16% the footprint, and runs on a third of the operating cost when compared to a traditional stainless-steel facility. Switching to single-use has also enabled significant reductions in water and energy consumption. [16]

At the time, single-use technology development was still continuing. As the technology gained broader acceptance, manufacturing sites within Amgen began to work with various suppliers and adopt different designs and components that suit their needs. While ASM had a standard connector built into their process from the beginning, other sites had the freedom to choose whichever connector they deemed best for their application or was recommended by the vendor they were working with at the time. There was no central group to provide technical guidance or control the proliferation of designs and components.

In 2017, Amgen realized the need to take a centralized network approach to single-use assembly design. Clinton Rendall's thesis was published around this time and discusses the unsustainable proliferation of assembly designs and the case for modularity. [24] Soon after, Amgen established the Early Engagement (EE) program with the goal of centralizing design reviews throughout the network, promoting competitive sourcing, and initiating documentation management prior to deployment of an assembly in manufacturing. The single-use systems EE network team, shown in Figure 9, comprise of engineering, supply chain, quality, process development, materials science, and specification management. Engineering governs and runs the EE process with the end-goal of controlling the

proliferation of single-use assembly designs throughout Amgen's internal manufacturing network.

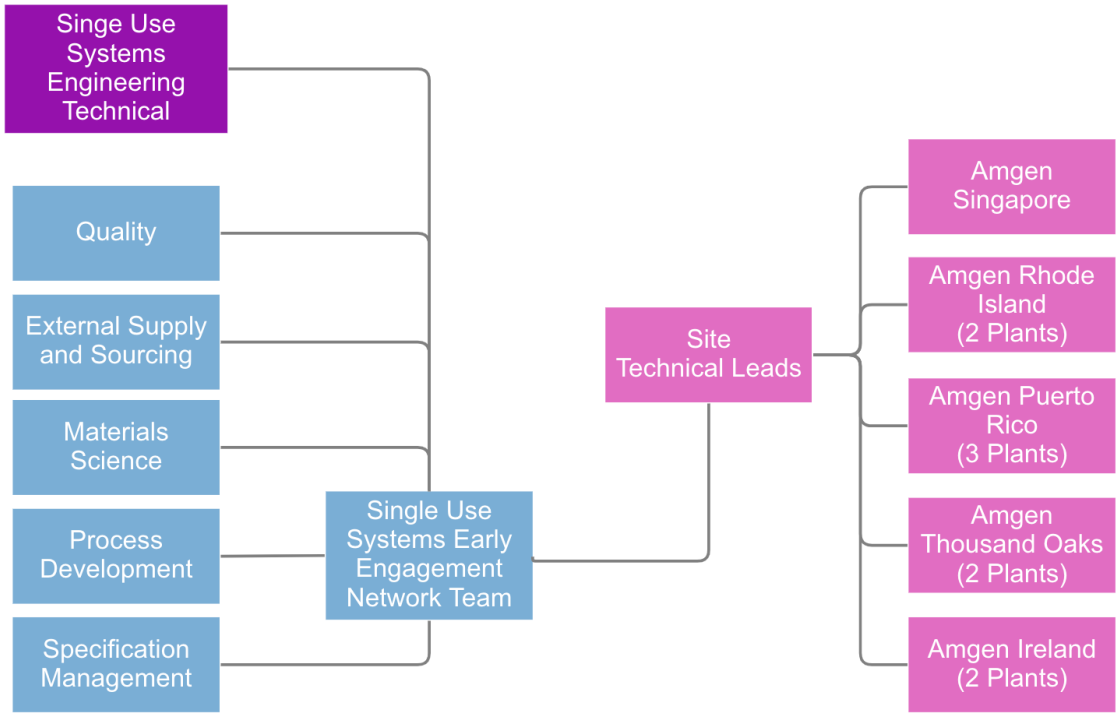


Figure 9. The single-use systems early engagement network team

In the EE process, the request for a new design is submitted by the respective manufacturing site technical leads, requiring review of existing materials and justifying the need for a new assembly. Once they confirm that a new custom assembly is required, they fill out a User Requirements Specification outlining the needs of their process. The EE team then reviews the technical details of the design taking into consideration modularity and universal use for other processes, so that each assembly is not tailored solely for one application. This balance of customization and standardization is one that the team treads carefully in the EE process.

Materials Science ensures that the appropriate material is selected for the application and that supporting data is available to justify the use of the material. Process Development and Engineering ensures that an appropriate design is implemented for the process, and that the customization is fit for the application without being overly specialized. Quality and

Specification Management ensures that the documents are aligned and prepared in compliance with quality system requirements. External Supply and Sourcing engages with the suppliers to identify the best fit for the project, as well as communicate timelines for delivery.

After the design review is completed, the new part request moves to competitive sourcing where Amgen's approved vendors provide drawings, quotes, and prototypes for the part. Once the part is finalized and a supplier is chosen, the new design moves to implementation and is entered into Amgen's systems for document and quality management as well as inventory management.

At present, the review process for new and revised single-use assembly designs has improved Amgen's ability to maximize utility of their custom assemblies. Even Amgen's suppliers spoke highly of Amgen's efforts to create designs that were not limited to one unique application. However, while the Single-Use Engineering Technical Authority (SUS-ETA) group has established guidelines on recommended aseptic connectors, they did not enforce standardization of connectors to a certain standard, limiting the transferability of components to only those that share the same connector platform. Furthermore, the EE program, from its inception, was designed to be forward-looking, implying that old and non-standard assemblies prior to EE implementation were grandfathered and remained in the single-use system library. These designs were only reviewed as they came up for design revision.

For aseptic connectors, Table 2 below outlines the various preferred connectors utilized by Amgen's manufacturing sites. Most drug substance (DS) plants have preferences between three connectors (A, B and C) while drug product sites have preferences for two other connectors (D and G). This means that most single-use assemblies designed for use in these sites utilize the aseptic connectors mentioned.

Table 2. Preferred aseptic connectors across Amgen's internal manufacturing plants

Plant	Plant 1	Plant 2	Plant 3	Plant 4	Plant 5	Plant 6	Plant 7	Plant 8
Operation	DS	DS	DS	DS	DS	DP	DP	DP
Aseptic connector	B and C	A	B and C	A	A, B and C	A, D and G	D	D and G

4.1.2. Challenges and supply disruptions

Amgen's suppliers began to struggle meeting market demands as their manufacturing capacities dwindled due to COVID-19 disruptions and various regions of the world shutting down. It became harder to source components for assemblies, creating new bottlenecks in supplies. The record-speed development of a COVID-19 vaccine, using single-use technologies, was a testament to the flexibility and efficiency of implementing single-use assemblies for biomanufacturing. However, the sudden uptick in demand did not allow time for suppliers to expand their manufacturing capacity. Raw materials, such as high-purity polymers also became a bottleneck as their supply was constrained. [22] [24] With vaccine development fast-tracked and priority given to vaccines through Operation Warp Speed, other large consumers like Amgen fell to the back of the line. Despite well-established communication lines and relationships, supplies were spread thin and even Amgen's top suppliers could not deliver.

Amgen recognized that in order to maintain continuity of their manufacturing operations, they needed a dedicated task force team that would focus on mitigating supply risks for the foreseeable future. Based on demand forecast generated by the planning system, the team was alerted of potential stockouts. They then worked with site representatives to assess feasible alternatives for substitute materials.

While the team was successful in alleviating disruptions that would have halted production, they knew that it was a short-term solution. To truly build long-term sustainability, further standardization of assembly components across the network was warranted. While aseptic

connectors are considered ancillary components in the manufacturing process, it became a primary barrier to network transferability of assemblies across sites. As shown in Table 2, Amgen's internal manufacturing sites were locked into specific connectors that their processes were developed to use. Given the training and documentation required to ensure that Amgen's products are made with the highest quality standards, shifting to a new connector was not a simple substitution. Further study was needed to establish the appropriate connector for standardization, as well as the benefit and burden of the change to the operation.

Furthermore, the time invested by the task force team for supply shortage mitigation was unsustainable for the long-term and was creating waste in the operation. The hours of discussions among the single-use system network team, site leads, and external suppliers along with the modifications to the process to allow temporary substitution of materials were taking time away from productive work. Instead of merely relying on their suppliers to deliver, Amgen resolved to move towards simplifying their design library, starting with standardization of their aseptic connectors.

4.2. Various connectors deployed at Amgen

4.2.1. Usage and defects

For the scope of our analysis, we selected a subset of aseptic connectors that can be standardized and substituted between each other based on their size, material of construction, and application. There are eight total aseptic connectors that fit these criteria and included in our analysis. Other connectors are used for specific applications based on the connection type, material of construction, or dimension and cannot be replaced without further studies to modify the process. To understand the adoption of these aseptic connectors, we summarized all the single-use assemblies with certain connectors in Amgen's single-use design library and determined the usage of each assembly from the data available in Amgen's enterprise resource planning software, SAP. The percentage data shown below represents the portion of all single-use assemblies purchased that have a specific connector, e.g., more than 40% of assemblies with aseptic connectors purchased by Amgen from January 2018 to April 2022 have connector A.

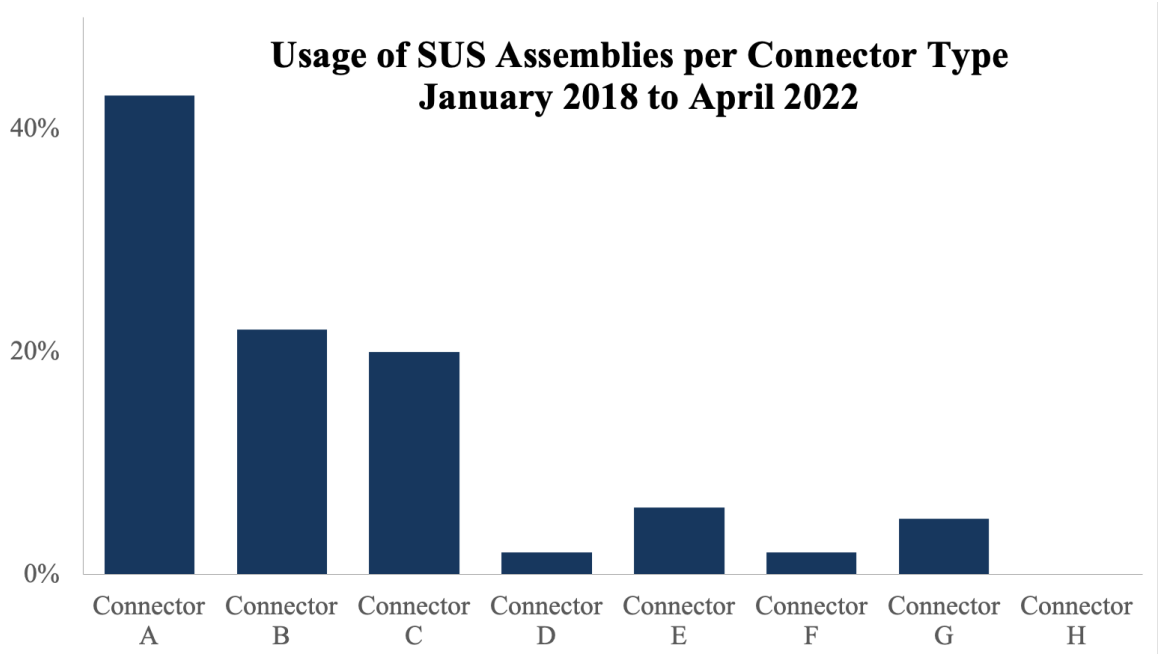


Figure 10. Usage of single-use assemblies with various aseptic connector types

The data shown above is aggregated for all Amgen sites from January 2018 to end of April 2022. We included data from 2018 since single-use technology became widely adopted throughout Amgen at that time. Connectors A, B, and C account for ~85% of the total usage of connectors included in the analysis. This makes sense since these three connectors are most used in drug substance manufacturing, which as shown in Figure 1 and Table 2, comprise of more unit operations requiring more connections per batch manufactured. Amgen Singapore and its twin site in Rhode Island, are also both standardized to the same exact manufacturing process utilizing single-use technology, and therefore, aligned to a common aseptic connector. Meanwhile, there are other connectors used in special applications and in drug product manufacturing which take less than 10% of the total usage since there are much fewer connections and lesser volumes handled in those processes per batch. Taking this analysis into consideration, standardizing to a widely adopted connector(s) would be more advantageous since the switching costs (including design revisions, inventory obsoleted, training, and process transition) would be lower given its high usage at present. It is important to note, however, that this analysis is inherently skewed towards the connectors used in drug substance manufacturing and may be biased towards certain types of assemblies that are more frequently used in the process e.g.,

transfer assemblies. Therefore, the data presented must be evaluated holistically along with other considerations.

We also analyzed the defect rate for each aseptic connector using data available from the External Supply Quality (ESQ) group. ESQ monitors deviations and trends associated with defective single-use assemblies, including leak at connectors, particulates, and missing, or damaged components. The data in Figure 11 summarizes defects associated with leaks at connectors. It is important to note that the defects reported here only include those that can be traced back to the supplier such as when a defective part was installed and caused a leak in the process. Examples of other defects not traced back to the supplier include operator or assembly error that happen during production. Like the usage data, we group assemblies by the type of connector and calculate the defect associated with the connector types using the equation:

$$Defect\ rate = \frac{\sum Defective\ assemblies}{\sum Usage * Number\ of\ connectors\ per\ assembly} \times 100$$

This equation calculates the number of defective connections over the total number of connections per connector type. We do that by summing the number of defective assemblies of a specific connector type and dividing that by the total number of connections made. The total number of connections made is the sum of the product of the number of the assemblies consumed with a specific connector ("Usage") multiplied by number of connectors per assembly. To illustrate this with an example, if we want to calculate the defect rate for connector A which is used in assembly 1 and assembly 2, and we have the following mock data:

Assembly 1 (with connector A): 10 defective units and 20 units consumed / used which have 2 connectors each

Assembly 2 (with connector A): 5 defective units, and 30 units consumed / used which have 2 connectors each. We calculate the Defect Rate as follows:

$$Defect\ Rate = \frac{10 + 5}{[(20 * 2) + (30 * 2)]} = 15\%$$

The database did not include data on how many of the connectors in each assembly were leaking, hence this calculation assumes that every assembly with a defect only has one defective connector. Based on Amgen's experience, this is a reasonable assumption.

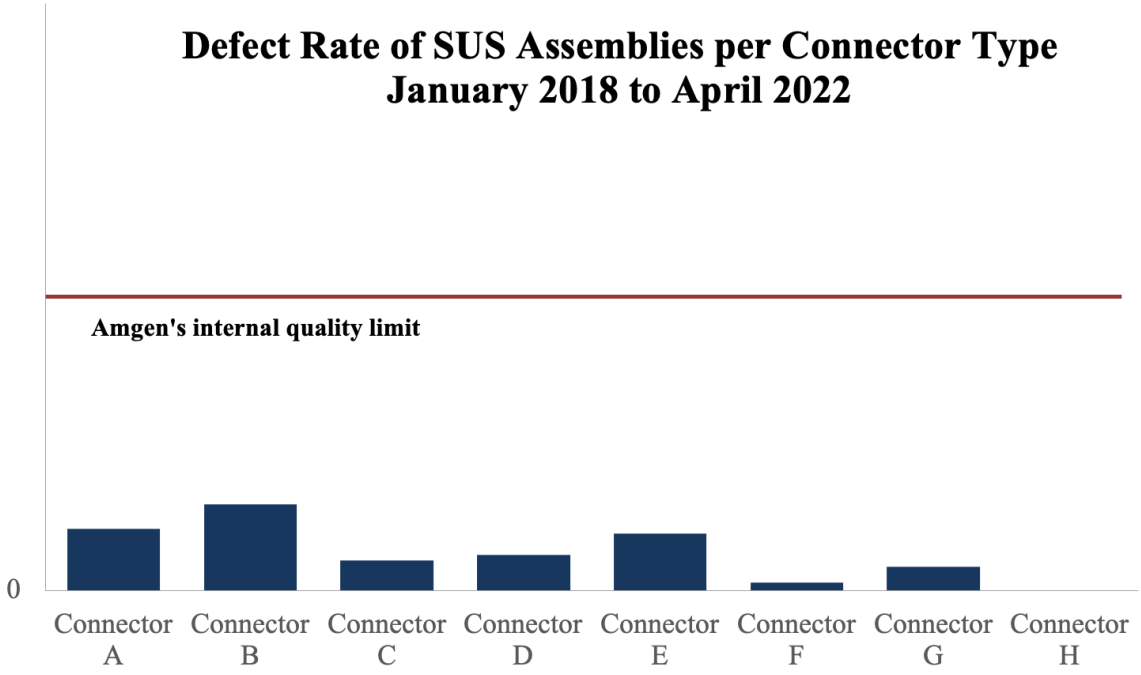


Figure 11. Defect rates of various aseptic connector types

As shown in Figure 11, all the defect rates for the various connectors were well below the defect limit set by the quality group at Amgen and there is no significant variation among connectors with the highest usage. Connectors B and C are used in conjunction with each other due to size differences, and together, these two have a defect rate of <0.1%. One consideration in evaluating this data is understanding whether the defect stems from a design flaw in the component (aseptic connector) or the assembly (aseptic connector attached to a tubing and other components). If a recurring defect is due to a design flaw of the connector, this will have to be resolved with the original manufacturer which may be different from the supplier or integrator of the assembly. Meanwhile, if the defect is due to the assembly design or integration, then it will have to be resolved with the integrator. With the aggregated data available, it can be challenging to dissect and understand if the leaks are due to the assembly or the aseptic connector itself, though based on Amgen's previous

experience, with defect trending data over time, they have been able to identify specific issues related to the aseptic connector itself.

In conversations with manufacturing associates and site technical leads, we also learned that the data captured in the defect tracker is limited. For instance, if a bad connection or bad pull occurred on a specific assembly due to difficulty with assembling, it will not be recorded in the defects sheet. Furthermore, defects that occur due to operator error which can be rectified before a production run is started, i.e., during setup, are typically resolved by the operators without initiating a defect report. To our knowledge, these data are not captured at this time, unless they are escalated by manufacturing or lead to a product defect. Therefore, these "operation-related" defects cannot be fully analyzed at this time.

4.2.2. Ease of use and defect risk

To understand the user experience of the manufacturing associates putting together these assemblies and "qualitatively" supplement the defect information gathered from the previous analysis, we sought operator feedback on various aseptic connectors through a user experience survey. We distributed the survey to all eight of Amgen's internal manufacturing sites and the respondent counts can be found in the Appendix. The survey asked subjects to identify the aseptic connectors they use in production and rate them based on their ease of use, preference, and defect risk. Specifically, we asked them to consider the training required, techniques, ergonomics, and defect issues they encounter. The ratings were split into most preferred, acceptable, and least preferred. To easily capture the ratings into a quantitative measure, we calculated the Net Promoter Score (NPS) [35] for each aseptic connector.

$$Net\ Promoter\ Score\ (NPS) = \%\ Promoters - \%\ Detractors$$

In our application, votes for most preferred were considered promoters, least preferred were considered detractors, and acceptable were neutral. Traditionally, NPS is a metric used by companies to track customer satisfaction and to benchmark themselves against their competitors. Here, we use NPS to rank the various connectors and to measure operator satisfaction with the aseptic connectors they work with on a day-to-day basis. Figure 12 shows the results of the analysis. The overall NPS score can range from -100 (all detractors)

to +100 (all promoters) and the interpretation of the score can vary from industry to industry. Generally, a score above 0 is considered good since it implies there are more promoters than detractors. In our analysis, we have four connectors (Connector A, B, D and F) with positive scores. We take this into consideration in our final assessment of all connectors.

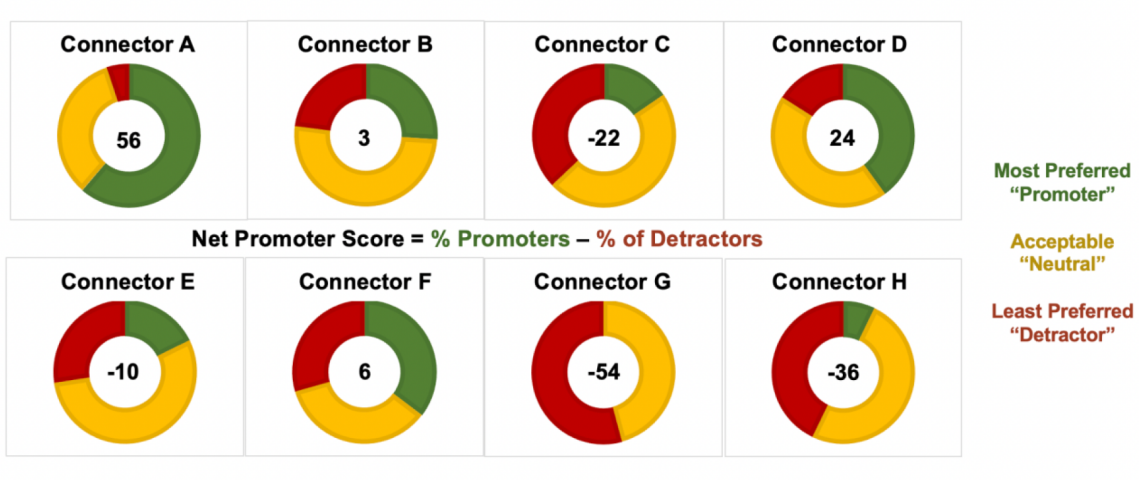


Figure 12. Net promoter score results of the various connectors

4.2.3. Other internal insights

Through data analysis, informational interviews, and the survey, we also found other areas of opportunity to improve the performance of aseptic connectors and the experience of Amgen's manufacturing associates. These include training and specific improvements associated with certain connectors.

- More robust training for associates – according to survey results and interviews, training was suggested as an improvement area to reduce defects and increase the comfort level of operators working with aseptic connectors. There were mentions of limited connectors available for training, leading to lack of practice before operators are expected to perform connections during manufacturing runs. Additionally, there are variations in training protocols across different sites, suggesting that standardization of training can also be implemented.

- Safety issues and defect issues with some connectors – also mentioned in anecdotes during informational interviews as well as the survey are safety concerns associated with ergonomics of certain connectors. Some have mentioned experiencing anxiety and hands trembling when making a connection due to design flaws such as easily torn membranes and inconsistency with the amount of torque needed to secure the connectors in place.

4.2.4. Overall assessment of all connectors

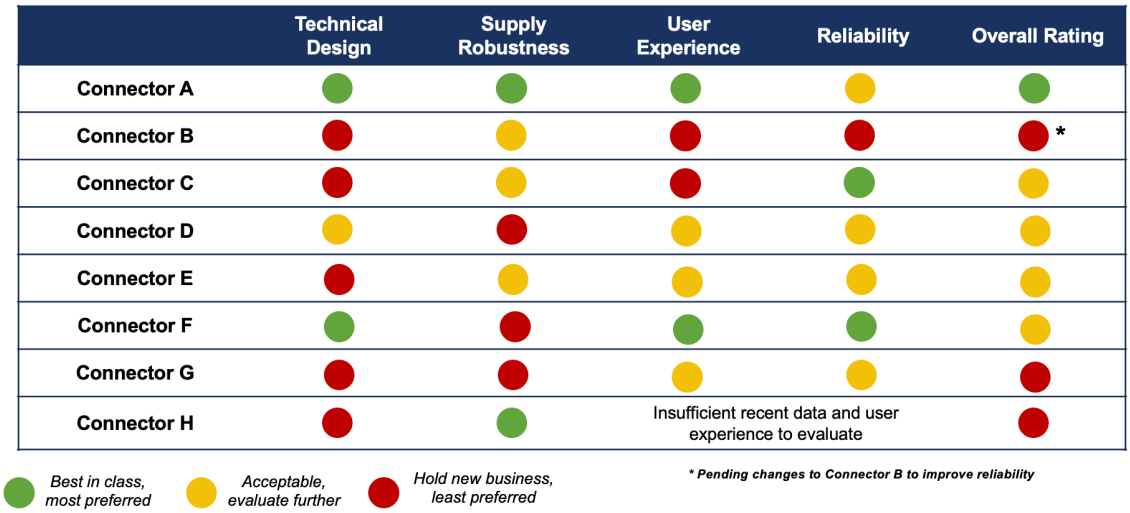


Figure 13. Summary assessment of all aseptic connectors at Amgen

Combining all the data gathered and analyzed, we assessed the various aseptic connectors according to the four considerations we summarized from our internal research and external benchmarking – technical design, supply robustness, user experience, and reliability. Figure 13 above summarizes the assessment. The ratings assigned for each category ranged from Green, Yellow, and Red. Green indicates that the connector stands as best in class or most preferred in that category. Yellow indicates acceptable performance currently with further evaluation required. Lastly, red indicates a critical assessment in that category leading to a low preference and a risk to the business.

Under technical design, a connector received superior rating for having a genderless design, a chemically resistant material of construction, and a technically well-supported product by the manufacturer. We evaluated each connector's technical data sheet and

gathered information on the technical support experienced by the team at Amgen. Under supply robustness, higher ratings were assigned to connectors with shorter lead times, excess manufacturing capacity for volume growth, and manufacturers with redundancies and business continuity plans built into their operation. We assessed each connector based on our discussions with the manufacturers and prior experience of Amgen's sourcing team. Red marks were assigned to connectors with current and foreseeable supply constraints as communicated by manufacturer. Under user experience, we used Amgen's manufacturing associate ratings from the survey along with data gathered from informational interviews and comments shared in the survey. We assigned the lowest ratings to connectors with ergonomics issues, some leading to injury as the connections are secured in place. Lastly, under reliability, we utilized data from the defects analysis and again, data gathered from informational interviews and comments in the manufacturing associate survey.

We tallied all the results into a final rating that represents the proposed action for each aseptic connector – green is best in class and recommended, yellow needs further assessment and action, and red is hold new business and evaluate for substitution.

Chapter 5. The case for standardization

5.1. Options under consideration

Should Amgen decide to pursue standardization, we took into consideration three potential paths moving forward – 1) preserving the current state of aseptic connectors, 2) standardizing to two aseptic connectors (one for drug substance manufacturing and one for drug product manufacturing), and 3) standardizing to one aseptic connector for both drug substance and drug product manufacturing. Note that in the future, there may be certain exceptions to the standard in unique use cases, and these will need to be approved by the engineering technical authority group. We evaluate the costs, benefits, and risks of each option in the following sections, and provide a suggested implementation plan moving forward.

Keeping the current state preserves the status quo at Amgen. The Engineering Technical Authority group will keep their current technical guidelines on aseptic connectors as recommendations without active efforts to standardize. The ultimate decision on a connector to use for a specific process will remain at the discretion of the manufacturing plants. Upon introduction of new technologies and new site builds, an aseptic connector will be decided as part of the design process and there will not be a set standard aseptic connector(s) to implement by default.

Standardizing to two connectors allows Amgen to choose different standard aseptic connectors for their drug substance and drug product manufacturing processes. This allows them to delineate the standard based on process criticality of drug product processes which require higher quality and robustness to ensure product sterility and purity. One design factor to consider here is the versatility of genderless connectors versus the error-proofing advantage that gendered connectors provide. Since gendered connectors can only be installed in one direction, it can help ensure that components such as filters are installed in the proper orientation. While gendered connectors take more effort to assemble, this may be acceptable in drug product operations where there are fewer connections to be made during setup. Meanwhile, in drug substance operations, the versatility and ease of use rendered by genderless connectors are preferred since there are more connections to be

made. It is also more beneficial to have flexibility to install assemblies in any direction as it allows the same assemblies to be used repeatedly for different applications in the process.

The last option is to standardize to one standard aseptic connector, allowing Amgen to standardize exhaustively throughout its internal manufacturing network and enable transferability of assemblies such as storage bags and filter assemblies across both drug substance and drug product operations. This option holds if the design advantage of choosing a different connector for drug product operations do not outweigh the potential costs and risks to Amgen. In the sections that follow, we discuss the cost, benefits, and risks considered for each scenario.

5.2. Costs and benefits

Costs considered in the analysis include the amount of labor manhours required to revise designs to utilize the new aseptic connectors. The internal work includes design reviews, sourcing, and documentation revisions for drawings, specifications, part numbers and bill of materials. The timeline for the change will include not only the estimated labor at Amgen but also the lead time from the suppliers. Table 3 below outlines Amgen's hands-on labor manhours associated required for the different tasks per assembly to be revised. The data was provided by stakeholders in the Early Engagement network team based on their experience and standard processes.

Table 3. Labor cost of single-use design revisions

Task	Labor hours per assembly
Design review	11-12 hours
Sourcing	6 hours
Document revisions	6 hours

If Amgen decides to proceed with design revisions involving suppliers, it is also worth noting that the external supply team estimates a 4-week lead time for suppliers to revise designs and provide quotes, which under the pandemic constraints have been stretching to

as long as three to four months depending on the supplier. These estimates must be considered in the implementation timeline.

Depending on the standardization option chosen, there are other less quantifiable costs and benefits to be considered such as the flexibility to move supplies across the network during supply disruptions; streamlining of the single-use design library and reduced maintenance efforts required; and efficiency of technology transfers when products are moved to a different site either during the evolution of its development or to establish redundancy. When connectors are standardized, there is less design, training, and documentation required during the technology transfer. Stakeholders during interviews shared several instances where the shortage of an assembly cannot be mitigated despite availability of similar assemblies in other sites due to connector differences between sites. Prior work on streamlining technology transfers also revealed that connector differences between sites cause additional time for revising current assemblies and/or for generating additional documentation (such as standard operating procedures) and training to enable use of a different connector at another site.

Decreasing customization through standardization of aseptic connectors also have the potential to reduce lead time for assemblies as we move away from connectors with supply constraints and long lead times. As Amgen witnessed during the pandemic, coordination and communication with various suppliers unable to meet demand took significant additional manhours. This is in addition to the work already being done by the supply shortage mitigation task force to find alternative parts when supplies are not delivered on time. These create inefficiencies and waste that can be reduced through standardization of aseptic connectors. Furthermore, higher order volumes of a smaller number of assemblies can lead to potential economies of scale and increased buying power. These benefits can be quantified but are out of scope for the current project as we wanted to avoid engaging suppliers before a decision was made within Amgen to pursue standardization.

5.3. Risks

The biggest risk of standardizing connectors comes when the standard implemented have critical flaws in the four areas of consideration mentioned in Chapter 3.2 – technical design specification, supply robustness, reliability, and user experience. The lack of optionality can be disastrous if the supply or technical performance of the chosen connector becomes unreliable. Hence, for this project, we did a thorough assessment of the current aseptic connectors at Amgen to ensure that we are selecting the best aseptic connector option as a standard and understand its limitations. We also want to ensure that we hear input from the manufacturing associates since they are ultimately the ones impacted by the change daily as they assemble these connectors during production. If the aseptic connector is not appropriate for safe, ergonomic, and effective use, they may find their own ways to circumvent the standard and to improve their work.

As outlined in the assessment in Figure 13, we can see that at present, no aseptic connector is flawless (all green). Some are better than others in more categories than one, but depending on the connector chosen, we encounter risks according to their limitations highlighted in the assessment. As mentioned previously, understanding and actively mitigating risks builds supply chain resiliency. By assessing the connectors, we gain knowledge on the vulnerabilities of our current supplies. We explore these risks further and how to mitigate them:

- Continuity of supply – with robust relationships established with Amgen's suppliers, we were able to get transparent information regarding the future of aseptic connector supply directly from the manufacturers. As mentioned before, there are varying levels of capacity available, as well as redundancies and business continuity plans built into each manufacturer's operation. Considering that the reliable supply of these aseptic connectors is key to resiliency, we strongly suggest moving away from connectors marked red in this category in order to secure Amgen's future. For green marks in this category, we have ensured that the supplier not only has excess capacity to more than double Amgen's potential demand post-standardization, but also has secured their operations from unforeseen occurrences that may affect their ability to supply. We also consider other ways to further shield

Amgen from this issue by considering welding as an option for sterile connections and retaining the current drawings and part numbers in the system to serve as a backup.

- Technical design and reliability – to enable standardization, we need to select a versatile aseptic connector with robust design to enable its use across various applications including those with harsh chemicals involved. A connector that is not versatile to be compatible with all applications across Amgen's operations would be ineffective as a standard and is bound to fail and lead to defects. In recommending a standard, we strongly advise against those with red marks unless if the connector is currently being redesigned for improvement.

- Ergonomics and user friendliness – manufacturing associates have expressed issues with ergonomics and user friendliness of certain aseptic connectors. It is important that we take this feedback into consideration. Should it be necessary to select a standard against their feedback, Amgen will have to justify and explain the selection process and provide tools to improve ergonomics of the task. It may also involve further training to improve their comfortability working with the connector.

Chapter 6. Evaluation

Table 4. Evaluation of standardization options

Options	Costs	Benefits	Risks
1) Preserve the current state	**Less flexibility** to transfer supply across the network during a disruption **Higher cost** to transfer technologies and products Sustained efforts to **maintain** assemblies	More **autonomy** for plants to optimize their own designs and processes	Suppliers with varying **supply robustness** and business continuity plans **Supply shortages** of certain connectors; constrained for the foreseeable future Adoption of designs that are **unergonomic and less user-friendly**
2) Align to two connectors (one for DS and one for DP manufacturing)	Revision of **assemblies** ~5000 manhours	Network **transferability** and potential **economies of scale** **Consolidated connection practices** – efficient tech transfers and training **Separate DP connector** to account for process criticality	**Open investigations** that need further resolution **Supply shortages** of certain connectors; constrained for the foreseeable future
3) Align to one connector for all manufacturing operations	Revision of **assemblies** ~6000 manhours	Network **transferability** and potential **economies of scale** **Consolidated connection practices** – efficient tech transfers and training **Shorter lead times** for production orders	**Open investigations** that need further resolution **One connector** for all assemblies may be too **risky** when single-sourced

Selecting the right standard is a critical aspect of this project to minimize the risks associated with the change and improve supply chain resiliency. Section 4.2 discusses the evaluation of current aseptic connectors at Amgen and Figure 13 shows a summary of the assessment. Our data supports a candidate aseptic connector to be chosen as the standard, and, at the time of the project completion, the selection has yet to be finalized and approved by management. To determine the appropriate standardization path forward, we also evaluated the cost, benefit, and risk of the standardization to Amgen's operations. A summary of the assessment is shown in Table 4.

Standardization with two or one connector (Option 2 and 3, respectively) enables simplification of Amgen's current single-use design library and improves supply resiliency through transferability of their supplies across the network in the event of a supply disruption. Commonality of assemblies across sites also enable a network-approach to purchasing, increasing Amgen's order volume and buying power with their vendors, and potentially unlocking greater economies of scale. In the literature review chapter, we discussed the components of a resilient supply chain including flexibility, velocity, visibility, and collaboration. Standardization bolsters each of these components – improved **flexibility** to transfer supplies across the network, increased **speed** and efficiency through sourcing of a streamlined library of single-use assemblies, better **visibility** of common supplies used in different sites with inventory management at the network level, and greater **collaboration** between sites that utilize the same connector technologies and similar assemblies.

To realize these benefits, however, standardization at present will take thousands of manhours to undertake, not including the lead time from Amgen's suppliers to revise the designs and build inventory of the assemblies. Labor estimates were calculated based on the estimated manhours provided by members of the single-use network team in Table 3 and the number of assemblies to be revised. Between options 2 and 3, aligning to one versus two connectors also increases the labor cost by 20% (5000 manhours vs 6000 manhours of design revisions). However, since the primary connector for drug product manufacturing is currently facing supply shortages due to capacity constraints, the supply risk outweighs

the additional labor cost. Given that we are optimizing for supply chain resiliency, we eliminated option 2 from our consideration.

We also need to further consider the costs of not standardizing (Option 1 – preserving the current state) including the operational, cultural, and competitive costs. Operationally, the cost of not having a standard connector will only increase along with the switching cost should the company decide at a later time to implement a standard. The manhours and inefficiencies brought on by limited ability to transfer assemblies today and the management of an extensive single-use design library will only continue to grow as designs with various connectors proliferate. Culturally, it can also be damaging to employee morale to tolerate the challenges and ergonomic issues that Amgen's manufacturing associates continue to experience as they work with certain connectors. Furthermore, certain connector suppliers have been upfront and clear about uncertainty in their ability to meet demands for the foreseeable future and bearing these risks would be against Amgen's operational strategy to strive towards reliability, efficiency, agility, and differentiation. Competitively, we have seen in our external benchmarking that most of Amgen's peers are not only implementing single-use technologies but also actively standardizing these technologies. Amgen being one of the first to adopt single-use technology for biomanufacturing can again consider being a leader in moving the industry towards standardization. In Moon and Lee's paper on the primary actors of technology standardization [25], they discuss network effects and how "core companies" influence standards as well as the adoption decisions of other companies. These core companies gain first-mover advantage and ultimately dominate the industry with their preferences being accepted as the dominant design. Figure 14 illustrates the advantages of assuming a core company role in a Subject (S), Action, (A), Object (O), Problem (P) concept map.

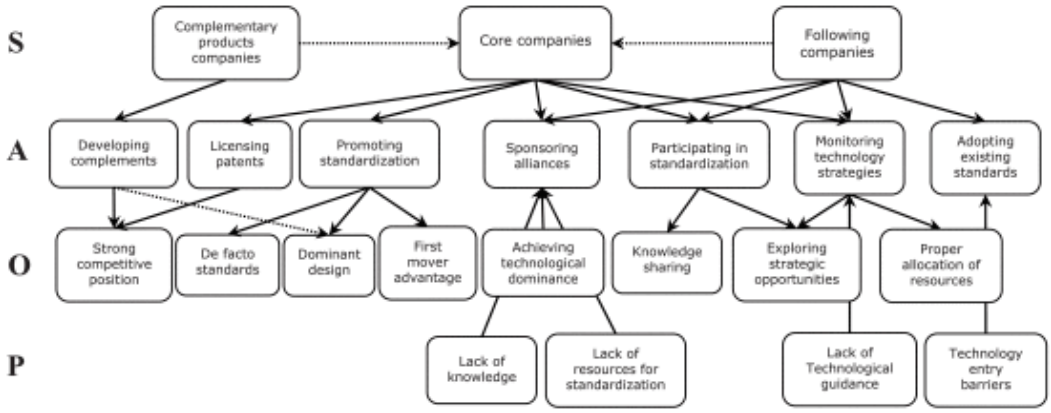


Figure 14. The primary actors in technology standardization and their roles

With the financial and labor costs associated with standardizing all aseptic connectors at once, our recommendation for implementation is to standardize designs upon introduction of a new technology, product, or site build. A potential case study for this is the new site in North Carolina. As the new facility construction is underway and single-use technologies are being evaluated for the site, we analyzed how a new standard implemented will impact the single-use design library. We found that the revision of ~100 assemblies will account for over 60% of the current single-use assemblies used in two other sites. This sets the stage and lessens the effort required of those fully single-use sites to adapt the change as they decide to align with the new standard aseptic connector.

Lastly, to de-risk Amgen's current operations, we still strongly recommend switching current aseptic connectors with supply continuity risks to another connector with better ratings based on our assessment in Figure 13. As sites begin to adopt the standard, they can also consider having the current drawings as backups in the event of an unforeseen issue with the standard aseptic connector. Further studies to determine welding feasibility with certain tubing are needed to designate tube welding as another backup option.

Chapter 7. Conclusion and recommendations for future work

Single-use technology continues to hold great promise for improving the efficiency and flexibility of the biopharmaceutical industry. The technical design of single-use components is improving and over the next 4 years, the single-use industry will continue to grow at a CAGR of 17%, increasing by a total of $10.60B from 2021 to 2026. [36] As the adoption of this technology expands, companies and the industry must implement standardization to truly harness the benefits of the technology while alleviating the supply chain disruptions experienced during the pandemic. A rationally designed and controlled single-use assembly library contains versatile designs that can be used across various manufacturing operations, enabling network transferability in the event of a disruption, and enhancing vendor relationships as purchase volumes of a smaller subset of parts grow.

As we have seen at Amgen, when standardization is undertaken later in the adoption and development of single-use technology, the standardization efforts can be costly. Here we examine the standardization of aseptic connectors, and due to the labor associated with the change, it has become limiting to revise all current assemblies into one connector despite compelling benefits to do so. An alternative approach to accomplish this goal is then to align on a standard and implement the change as new technologies are introduced and new facilities are built. In this manner, the change is coupled with other value-adding activities. Fortunately for Amgen, this aligns with the construction of a new site in North Carolina which will cover a portion of the revisions of the current single-use design library. This lowers the barrier to entry for other sites as they extend the new designs into their system.

We have completed a thorough assessment of aseptic connectors deployed at Amgen based on technical design, supply robustness, reliability, and user experience. While some connectors have stood out better than the rest, there are still a few limitations that Amgen must address to manage risk and implement the change successfully. We recommend the following for future work related to the project:

1) Select a standard aseptic connector and align all stakeholders – the data presented in this project can be used as supporting evidence for the recommendation of an appropriate connector. Ultimately, the success of the standardization effort will

need buy-in and support from all levels of the organization from manufacturing associates to plant leadership and corporate leaders.

2) Address gaps for the selected connector – every connector we evaluated had an assessment criterion where the connector was marked yellow in Figure 13. To mitigate risks associated with the change, we suggest taking further action to move all the ratings of the selected standard connector from yellow to green. For example, one of the connectors was marked yellow for defects due to open investigations related to leaks. This issue should be closed out before selecting this connector.

3) Address risks identified in the assessment – some of the connectors had ongoing ergonomics, reliability, and supply issues that were highlighted during the project. Since standardization will be phased in upon introduction of new technologies, some of these connectors with known issues will continue to be used. We recommend addressing the most pressing issues related to supply and ergonomics to ensure continuity of operations and resolve the issues raised by operators.

4) Defects data management – centralize a defect tracking system that captures other defects not currently recorded e.g., defects related to operator error and other issues beyond those related to supplier.

5) Further build structure in the single-use data library – include detailed bill of materials and "where used"/unit operation information for all assemblies to enable searchability of similar assemblies that can be interchanged in the event of a supply disruption.

6) Further studies to establish sterile welding as a backup – sterile welding is a feasible backup in the event of an aseptic connector shortage, however, not all tubing formulations are compatible or weldable. Plants across Amgen also utilize this technology at varying levels with potential skill gaps. Further studies and training are needed to implement this as a backup option, especially when different tubing types are involved.

7) Quantitative benefits assessment – data on potential order volume changes with consolidation of single-use assembly designs can be further explored with vendors to quantify savings from economies of scale. Amgen can also further explore network level purchasing of common assemblies utilized in multiple sites to enable inventory pooling and lower safety stocks.

Chandra and Mukhopadhayay discussed the role of leadership support and culture in the success of standardization [37]. Amgen already possess both of these components with their strong operations leadership and culture of continuous improvement. Recognizing that standardization aligns with their vision of serving “every patient, every time”, the organization must continue to leverage their culture to effectively manage this change. It is not an easy undertaking but one that can be achieved with the company’s clear strategic focus on reliability, efficiency, agility, and differentiation.

References

[1] S. Hawkins, "Biomanufacturing: How Biologics Are Made," *Biotech Primer WEEKLY*, Jun. 16, 2020. https://weekly.biotechprimer.com/biomanufacturing-how-biologics-are-made/ (accessed Mar. 24, 2023).

[2] Jasmin J Samaras, Martina Micheletti, and Weibing Ding, "Transformation of Biopharmaceutical Manufacturing Through Single-Use Technologies: Current State, Remaining Challenges, and Future Development," *Annual Review of Chemical and Biomolecular Engineering*, vol. 13:73-97, doi: https://doi.org/10.1146/annurev-chembioeng-092220-030223.

[3] "About Amgen," *Amgen*. https://www.amgen.com/about (accessed Jan. 20, 2023).

[4] "Amgen Manufacturing," *Amgen*. https://www.amgen.com/science/manufacturing (accessed Jan. 17, 2023).

[5] "More Biotech Medicines, More Manufacturing Sophistication," *Amgen*. https://www.amgen.com/science/manufacturing/stories/biotech-manufacturing-advance (accessed Jan. 17, 2023).

[6] "Using pharmaceutical manufacturing to compete | McKinsey." https://www.mckinsey.com/industries/life-sciences/our-insights/operations-as-a-competitive-advantage-in-biotechnology (accessed Jan. 17, 2023).

[7] "Amgen Reliability," *Amgen*. https://www.amgen.com/science/manufacturing/reliability (accessed Jan. 17, 2023).

[8] "Amgen Breaks Ground on New Drug Substance Manufacturing Facility in North Carolina." https://www.amgen.com/stories/2022/03/amgen-breaks-ground-on-new-drug-substance-manufacturing-facility-in-north-carolina (accessed Jan. 20, 2023).

[9] "Amgen Selects Newest Location in U.S. Manufacturing Network Expansion Plan." https://www.amgen.com/stories/2021/06/amgen-selects-newest-location-in-us-manufacturing-network-expansion-plan (accessed Jan. 20, 2023).

[10] Tuesday, October 23, and 2018, "Biopharmaceutical Manufacturing is Shifting to Single-Use Systems. Are the Dinosaurs, the Large Stainless Steel Facilities, Becoming Extinct?" http://www.americanpharmaceuticalreview.com/Featured-Articles/354820-Biopharmaceutical-Manufacturing-is-Shifting-to-Single-Use-Systems-Are-the-

Dinosaurs-the-Large-Stainless-Steel-Facilities-Becoming-Extinct/ (accessed Jan. 17, 2023).

[11] E. S. Langer, "Single-Use Technology in Biopharmaceutical Manufacture and Beyond," *Chemie Ingenieur Technik*, vol. 94, no. 12, pp. 1892–1901, 2022, doi: 10.1002/cite.202200095.

[12] "VWR® Single-Use Silicone Tubing Assemblies," *VWR*. https://us.vwr.com/store/product/23132912/vwr-single-use-silicone-tubing-assemblies (accessed Mar. 31, 2023).

[13] ThermoFisher Scientific, "HyPerforma Single-Use Bioreactor (S.U.B.)." [Online]. Available: https://assets.thermofisher.com/TFS-Assets/LSG/brochures/hyperforma-5-1-bioreactor-brochure.pdf

[14] "Meissner: Single-Use Tubing and Filter/Tubing Assemblies," *Pharma Manufacturing*, May 02, 2011. https://www.pharmamanufacturing.com/directory/product/11350601/meissner-single-use-tubing-and-filter-tubing-assemblies (accessed Mar. 31, 2023).

[15] The Medicine Maker and Millipore Sigma, "Globalization of Single Use." Feb. 24, 2017. [Online]. Available: https://themedicinemaker.com/manufacture/globalization-of-single-use

[16] "10 Things You Should Know About Amgen's Manufacturing Network." https://www.amgen.com/stories/2021/02/10-things-you-should-know-about-amgens-manufacturing-network (accessed Jan. 17, 2023).

[17] "Amgen Singapore Manufacturing Capabilities," *Amgen, Inc*. https://www.amgen.com.sg/about/amgen-singapore/amgen-singapore-manufacturing-capabilities (accessed Jan. 20, 2023).

[18] "Biotechnology & Biomanufacturing." https://www.ipsdb.com/expertise/industries/biotechnology-biomanufacturing (accessed Mar. 09, 2023).

[19] "Extractables & Leachables: Not the Same," *ISPE | International Society for Pharmaceutical Engineering*, Mar. 08, 2023. https://ispe.org/pharmaceutical-engineering/may-june-2017/extractables-leachables-not-same (accessed Mar. 09, 2023).

[20] R. H. Allen and R. D. Sriram, "The Role of Standards in Innovation," *Technological Forecasting and Social Change*, vol. 64, no. 2, pp. 171–181, Jun. 2000, doi: 10.1016/S0040-1625(99)00104-3.

[21] "How USB Became the Most Successful Interface in Computing History," *Intel*. https://www.intel.com/content/www/us/en/standards/usb-two-decades-of-plug-and-play-article.html (accessed Jan. 20, 2023).

[22] J. L. Lock Austin, "Single-Use Standardization: Benefits for Industry," *BioProcess International*, May 21, 2021. https://bioprocessintl.com/manufacturing/single-use/benefits-of-single-use-standardization-adopting-a-standard-design-approach/ (accessed Jan. 20, 2023).

[23] D. R. Schmidhalter, A. C. Schmidt, S. Beck, and S. A. Morgenstern-Egli, "A Strategic Approach to the Management of Single-Use Technology," *Chemie Ingenieur Technik*, vol. 94, no. 12, pp. 1902–1913, 2022, doi: 10.1002/cite.202200146.

[24] C. S. Rendall, "Enhancing the Design and Procurement of Single-Use Assemblies in Biomanufacturing by Implementing Modular Specifications," Massachusetts Institute of Technology, 2018.

[25] S. Moon and H. Lee, "The Primary Actors of Technology Standardization in the Manufacturing Industry," *IEEE Access*, vol. 9, pp. 101886–101901, 2021, doi: 10.1109/ACCESS.2021.3097800.

[26] "Standardizing Single-Use," *The Medicine Maker*. https://themedicinemaker.com/manufacture/standardizing-single-use (accessed Jan. 20, 2023).

[27] S. Radhakrishnan, B. Harris, and S. Kamarthi, "Supply Chain Resiliency: A Review," in *Supply Chain Risk Management: Advanced Tools, Models, and Developments*, 2018, pp. 215–235. doi: 10.1007/978-981-10-4106-8_13.

[28] W. D. Micheletti Martina, "Scientifica and Technological Applications of SUT in Biomanufacturing: A Conference Report," *BioProcess International*, Apr. 17, 2019. https://bioprocessintl.com/manufacturing/single-use/scientific-and-technological-advancements-in-applications-of-single-use-technology-a-conference-report/ (accessed Jan. 17, 2023).

[29] “Opta® SFT Sterile connector | Sartorius.” https://www.sartorius.com/shop/ww/en/usd/products-bioprocess-tubing-%7C-dis--connectors/opta-sft-sterile-connector/p/M_Opta_Sterile_Connectors (accessed Mar. 31, 2023).

[30] “Lynx S2S Connector for sterile-to-sterile connection - Connectors, Crimping and Tubing.” https://www.emdmillipore.com/US/en/product/Lynx-S2S-Connector-for-sterile-to-sterile-connection,MM_NF-C9502 (accessed Mar. 31, 2023).

[31] “Inside the Presto Connector.” https://www.pall.com/br/pt/biotech/landing/inside-presto-connector.html (accessed Mar. 31, 2023).

[32] “New AseptiQuik® Connector Features Robust Advanced Material PPSU Withstands Harsh Chemical Exposure.” https://www.bioprocessonline.com/doc/new-aseptiquik-connector-features-robust-ppsu-withstands-harsh-chemical-exposure-0001 (accessed Mar. 31, 2023).

[33] “Amgen Innovation,” *Amgen*. https://www.amgen.com/science/manufacturing/innovation (accessed Jan. 21, 2023).

[34] J. Sterling, “COVID-19 Drives Surge in Growth of Single-use Technologies,” *GEN - Genetic Engineering and Biotechnology News*, Jul. 27, 2022. https://www.genengnews.com/topics/bioprocessing/covid-19-drives-surge-in-use-of-single-use-technologies/ (accessed Jan. 21, 2023).

[35] “Measuring Your Net Promoter Score,” *Bain*. https://www.netpromotersystem.com/about/measuring-your-net-promoter-score/ (accessed Jan. 21, 2023).

[36] “Single-use Bioprocessing System Market by Product, Application, End-user, and Geography - Forecast and Analysis 2022-2026,” *Technavio*. https://www.technavio.com/report/single-use-bioprocessing-system-market-industry-size-analysis (accessed Jan. 21, 2023).

[37] G. Chandra and A. Mukhopadhayay, “Industry Standards and Standardization: An Expert Survey on Opportunities and Challenges,” in *2021 International Conference on Information Technology (ICIT)*, Jul. 2021, pp. 284–289. doi: 10.1109/ICIT52682.2021.9491725.

Appendix

Total Count of Respondents for the Manufacturing Associates' User Experience Survey