Enhancing the Design and Procurement of Single-Use Assemblies in Biomanufacturing by Implementing Modular Specifications

By

Clinton Scot Rendall

Submitted to the MIT Sloan School of Management and the 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 2018

© 2018 Clinton Scot Rendall. All rights reserved.

The author hereby grants MIT permission to reproduce and to distribute publicly copies of this thesis document in whole or in part in any medium now known or hereafter created.

Signature redacted

Signature of Author _____

MIT Sloan School of Management, Department of Mechanical Engineering
May 11, 2018

Signature redacted

Certified by _____

Dr. Stephen Graves
Thesis Supervisor, Abraham J. Siegel Professor of Management

Signature redacted

Certified by _____

Dr. J. Christopher Love
Thesis Supervisor, Associate Professor of Chemical Engineering

Signature redacted

Certified by _____

Dr. Daniel Whitney, Thesis Reader
Senior Research Scientist Emeritus and Senior Lecturer, Department of Mechanical Engineering

Signature redacted

Accepted by _____

Dr. Rohan Abeyaratne
Chair of the Committee on Graduate Students, Professor of Mechanical Engineering

Signature redacted

Accepted by _____

Maura Herson
Director of MBA Program, MIT Sloan School of Management

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
JUN 07 2018
LIBRARIES
ARCHIVES

This page has been intentionally left blank

Enhancing the Design and Procurement of Single-Use Assemblies in Biomanufacturing by Implementing Modular Specifications

By

Clinton Scot Rendall

Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering on May 11th, 2018 in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration

And

Master of Science in Mechanical Engineering

Abstract

Usage of single-use systems (SUS) in biomanufacturing has expanded rapidly in recent years. Amgen uses SUS at several commercial manufacturing sites, in addition to pilot plants and clinical production. Each single-use assembly is typically custom designed and manufactured by a third-party integrator. This has led to the proliferation of single-use specifications, with hundreds of assemblies in the Amgen library. These specifications collectively require tens of thousands of manhours to create, maintain, and eventually decommission. In addition, the purchase of so many unique assemblies hinders the ability to competitively bid on each design, increasing commercial risk. Finally, each Amgen site must maintain required inventory levels of its specific assemblies, with few opportunities to optimize safety stock between facilities.

The goal of this project is to evaluate the hypothesis that increasing the usage of modular design principles will reduce procurement cost, supply risk, and inventory requirements. In addition, standardization of SUS will result in the creation of fewer unique assemblies, greatly reducing the overhead requirement from the engineering, quality, and process development organizations. This thesis proposes actions Amgen may implement to achieve a more modular SUS design framework and to realize the aforementioned benefits.

Studies completed during this research are supportive of increased modularity. An inventory analysis showed that safety stock levels decrease by 30% when a sample of similar assemblies are shared between sites. A study of a new single-use process at an Amgen site suggests that adopting two modular approaches – genderless aseptic connectors and sterile welding – yield the most desirable outcome, with 5-year NPV savings exceeding $3 million USD. This number would increase substantially if applied to SUS across commercial manufacturing. While only modestly reducing the number of required assemblies, this scenario also involves the least amount of time required to connect the assemblies and address nonconformances. Some modular design practices, such as utilizing standard lengths and building large assemblies out of small ones, are counterproductive due to the increased number of connectors and potential for leaks. Therefore, a moderate modular approach is recommended, along with the adoption of supplier standard designs when available.

Thesis Supervisor: Dr. Stephen Graves, Abraham J. Siegel Professor of Management

Thesis Supervisor: Dr. J. Christopher Love, Associate Professor of Chemical Engineering

Thesis Reader: Dr. Daniel Whitney, Sr. Research Scientist Emeritus, Department of Mechanical Engineering

This page has been intentionally left blank

Acknowledgements

I would like to thank Amgen Inc. for providing the opportunity to explore single-use systems in such detail. I would like to specifically thank Sheryl Kane for providing day-to-day guidance and direction to ensure project success, Takeshi Nishiura for his technical expertise and candid feedback, and Christian Wood for answering so many questions. In addition, Jeff Ranney was an effective mentor and I appreciate his efforts to keep the project headed in the right direction.

At Amgen, the support structure for LGO interns is significant. I am grateful to Dollie Grajczak and Derek Miller for providing so many opportunities to learn more about the company and meet some of its most distinguished leaders. I would like to thank Aine Hanly for serving as the LGO executive sponsor and taking the time to meet me and attend my presentations. And several LGO alumni also deserve recognition for their support: Kerry Weinberg, Jeff Schacherl, Matt Dumouchel, Chris Garvin, and Leigh Hunnicutt.

The MIT community was critical to the success of the internship. My thesis advisors – Dr. Dan Whitney, Professor Stephen Graves, and Professor Christopher Love – all made significant contributions to this work, and were patient mentors. I also appreciate the leadership guidance from Dr. Leigh Hafrey. My LGO classmates provided several good ideas and were generous in sharing best practices from their own internships.

Finally – and most importantly – I would like to thank my wife Margeux, who has steadfastly supported me and cared for our young children during the MIT phase of our great life adventure. Her dedication to our family and encouragement of my academic aspirations have been indispensable during a challenging and exhilarating two years.

This page has been intentionally left blank

Table of Contents

List of Figures

List of Tables

Glossary

BPOG: BioPhorum Operations Group

CHO: Chinese Hamster Ovary

CMO: Contract Manufacturing Organization

CIP: Clean-In-Place

DP: Drug Product

DS: Drug Substance

DSMT: Drug Substance Manufacturing Technologies

EDMQ: Electronic Data Management – Quality

ERP: Enterprise Resource Planning

ESS: Expected Safety Stock

FDA: Food and Drug Administration

GMP: Good Manufacturing Practice

GSS: Global Strategic Sourcing

IM Material: Inventory-Managed Material

ISO: International Organization for Standardization

kGy: kiloGray (radiation absorbed dose unit)

LFM: Leaders For Manufacturing

LGO: Leaders for Global Operations

MIT: Massachusetts Institute of Technology

PLM: Product Lifecycle Management

RFP: Request for Proposal

RMD: Raw Materials and Devices

RMS: Raw Material Specification

SAL: Sterility Assurance Level

SAP: Systems, Applications, and Products (enterprise management software)

SDD: Standardization of Disposables Design

SDR: Specification Development Report

SIP: Steam-In-Place

SME: Subject Matter Expert

SQM: Supplier Quality Management

SRE: Supplier Relationship Excellence

SUS: Single-Use Systems

SVP: Sub-Visible Particulates

TPE: Thermoplastic Elastomer

USP: United States Pharmacopeia

ZHE1: Amgen's SAP equivalent to a SKU

Introduction

To paraphrase the words of Amgen CEO Bob Bradway, "the 21st century is the Age of Biology, just as the 20th century was the Age of Physics and the 19th century was the Age of Chemistry." There is no doubt that human innovation in the biological sciences is leading to rapid advancements in therapeutics, and treating diseases that only years prior would have been a death sentence. In the United States, a strong scientific community and realization of biotechnology profit margins (often in excess of 40%) have led to ever-increasing competition for companies like Amgen. As it has been for the last 30 years, success is dependent upon a robust pipeline of potential new medicines. However, with competitor products – even biosimilars – becoming commonplace, a key differentiator is now manufacturing excellence. At Amgen, next-generation biomanufacturing is becoming current-generation, with large-scale, versatile facilities such as Amgen Singapore Manufacturing coming online. An important component of next-generation biomanufacturing is the use of single-use systems (SUS), disposable components and assemblies used in the production of both synthetic and biologic therapeutics.

Project Motivation

Amgen has been using disposable components for decades; examples are pipets in the lab and syringes which are filled with the final drug product. However, it is only within the last seven years (2010 onward) that single-use manufacturing was implemented. Realizing the potential to lower capital expenses, reduce cycle times due to cleaning, and increase facility flexibility, Amgen and its peer companies have been advancing their utilization of SUS ever since. Suppliers of single-use technologies quickly evolved from several related industries, including lab equipment manufacturers (in the case of ThermoFisher) and stainless steel biopharmaceutical equipment (GE Life Sciences).

Due to the rapid adoption of SUS and specific requirements of each end-user, suppliers became adept at designing custom single-use assemblies for each specific customer application. This led to each supplier having many similar (but not identical) designs, each suited for a particular end-user – or even a single manufacturing site for the end-user. Due to the inexpensive nature of SUS relative to the value of the drugs being manufactured, biopharma companies absorbed the cost of this supply chain inefficiency. However, as margins tighten and usage of SUS expands, companies like Amgen are recognizing that efforts to streamline SUS design and procurement can have a substantial payoff, both financially and in terms of reducing time spent by personnel resources.

Problem Statement

By early 2017, Amgen had over 800 highly-customized single-use assemblies, nearly triple the number in 2010. This resulted from end-users (typically Amgen manufacturing facilities) being given significant latitude with regard to the design and specification of SUS. In addition, with few exceptions, a separate Raw Material Specification (RMS) was required for each individual assembly, the creation of which averages over 90 personnel hours each. The monetary and time cost to maintain such a design ecosystem is substantial, not to mention the reality that optimizing a supply chain with so many custom assemblies is near-impossible.

Taking a more 'modular' design approach, with standardized, versatile assemblies, is an oft-discussed topic in the industry, but no end-user or SUS supplier has achieved such a state. With the unique requirements of each process and each end user, the task of moving the industry toward modularity seems daunting. Amgen therefore seeks to explore opportunities to move toward a more modular state, with a goal to provide answers for the following questions:

- What is the "right" level of modularity in single-use systems? What are the important tradeoffs?
- What are the root causes of SUS design proliferation?
- How should sites communicate user requirements to suppliers, if not by specifying a custom assembly?
- How can the SUS database and inventory management systems be utilized to provide a greater understanding of existing options, when a new SUS design request is received?
- To what extent will quality suffer if user requirements are compromised in order to utilize assemblies that are acceptable, but not ideal, for the required application?
- Do the financial benefits of modularity outweigh the costs to modify the existing design system?

Thesis Overview & Hypothesis

This thesis seeks to answer the above questions and to propose the optimally modular single-use strategy in the current biomanufacturing environment. It commences with the requisite background information on the biotechnology industry, Amgen as a company, the Materials Science group, and an introduction to single-use biomanufacturing. A literature review, with emphasis on modular design in other industries as well as biopharma best practices, is presented. The analytical approach is described, including the investigation into the existing single-use design and procurement framework. The results of several modularity analyses are presented, along with discussions of the technical, economic, and strategic advantages of increased modularity. Several in-depth case studies are then explored, culminating in the application of various modularity frameworks

to an existing single-use manufacturing process. The thesis concludes with a discussion of an optimally modular future state and the actions required to achieve it.

Background

Biotechnology Industry Overview

Amgen is considered a member of both the *biotechnology* industry, which uses living organisms (cells) to manufacture biologic drugs, and the *pharmaceutical* industry, which uses chemical reactions to produce synthetic molecular medicines. However, since approximately 93% of Amgen's revenue results from the sale of biologics[1], it is appropriate to consider that Amgen is first and foremost a biotechnology company.

Modern biotechnology has its roots in the early 20th century, when Chaim Weizmann engineered a microbiological culture to produce acetone[2], an important raw material for the manufacturing of explosives during World War I. The mass production of penicillin during the early 1940's was the next significant advancement of biotechnology, and is credited with saving many lives during World War II.[3] Gene splicing was completed successfully in the 1970's, and in 1980, the United States Supreme Court ruled that a genetically modified microorganism can be patented, overturning a statement by the U.S. Patent Office Board of Appeals that living things are not patentable.[4] This provided a legal framework for companies to engineer complex biologic medicines, such as monoclonal antibodies, and enjoy commercial exclusivity for 21 years after patent filing and U.S. Food and Drug Administration (FDA) approval.

The present-day biotechnology industry (exclusive of pharmaceutical companies which also produce biologic therapeutics) is valued at $595 billion as of May 2017.[5] Financial returns are considered volatile relative to other industries, mainly due to the lengthy and costly path to commercialization for each new drug. Companies may spend billions on developing a biologic medicine, only to have it underperform or prove unsafe in clinical trials. On the other hand, companies that develop and patent even a single so-called "blockbuster drug" may enjoy healthy profits for many years.

One of the most significant changes occurring in the industry is the development of *biosimilars*, or roughly the equivalent of generic versions of biologic drugs (with important differences). In the 1990s and early 2000s, most major biologic drugs were still under patent protection. However, since then, 20 biosimilar drugs have been approved in Europe.[6] In this new paradigm of competition, the manufacturing cost per dose becomes very important, and companies are turning to flexible manufacturing techniques (such as SUS) in order to lower manufacturing costs and design correctly-sized processes for a variety of products. In fact, Jacquemart et al. suggest modular, small-scale SUS-based manufacturing facilities – in stark contrast to the large-scale, centralized biomanufacturing facilities of today – will be the ultimate outcome of manufacturing and supply-chain cost-reduction efforts in the industry.[7]

Amgen Inc.

Amgen, Inc. (Amgen) was founded in 1980 as Applied Molecular Genetics, and was known as Amgen following its initial public offering in 1983. Its first "blockbuster" drug, Epogen, was approved in 1989 and treats anemia. The 1990s were characterized by rapid growth of the company, both organically and via acquisition. As of 2017, the company completed 18 acquisitions over its 37-year life. It is now a top-50 company within the S&P 500, and provides therapies for a wide variety of serious medical conditions, including neutropenia, arthritis, cancer, osteoporosis, and psoriasis. As of December 2017, Amgen is the largest member of the biotechnology industry, with a market capitalization exceeding $128 billion.[5]

Headquartered in Thousand Oaks, CA, Amgen has a variety of R&D and manufacturing facilities located around the world. The author was based at Amgen's Cambridge, MA location, with primarily process development personnel. This location also contains a scale-up lab to trial new technologies and to aid in transitioning promising molecules from the lab scale to clinical quantities. At the time of writing, single-use manufacturing technologies were in use in the following commercial manufacturing locations, all of which provided input to this thesis:

Amgen Dun Laoghaire (Ireland)

Amgen Rhode Island

Amgen Woburn (Massachusetts)

Amgen Thousand Oaks (California)

Amgen Singapore

Amgen Puerto Rico

Historically, Amgen's core business has consisted of the discovery, development, and manufacture of "large molecule" biologic therapeutics. Large molecules cannot be chemically synthesized, and so must be produced in living organisms; typically, Chinese Hamster Ovary (CHO) cells are used. The traditional production process of a large molecule, such as a monoclonal antibody, is shown in Figure 1. First, an optimal cell which produces high concentrations of the target protein is engineered. Then these cells are transferred to bioreactors of increasing size, and kept in optimal conditions (temperature, pH, media) for continued growth. The drug substance is then harvested from the final bioreactor, and purified to remove dead cells, viruses, and impurities. The fill/finish process then prepares the drug product for shipment and warehousing, prior to distribution to end users worldwide. This is inherently a batch process, and once a batch progresses through one stage, that equipment is cleaned (or discarded, in the case of SUS) and readied for the next batch.

Each step of the process must be rigorously monitored and kept in accordance with Good Manufacturing Practice (GMP) guidelines in order to comply with regulations. More recently, Amgen has transitioned to a "modality independent" philosophy, and has developed treatments of other types, including synthetics (small molecules), viral therapies, and peptides. With ten distinct modalities across its product portfolio and clinical pipeline[8], Amgen is equipped to fight disease in a variety of ways.

Figure 1. Typical Production Process for a Large Molecule, such as a Monoclonal Antibody[9]

Materials Science

Materials Science (MS) is a small and diverse team within the Drug Substance Technologies group. See Figure 2 for a more complete representation of where MS sits in the larger organization. The MS team is responsible for providing subject matter expert (SME) support for all of the raw materials consumed in Amgen's clinical and commercial manufacturing. This includes oversight of chemicals, media, excipients, filters, chromatography resins, and SUS. Unlike many Amgen employees who work on one specific product, the MS team works with all molecules that have progressed into clinical trials or commercial production. Primary responsibilities of the team include:

- Investigating and solving raw material non-conformances, such as quality or incompatibility issues
- Providing SME support to procurement of new raw materials
- Maintaining relationships with critical suppliers
- Performing technical visits to supplier manufacturing sites
- Supporting regulatory inspections of Amgen manufacturing
- Sharing knowledge across the biopharmaceutical industry via participation in forums such as the BioPhorum Operations Group (BPOG) and the International Society for Pharmaceutical Engineering (ISPE)

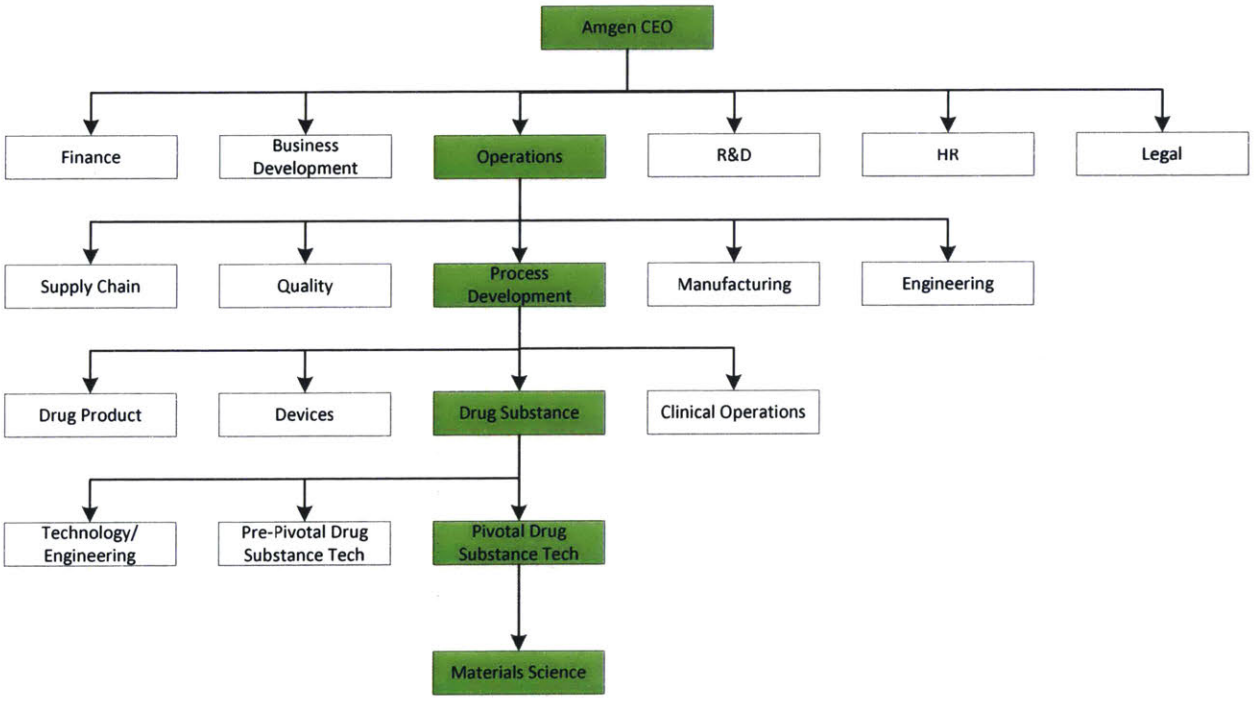


Figure 2. Materials Science Team Location in Simplified Amgen Organization Chart

Single Use Systems

While the last decade has seen the most significant growth of single-use systems, there are many earlier examples of disposable containers for pharmaceutical and medical processes. The earliest precursors to modern SUS were plastic blood bags, first developed by Fenwal in 1953.[10] Other types of disposable equipment, such as plastic pipettes and hollow fiber bioreactors, first gained popularity in the 1970's. The first commercial-scale SUS were invented in the 1980's, when filter assemblies traditionally made of stainless steel were replaced with single-use, plastic versions.[11]

There are numerous advantages to using SUS instead of traditional biomanufacturing in stainless steel equipment. The first is elimination of the need for time-consuming Clean-In-Place (CIP) and Sterilization-In-Place (SIP) steps between manufacturing runs. Depending on the complexity of the bioreactor, tubing, and associated equipment, cleaning and sterilization can take up to several days. During this time, large amounts of steam and toxic chemicals are typically consumed. Despite the development of cleaning and sterilization best practices across the industry, contaminations do occur and can be serious enough to reject entire batches of drug substance or drug product. With SUS that have been pre-sterilized either by gamma irradiation or autoclaving, the cleaning step is not required and therefore manufacturing equipment utilization can be increased dramatically.

Implementation of SUS in a biomanufacturing process also significantly reduces the initial investment required, particularly if designed into a new facility. A 2001 study by Novais et al. found that capital investment for a SUS-based manufacturing process is less than 60% of a conventional stainless steel plant, the type of biomanufacturing exclusively used prior to the introduction of SUS.[12] The same analysis found that operating costs were 70% higher for the SUS facility due to the requirement to continually purchase disposable equipment. This leads to NPV parity between the two options when the shorter time to market is considered. Since that study was performed, the proliferation of SUS use and technology development has likely led to a substantial NPV advantage for SUS; this is especially likely to be true for high-mix, lower-volume applications which do not justify the purchase of large stainless equipment.

In the past, the price of biologic drugs such as those manufactured by Amgen typically has been set based on what the market will bear, with little correlation to the cost of R&D and manufacturing.[13] However, several factors, including the emergence of biosimilars, political pressure, and increased competition, now make operational efficiency a critical lever toward sustained profitability in biotechnology. This was a factor in Amgen's decision to build the first all-SUS, large-scale commercial manufacturing plant in Singapore. This facility uses 80% less energy and water compared to traditional manufacturing, and requires only 25% of the square footage.[14]

There is also a compelling environmental case to be made for the adoption of SUS. At face value, a technology involving disposal of large volumes of plastic components doesn't seem more sustainable than reusable stainless equipment. However, the holistic environmental impact must be considered, and several studies estimate that SUS outperform traditional stainless in terms of total sustainability.[15] Due to the elimination of CIP/SIP, SUS facilities require only a small fraction of the water of traditional plants, and almost no harsh solvents or other chemicals. Sartorius Stedim Biotech, one of the largest suppliers of SUS, estimate savings as shown in Figure 3. Cox et al find that a SUS facility has a 25.5% smaller carbon footprint, due in part to the smaller number of employees required to drive to work.[16] The reduced headcount is mostly attributed to the decrease in labor-intensive cleaning activities.

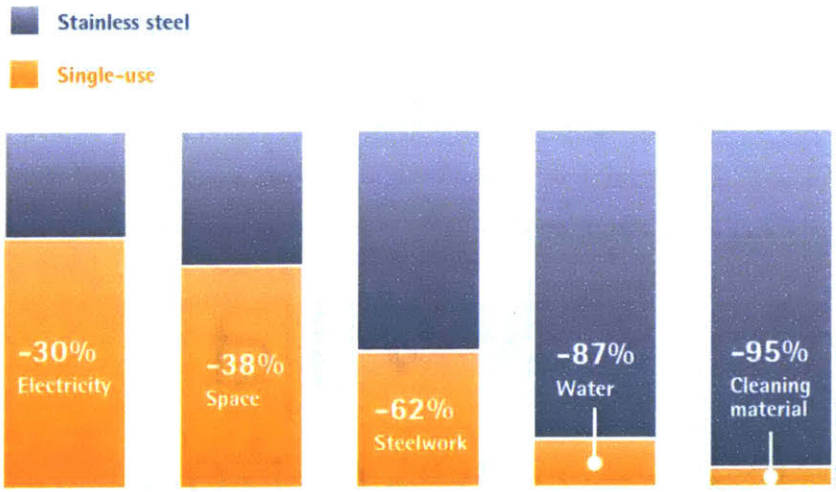


Figure 3. Reduction in Environmental Footprint of SUS[17]

A complete SUS manufacturing process is typically comprised of dozens of single-use assemblies, connected together through a variety of sterile, non-sterile, and welded connections. Some parts of the process do not lend themselves to single-use, so SUS assemblies will be used upstream and downstream. As the batch moves along – for example, from shake flasks to wave bags and finally bioreactors – earlier stages of the process can be disconnected and readied for the next batch.

Single-use technology encompasses a broad range of component types. The most common are:

- Bags: two-dimensional and three-dimensional
- Connectors: aseptic and non-sterile
- Tubing
- Rigid vessels
- Filters

- Sensors

Examples of two aseptic connectors, which will be discussed in detail later in this document, are shown in Figure 4. A common bioreactor, the Xcellerex model from GE Life Sciences, is shown in Figure 5 (note that the plastic bag and connections are the single-use elements, not the stainless steel holding vessel. A single-use assembly is comprised of two or more single-use components. Assemblies typically have a defined purpose, and can be defined in the following categories:

- Bag Assemblies: bioreactors, mixing bags, storage bags
- Filling Assemblies: for dispensing a fluid (usually drug substance or drug product) into container(s)
- Filter Assemblies: comprised of tubing and one or more filters, can have a number of purposes including protein purification and viral filtration
- Sampling Assemblies: used to take samples of the fluid of interest
- Transfer Assemblies: for transporting a fluid from one or more unit operations to another, these can range from simple straight extension hoses to complex manifolds

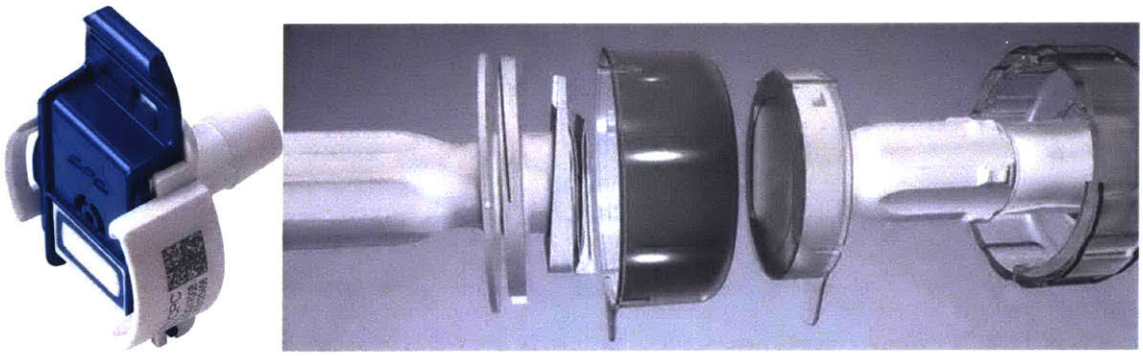


Figure 4. The Aseptiquik® G Connector[18] (left) and Opta® Male/Female Connectors[19] (right)

Unlike stainless steel equipment, SUS require that inventory of the single-use assemblies be kept on site and periodically replenished. Since each assembly is only utilized for a number of weeks, cycle stock is required to ensure constant supply of new assemblies to the manufacturing floor. After each product lot is completed, all SUS associated with that lot are discarded. Safety stock is required due to the potential for quality issues, break-in scheduling of lots, and to ensure that high-value manufacturing can continue without fear of stock-outs of relatively low-value SUS assemblies.

Figure 5. A GE Life Sciences Xcellerex Single-Use Bioreactor[20]

Maintaining consistent quality and ensuring that SUS do not impact the final drug product is of utmost importance to SUS suppliers and end-users alike. Demonstrating that strict requirements of the FDA and its peer organizations are met ultimately falls to the end-users. Detailed extractables and leachables studies are done on every fluid-contacting SUS component, to understand whether product contact can cause leaching of unwanted contaminants from the plastic into the fluid. This is a much greater consideration in bags and containers, which typically have a much longer contact time and larger surface area-to-volume ratio than tubing and filters. SUS must also be free of endotoxin, which can trigger immune responses in patients, to the same level as medical devices. Equally important is that SUS must be sanitized to ensure no microbial contamination. Depending on the unit operation, each single-use assembly at Amgen is assigned to one of the following contamination control groups:

Contamination Control Group	Bioburden Requirement	Endotoxin Requirement	Sub-visible Particulate Requirement
A: Microbial Control	Microbial control via irradiation at ≥25 kGy	Supplier controls to meet USP <85> with a limit of <0.25 EU/mL	No requirement (basic supplier controls expected)
B: Sterile	Sterile with an SAL of 10^{-6} per ISO 11137 or equivalent	Supplier controls to meet USP <85> with a limit of <0.25 EU/mL	No requirement (basic supplier controls expected)
C: Sterile Plus SVP	Sterile with an SAL of 10^{-6} per ISO 11137 or equivalent	Supplier controls to meet USP <85> with a limit of <0.25 EU/mL	Per lot testing to pass USP <788>, EP 2.9.19, or JP 6.07

Table 1. Contamination Control Groups for SUS at Amgen. Courtesy: Sheryl Kane

There are many design tradeoffs inherent to the specification of a single-use assembly. One important consideration for many assemblies is the type of tubing to be used. Silicone tubing is preferred in many applications, especially those involving high pressures or aggressive chemicals. However, its major disadvantage is its inability to be welded, necessitating connectors in all applications. Thermoplastic elastomers (TPE) are used in lower-pressure applications, and are weldable. However, typically a specific TPE formulation is approved to be welded only to tubing of the exact same formulation; welds between dissimilar formulations have to be qualified in a rigorous process and are usually avoided. Certain tubing formulations have also been developed specifically to minimize spallation (particle generation) during peristaltic pumping.

Tubing diameter is another important design selection. There are several common tubing internal diameters (IDs), specifically ¼", 3/8", ½", and ¾". Both larger and smaller tubing sizes are also available. Within each tubing ID class, the tubing is offered in a variety of thicknesses to suit different pressure applications and to fit different peristaltic pump heads.

Unlike tubing and connectors, which are typically stocked and sold by many third-party integrators as well as the original manufacturer, some components are highly proprietary. For example, certain bioreactor bags and filters are only sold by the company that manufactures them, and sometimes only as part of a pre-assembled, skid-mounted package. This forces end users such as Amgen to accept any other components (typically including tubing and connectors) that come with the proprietary component. This poses challenges for standardization; for example, if the skid connectors don't match an end-user's platform connector, then adapters will be required. Tubing from different manufacturers may need to be qualified if it hasn't been used by the end user previously. For these reasons, whenever possible, it is advisable for end users to select non-

proprietary components with maximum flexibility of design and supply. End users may also wish to qualify similar components (such as different brands/formulations of silicone tubing) as interchangeable.

Summary

SUS are destined to play a major role for biotechnology in the coming years. Recognizing this, Amgen has continued to expand its capabilities in this area, and SUS subject-matter experts sit in various positions throughout the company, including within the Materials Science team. Lessons learned from SUS usage over the past decade have led to better designs, stronger supplier relationships, and more reliable manufacturing. During this time, the associated costs of SUS – both in terms of materials and time – continue to grow, so it must be determined whether modularity can help reverse this trend. It is worthwhile to now consider academic and industry perspectives which address modularity and standardization in emerging technologies.

Literature Review

The review of literature relating to modularity starts with a more basic concept: what constitutes a good design, especially in complex systems? How can product architecture be optimized to meet functional requirements while minimizing manufacturing expense? Commonality and modularity are then formally defined, followed by a review of how other industries have approached these questions. Finally, the current state of best practices for SUS design in biotechnology is explored.

Academic approach to specification design

There is a great deal of literature on the design of specific objects and systems; however, the study of design itself, especially the development of design specifications, is less mature. In the late 1970s, Nam Suh, Professor of Mechanical Engineering at MIT, proposed "Axiomatic Design Theory," which espouses to set forth a fundamental set of principles that determine good design practice.[21] Independent of any specific industry, Axiomatic Design proposes a rigorous design process of iterating between functional requirements, design parameters, and process variables to achieve an elegant final design. While it does not explicitly develop a framework for modularity, Axiomatic Design stresses the importance of avoiding designs that are highly coupled in the *functional* domain. In highly coupled designs, a small modification to one design parameter to better suit one functional requirement can negatively impact other functional requirements and design parameters, which could in turn require other changes to mitigate the first. Instead, decoupled (or optimally) uncoupled designs are usually preferable; note, however, that *physical* coupling is often advantageous or even necessary, such as in the case of single-use assemblies which are connected together.

Karl Ulrich, formerly of MIT's Sloan School of Management, expanded upon Suh's ideas in the 1990s by exploring the relationship of product architecture to business decisions. He defines product architecture as "the scheme by which the function of the product is allocated to physical components."[22] This is directly analogous to Suh's functional requirement – design parameter association. Ulrich suggests that good product architecture can differentiate a firm from its competitors, increasing the chances of business success. He suggests that one of the key attributes of good product architecture is component standardization, which makes modular design possible. He is not the first to articulate this aspect of design; the literature on modularity has emphasized the importance of standard module interfaces for over 50 years. In a 1965 *Harvard Business Review* article, Starr states "It is the essence of the modular concept to design, develop, and produce those parts which can be combined in the maximum number of ways."[23]

Ulrich makes a number of other important observations. He notes that while standardized components are typically cheaper than custom components, there are circumstances where their use is disadvantageous. For

example, the standardized component may greatly exceed the capability required of a specific application, resulting in unnecessary expense. Conversely, adapting a design to utilize a standard component instead of a custom one could cause unacceptable design tradeoffs. In addition, widespread use of a standard component in a design (or across a suite of designs owned by a firm) can cause the organization to delay adoption of superior components, due to the need for significant re-engineering. These considerations all strongly impact today's modern biopharmaceutical industry, and especially their development of single-use assemblies.

At this point, it is appropriate to provide specific definitions of *commonality* and *modularity*. In her 1991 MIT Master's Thesis, Karen Tung defines these terms as follows:[24]

Commonality: the use of a common component by several separate products

Modularity: the use of interchangeable variants of a module in one product

Both of these design strategies have important implications in SUS. "Standardized components," which exhibit *commonality*, are being established, particularly in the simpler component types, such as tubing and connectors. These will be discussed in more detail later in this thesis. On the other hand, at the assembly level, *modularity* is the most desirable trait. For example, in a specific unit operation, perhaps a filter is required between two major process units. Depending on the size of the process, or customized requirements per molecule, it is advantageous from a business perspective to have a variety of filter assemblies which can be used in this application. However, doing so requires forethought with regard to the connectors, tubing diameter, and materials used; hence modularity typically does not develop on its own.

It should be noted that modularity is defined in other ways as well within industry and academia. In fact, Nuffort identifies six distinct types of modularity.[25] The common thread for all attempts at "modularization" is the desire to decrease the amount of customization required, and to increase the versatility of the design, either at the system, assembly, or component levels.

Modular specifications in other industries and applications

Single-use technology is still in an immature phase of development, with an evolving landscape of suppliers, assembly designs, and attempts at modularization. Therefore, it is worthwhile to consider how other, more established industries have approached the development of modular specifications. In 1996, Callahan and Heisserman developed a standardized method of representing hierarchical assemblies in the aerospace industry.[26] They present a framework, easily extendable to other industries, which clearly demonstrates the interactions between a single module, its component parts, and other modules both up and down a hierarchical structure. Their premise is that this level of design transparency is critical to identification of opportunities to

implement component commonality. The sheer complexity of aircraft systems necessitates the need for this level of structured design, so it comes as no surprise that companies like Boeing are among the intellectual leaders in this space.

The computer industry is also well-known for its success in modularizing key components. In the 1960s, with the development of its System/360 modular computer, IBM established and enforced visible design rules that determined how modules within the system would interact.[25] Competitors adopted the same design rules, and today, PC manufacturing consists of assembling a number of standardized modules (such as a hard drive, memory, USB ports, keyboard, etc.) which can be purchased from a variety of component suppliers. In the event that one supplier becomes undesirable (whether for quality, cost, or other reasons) it is a simple matter to switch to a different supplier.

Past LGO and LFM theses from other industries have also addressed modularity in great detail. The most recent example is Hsin-Wei (Wanda) Juan's project at Maschinenfabrik Reinhausen, a German manufacturer of equipment for the electric power sector. She finds that employing a modular product structure supports a better understanding of the technical dependency between systems and components, ultimately leading to the ability to generate data-driven make-or-buy decisions at the component level. While make-or-buy decisions are not the focus of this project, there is an important parallel, in that SUS modularity is driven in large part by connector strategy. By gaining understanding on a quantitative level how connectors impact the success of SUS biomanufacturing (number of assemblies using a specific connector type, number of connector failures, etc.) companies like Amgen can make informed decisions on connector strategy, both at a company-wide and individual assembly level. As in other highly complex systems comprised of many components and sub-assemblies, interface management is a key consideration for SUS and will be explored in-depth throughout this project.

Biotechnology industry best practices

Modularity of single-use systems in biomanufacturing is currently a topic of intense interest within the biotechnology industry. To date, high levels of modularity haven't been achieved, and suppliers and end-users alike recognize the inherent inefficiencies of the status quo. ASTM Standard E3051 states the following:

6.4.3 Adopting a modular design approach allows for the interchangeable use of functionally equivalent components and provides flexibility, which can be used to the advantage of both the end user and supplier to manage the risk of supply continuity, subject to the appropriate qualification of alternative suppliers, materials, components, and designs and the existence of a well-planned connectivity strategy.[27]

While highlighting flexibility as a principle benefit of modularity, E3051 provides no further guidance on how to achieve it, leaving the particulars to individual companies. In 2014, the Parenteral Drug Association released Technical Report No. 66, Application of Single-Use Systems in Pharmaceutical Manufacturing. This report, produced as a collaboration between industry experts, provides several specific recommendations on how (and the extent to which) to standardize SUS, such as providing weldable tubing and a typical connector on a single assembly, allowing flexibility to connect to a variety of other assemblies.[28] However, it stops short of suggesting specific tubing, connectors, or other components.

Industry publications such as BioProcess International provide further insight into how standardization of SUS across the industry might occur. In their 2015 article "The Single-Use Watering Hole: Where Innovation Needs Harmonization, Collaboration, and Standardization," Vogel and Eustis[29] propose that there are too many different industry groups scrambling to standardize SUS, and the end result is quite the opposite – perpetuation of non-standard practices. Instead, they argue that all of the major players must work together toward a common solution. They note that the general progression of SUS maturation starts with the elevation of user and supplier best practices into technical reports and guidelines, which then form company specifications. These may eventually be adopted into industry standards, with ever-increasing levels of detail.

In a subsequent article in BioProcess International, Dave Wolton of PM Group, a biopharmaceutical consulting company, introduces the Standardization of Disposables Design (SDD) initiative. Wolton and his team developed a portfolio of standardized single-use assemblies based on feedback from 27 end users and 17 suppliers.[30] As of December 2017, four suppliers have integrated SDD assemblies into their product catalogs. The advantage of SDD assemblies is a greatly reduced number of individual components, alignment on a single aseptic connector, and utilization of standard tubing lengths. The industry has been slow to embrace SDD, with no orders completed as of mid-2017, but it offers a compelling vision of a future modularized SUS paradigm.

Individual suppliers, with vested interests in their own components, have put forth impassioned arguments for adoption of their equipment over that of competitors. In a 2017 whitepaper, Colder Products Company presents a well-reasoned argument for the adoption of genderless aseptic connectors (which they sell) in the industry.[31] They argue that gendered connectors unacceptably restrict the flexibility in adapting an existing assembly to a new purpose (i.e. an otherwise suitable assembly with a male connector where a female is needed will require a separate adapter assembly to be compatible). The inventory requirements are substantially higher for gendered connectors as well, since assemblies must be offered in a variety of configurations to suit both genders. Since gendered connectors were available first, their use is more widespread, and continuing efforts by companies like Colder are required in order for the industry to adopt more versatile aseptic connectors.

Finally, there have been at least two prior LGO projects focusing on SUS, though neither emphasized modularity in design. In 2012, Edward Alfano found that adopting SUS over incumbent stainless steel components provides a substantial reduction in both cost and complexity in the production of vaccines.[32] This is consistent with the general industry trend over the past decade of converting existing traditional processes to SUS and specifying SUS for new processes. In 2015, Daniel Kress worked with Pfizer to generate a financial model of a new clinical production facility utilizing SUS for manufacturing monoclonal antibodies, showing that building a low-cost, in-house SUS facility is much cheaper than out-licensing a product to a Contract Manufacturing Organization (CMO).[33] This confirms the likelihood of strong SUS growth continuing into the foreseeable future.

Summary

Modularity has been a popular topic in engineering over the past half-century. Specific to single-use, recognizing that component standardization is an enabler of modular design means consideration of reducing the number of unique suppliers, and adopting platform components where possible. However, the increased difficulty of changing platform components is noted, and the SUS manufacturing network may be hesitant to adopt superior parts due to the risk and cost of change. These tradeoffs must be assessed and understood to establish an appropriate modular design framework.

Transparency in design is critical it identify commonality opportunities, and for Amgen, this means continuing and expanding the communication between SUS stakeholders across the company. Sharing best practices between sites and aligning on component selection at the design stage will pay dividends for years to come. Finally, a review of biotechnology literature relating to modularity was conducted, and while there is a clear desire to move toward industry alignment, harmonization of a path to achieving it has not yet occurred.

Analytical Methodology

Overview of approach

If you cannot measure it, you cannot improve it. – Lord Kelvin

Amgen, along with its peers in the biopharmaceutical industry, has for several years recognized a need to reform the way that SUS are designed and procured. The status quo is comprised of substantial and rising material costs, inventory requirements, and overhead devoted to single-use manufacturing. However, as of early 2017, there were few metrics available to assess SUS design proliferation and understand the extent of the problem. Therefore, the first investigative step was to complete a current state assessment. This meant gaining a comprehensive understanding of SUS at Amgen – including characterizing the design process, researching the number of specifications and amount of inventory at each manufacturing site, and estimating the cost to create and maintain each SUS specification.

Once the current state was thoroughly understood, the next step was discovering the reasons behind design proliferation. By analyzing the existing SUS assembly library, several drivers for the abundance of customized assemblies became apparent. We were then able to use this knowledge to propose changes to the design and procurement process that would result in more modular SUS assemblies, which are more versatile in nature and can be shared between processes and manufacturing sites. These proposed changes are more specific components of the overall hypothesis that modular design specifications for SUS assemblies will result in a more efficient engineering and procurement process, while providing Amgen with superior SUS quality and security of supply. In other words, adopting more modular and standardized design principles may be an effective way of mitigating the growing complexity of SUS faced by Amgen. The sub-hypotheses are then tested via cost/benefit analyses and case studies, which serve to confirm and quantify the perceived advantage.

Current state assessment

The first step to reducing proliferation of SUS designs is understanding the extent of the problem. At Amgen, raw materials (including SUS) are categorized in SAP as illustrated in Figure 6. Each Manufacturer Part Number (alternately referred to as a SKU or Amgen's SAP term, ZHE1) is assigned an Inventory-Managed (IM) Material Number. Each IM Material is in turn assigned to an RMS. In general, only functionally equivalent SKUs are grouped together under an IM material; however, the definition of "functional equivalence" is

indistinct at best for SUS. The limited examples of multiple ZHE1 numbers per IM Material Number represent commoditized, off-the-shelf items which are identical between suppliers.

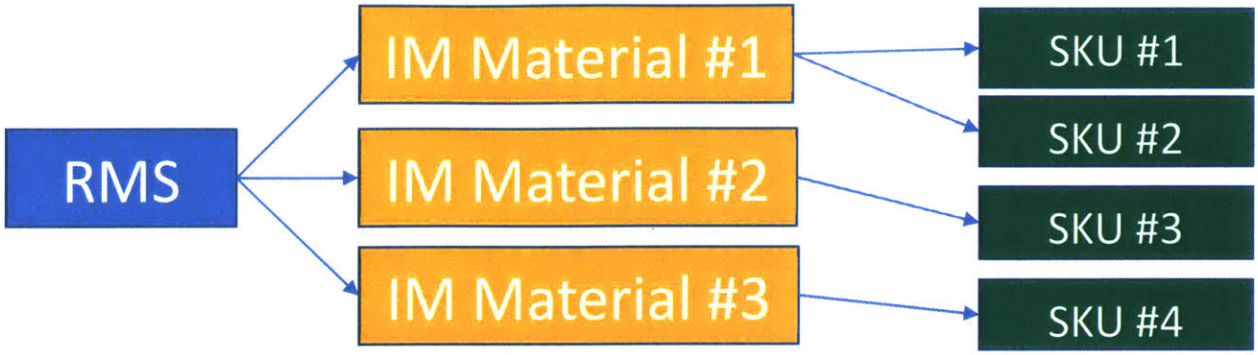


Figure 6. Raw Material Specification Hierarchy

In a similar fashion to ZHE1 material numbers, the grouping of multiple IM Material numbers under a single RMS has been inconsistently applied at Amgen. In some cases, two IM Materials share an RMS when one is a newer generation of the other, with the expectation that the older IM Material will eventually become obsolete and removed. At other times, several different sizes of the same catalog item are grouped together under an RMS number. The growth of each category – ZHE1, IM Material, and RMS number – is shown in Figure 7.

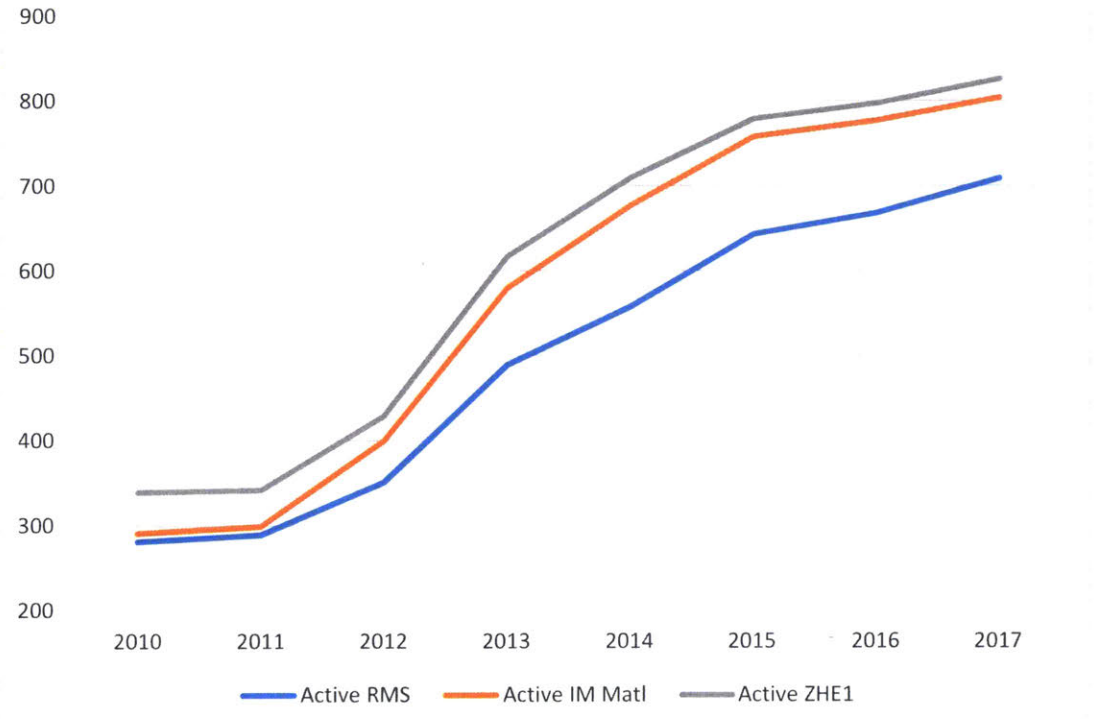


Figure 7. Growth of Amgen SUS assemblies, 2010-2017

The SUS Design and Procurement Process

There are a number of reasons that a new single-use assembly is required; the most common are as follows:

1. Starting commercial production of a new molecule requiring a new SUS process
2. Transitioning a legacy product from traditional stainless steel to SUS
3. Increasing or decreasing production batch size
4. Changed process requirements (e.g. chemical compatibility with a new buffer solution)
5. New manufacturing capacity (i.e. a new manufacturing line, suite, or facility)

Once the need for a new assembly is identified, the next step is to establish the design requirements. The Engineering Technical Authority team generates a standard form to be completed by the design requestor. At this point, the design requestor must conduct a search of the existing SUS design library and determine whether any existing assemblies meet the design requirements, or can be easily adapted. At the beginning of the project, this was done using a spreadsheet with a list of SAP descriptions of each assembly, limited to 40 characters each. The RMS for each candidate assembly would then have to be opened individually to confirm suitability. At the time of writing, implementation of the PLM database has made searching much easier, with more detailed descriptions, better metadata, and functional categorization of the available assemblies.

If the requestor determines that existing assemblies aren't suitable and a new one is required, the proposed design is considered at a 'SUS Design Triage' meeting. Attended by stakeholders in the Engineering Technical Authority, Raw Materials & Devices, and Materials Science teams, this meeting has several objectives:

1. Confirm that no existing assembly is suitable
2. Determine whether the user requirements match the requested design, the design and components adhere to expected quality standards, and that the design adheres to current SUS best design practices
3. Develop a sourcing strategy

If the request is approved at this meeting, the user requirements form and a Microsoft Visio sketch will be sent to the potential supplier(s). However, in practice supplier discussions have often already taken place prior to the SUS Design Triage meeting, particularly in cases where supplier design guidance is required. The supplier(s) then generate an engineering drawing of the proposed SUS assembly, which may require several iterations or even a prototype before being accepted by Amgen.

Once the design is finalized, a raw material specification request can be submitted. This initiates the specification development workflow for the Supplier Quality Management team, who will continue to work with the chosen supplier to ensure that all required information for a Good Manufacturing Process (GMP) specification is documented. This includes the Amgen user requirements, supplier engineering drawing, supporting component

data, storage and testing requirements, and a summary of changes over the life of the RMS. The order is often placed prior to the end of the specification development process, meaning there is risk of late design changes. However, the RMS must be completed and approved before Amgen can place the assembly into service.

Maintaining a raw material specification also requires a substantial time commitment. Over its lifetime, the RMS will likely undergo one or more changes. Historically, a minor (Level 1) change requires an average of 16.5 personnel hours to resolve, with contributions from the specification owner, Quality team, and one or more subject matter experts. A major (Level 2) change requires an average of 66 hours from the same teams. With approximately 30% of RMS requiring one or more changes annually, this easily equates to thousands of hours required each year to maintain existing specifications. When a specification reaches the end of its useful life, it requires an average of two hours to designate as obsolete and confirm disposal of remaining inventory.

The total projected lifecycle time requirement per specification, with an estimate of associated monetary value, is shown in Table 2. The information in this table was compiled from interviews with each contributing team, as well as observation of several end-to-end design cycles during the project. With over 700 RMS in Amgen's SUS library as of mid-2017, it is estimated that the sunk cost of developing these specifications exceeds $6.5 million and 65,000 hours. Note that a 38% savings is realized if the new material number can be added to an existing RMS, instead of requiring a new one.

New RMS and Material Number	# Hours	Hourly Rate	Total Cost
Initial Design, Testing, Review	16.5	$100	$ 1,650
SUS Design Triage (MS admin)	2.5	$100	$ 250
SUS Design Triage (PM admin)	2	$100	$ 200
SUS Design Triage (SME, Review Board)	5	$100	$ 500
Supply Chain / Sourcing	5	$100	$ 500
Spec Writing / SDR	19	$100	$ 1,900
Change Management	40	$100	$ 4,000
Obsoletion	2	$100	$ 200
Grand Total	**92**		**$ 9,200**
Total Specification Development Hours	**50**		
New Material Number Added to Existing RMS			
Initial Design, Testing, Review	16.5	$100	$ 1,650
SUS Design Triage	2.5	$100	$ 250
Sourcing	5	$100	$ 500
Spec Writing / SDR	2	$100	$ 200
Change Management	30	$100	$ 3,000
Obsoletion	1	$100	$ 100
Grand Total	**57**		**$ 5,700**
Ratio of Material # to RMS Cost			**0.62**

Table 2. Raw Material Specification Lifecycle Cost Estimate

Aseptic Connector Failure Data

Another aspect of understanding the current state of SUS biomanufacturing at Amgen is understanding the failure rates of various components. Anecdotally, two components are responsible for the majority of SUS quality problems: bag leaks and aseptic connector failures. The former will not be discussed here since bioreactors are typically process-specific and do not lend themselves to modularity. On the other hand, connectors are key to modularity; Amgen sites use a variety of different connectors, based mostly on user preference at the time of design. As with bags, connector failures typically take the form of leaks, but minor leaks are typically still contained within the housing of the connector. The consequence of such a leak can vary widely depending on location in the process and severity; it could be as simple as tube welding or replacement of the assembly, which results in only a slight delay to a manufacturing run. On the other hand, a severe leak could result in a contamination event, which can waste an entire lot of drug substance.

Aseptic connector failure data has been recorded to varying degrees by each manufacturing site. Some sites record no data specific to connectors, and only log a nonconformance. Others track connector failures by lot

number and location in the process. In order to assess which connectors were performing best in the long run, all available data was aggregated for the six most popular connector types. This data set spanned over five years and five Amgen manufacturing sites. The results are shown in Figure 8, and are notable for several reasons. For example, a large variance in connector reliability is observed. The long-term average failure rate is one out of 215 aseptic connectors, but this varied from 1 out of 833 (small-body Connector X) to 1 out of 20 (large-body Connector X). In general, smaller connectors outperform larger connectors, though Connector Y is notable in that it has a failure rate similar to that of the small-body Connector X, but is offered in sizes up to that of the large-body, ¾" Connector X.

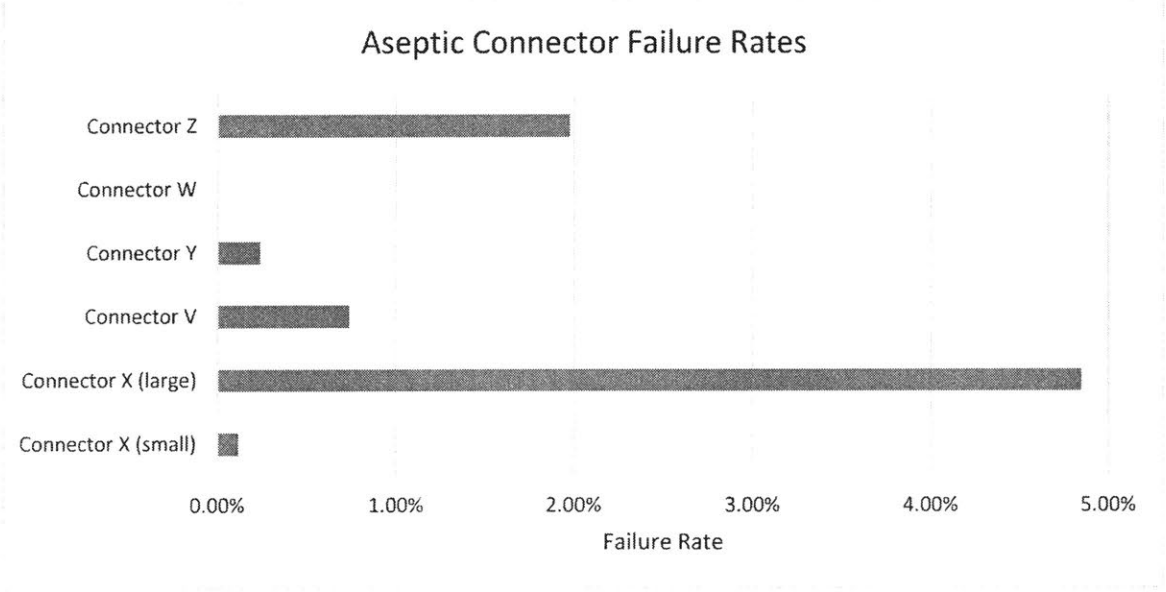


Figure 8. Failure Rates of Aseptic Connectors in Amgen Clinical and Commercial Manufacturing

Connector Z is used primarily at the 1" size, though some ½" connections are also utilized. For 1" connections, the only other available connector is the gendered Connector W, relatively new to the market and used less than 30 times at Amgen by the end of 2016. However, no failures occurred in that time.

At the smaller sizes, Connector X and Connector Y have very similar failure rates. See Table 3 for the raw data. A two-tailed, two-proportion z-test was used to determine if there is a statistical difference between the connectors. The null hypothesis is that $P_X - P_Y = 0$, indicating no difference in the failure rates. The alternative hypothesis is $P_X - P_Y \neq 0$, indicating that Connector X is superior.

	Total	Failures	Failure Rate
Connector X	6667	8	0.12%
Connector Y	2500	6	0.24%

Table 3. Comparison of Key Aseptic Connector Failure Rates

This test results in a z-score of -1.3104, corresponding to a p-value of 0.1902. If a reasonable significance level is chosen, $p = 0.05$, then we fail to reject the null hypothesis. This means that while Connector X has a lower observed failure rate than Connector Y, the difference is not statistically significant. This has important implications for standardization of connectors, discussed below, since Connector Y is a genderless design and promotes more modular assemblies.

SUS Design Proliferation Root Causes

There are several reasons that such a large number of highly customized SUS assemblies have been designed for Amgen's commercial biomanufacturing. Some root causes are difficult or impossible to address in a timely or efficient manner. These include:

1. Regulatory constraints: some assemblies and components, particularly in older processes, are defined in the regulatory filing as integral to the manufacturing process. In these cases, seeking a filing amendment to switch to a more modular design or standardized components isn't feasible or cost-effective.
2. Supplier Proprietary Equipment: Single-use suppliers often design their equipment so that it is not compatible with equipment supplied by competitors. Examples are SUS bag holders, mixing bag impeller connections, and aseptic connectors. This business practice resists the desire by end-users to commoditize certain elements of SUS manufacturing, which would erode supplier pricing power.
3. Highly Specific User Requirements: Each manufacturing process has various stages, which will be exposed to a variety of temperatures, pressures, and chemicals. In addition, the sterility requirements of each step in each process may vary. This makes it difficult and impractical to design assemblies versatile enough to accommodate such a wide range of process conditions. An assembly suited for a certain stage in one process may be compatible in every way but one with a unit operation at a different site; for example, a silicone tubing transfer assembly with tri-clamp connectors on each end is fairly common, but often must also be made available in a reinforced silicone variant for higher pressures.

Addressing these issues is beyond the scope of the project. Instead, this thesis focuses on addressing the root causes of SUS design proliferation which are more easily resolved, which have been identified as the following:

1. Difficulty of Searching Existing RMS Database

Prior to initial PLM implementation, the best method for ascertaining whether an existing design would suit a new requirement was consulting a spreadsheet of data extracted from SAP. The descriptions of each assembly in SAP are limited to 40 characters, which is insufficient to provide enough information to tell at a glance whether the assembly could be re-purposed. Therefore, the requestor would have to manually enter the specification number into EDMQ, the document management system, and retrieve the RMS. The RMS includes the engineered design drawing, from which the requestor can make a final determination of suitability. This iterative process can take hours with no guarantee of success, which almost certainly contributed to design proliferation. One actual example where this happened was a 90" silicone straight extension with tri-clamps on each end. This assembly was first utilized at one Amgen site in 2011. In 2012, a different Amgen site designed and procured an assembly identical in every way except that it was 98" long. While it is possible that the extra 8" was truly required, no effort seems to have been made to decide on a single length suitable for both sites. These assemblies are listed in separate RMS and still active as of 2017.

2. Inconsistent Connectivity Strategy

There are a wide variety of ways that single-use assemblies are connected; they can be welded together, if the tubing is made from a thermoplastic elastomer (TPE). Or they can be connected using a non-sterile connector, such as a tri-clamp quick-connect fitting. A third option is via aseptic connectors, which have gained widespread popularity for their ability to be connected relatively quickly outside of a biosafety cabinet while maintaining aseptic fluid pathways. Within each class of connectors, there are many styles and sizes, few of which are cross-compatible.

As of 2017, there is no organization-wide connectivity strategy for SUS at Amgen. Much of the assembly design has been done at the manufacturing site level, usually in coordination with a single supplier, which often proposes using its preferred connector. In addition, connector failure data has not been consistently gathered or communicated across the network. Finally, some supplier products are only available with their connectors, necessitating the need for adapters if another connector is preferred for the system as a whole. All of this has led to a multitude of different connection methods used across Amgen, and in many cases, assemblies may be physically equivalent except for one or more connectors.

3. Lack of Standardized Assembly Utilization

Only a few years ago, SUS suppliers did not offer any "standardized" assemblies. Recently, however, some of the largest suppliers – including Sartorius and Millipore – are now offering pre-designed SUS.

The value proposition of these end-user agnostic assemblies is that they are cheaper and faster to procure than custom assemblies due to the lack of engineering required.

Direct observation within Amgen and anecdotal feedback from suppliers suggest that uptake of standard assemblies has been slow. One reason for this at Amgen is that the SUS design guidelines do not ask the requestor to search supplier offerings prior to submitting requests for new custom designs. Furthermore, there is no suggestion to consider constructing a new assembly out of existing assemblies, or combinations of existing assemblies and supplier standard assemblies. Until end users embrace supplier standardized offerings as an intermediate step toward industry-wide modularization, they are unlikely to grow quickly. There will always be a demand for custom assemblies, but the functional requirements of some subset of these can be satisfactorily met by standard assemblies.

4. Unawareness of Inventory Implications of Customization

   Each manufacturing site at Amgen manages its SUS inventory individually. With the proliferation of customized SUS, this means that each site must carry enough safety and cycle stock to meet its own needs. If sites collaborated with each other to pool safety stock, Amgen's overall SUS inventory requirements would be greatly reduced.

Proposed Design and Procurement Changes to Enhance Modularity

After gaining an understanding of the SUS design and procurement process, the author consulted with a number of sources (internal and external to Amgen) to develop the following potential process changes in order to enhance modularity and enjoy its benefits. The merits of these proposed changes were assessed in a variety of ways, including cost-benefit analyses and with case studies.

Grouping of assemblies under common RMS: There is an opportunity to substantially decrease the number of raw material specifications generated during SUS design and procurement. This is discussed in depth as a case study. This encourages more modular designs by making similar assemblies more accessible, increasing the odds that manufacturing personnel will find a suitable existing assembly rather than having a new one custom designed. It also reduces the time required to search for existing designs.

Utilize off-the-shelf standard offerings whenever possible: SUS suppliers are beginning to offer off-the-shelf SUS assemblies that are not specific to a single end-user. In theory, mass producing these should make them available at a lower cost, and potentially with a lower defect rate as well. Case Studies #1 and #2 address this opportunity, and the potential supply chain benefits (including shorter lead times and ability to pool inventory

between sites) are considered as cost-benefit analyses. Because off-the-shelf assemblies are not specific to a particular process or user, they are typically more modular to suit a variety of needs.

Develop a coordinated connector strategy: For various reasons, individual sites gravitate toward specific aseptic connector(s). This leads to assemblies which are useful to one site only because of a particular connector, when the core functionality (i.e. filtering, fluid transfer, etc.) is common to other sites. Standardizing on a small number of aseptic connector types could significantly increase the modularity of Amgen's SUS library. The aforementioned connector failure rate discussion can help inform on connector selection, and the benefits of genderless connectors as discussed in the second cost-benefit analysis and in Case Study #3.

Increase tube welding: Sterile tube welding eliminates the need for aseptic connectors, one of the greatest barriers to increased modularity. However, there are technical challenges; welding takes longer, and the two pieces of tubing must typically be identical formulations (i.e. C-Flex 374). Dissimilar thermoplastic elastomers can be welded successfully in principle, but specific combinations of formulations would have to be validated before this could be performed in GMP manufacturing. Standardizing on TPE formulations and adopting tube welding as standard practice in some applications would make the associated assemblies more modular.

Optimize the connection-assembly tradeoff: SUS assemblies designed to be more modular typically contain fewer components, meaning more individual assemblies are required for a process. While this provides more flexibility in design, it also increases the number of connections, which require more assembly time and increase the number of potential leak points. For example, a long "wye" assembly could be assembled from a short "wye" assembly with three straight extensions on each end (four total assemblies) or could come from the integrator as a single assembly. Case Study #3 considers whether it is more advantageous to pursue maximum modularity (i.e. many small assemblies) versus the status quo, or whether an intermediate solution is preferred.

Cost/Benefit Analyses

A number of proposed changes were best analyzed via analyses of costs and benefits resulting from the change. Implicit in these studies is the assumption that process quality is either unaffected or improved by the change.

1. Grouping of IM Materials under Raw Material Specifications

One opportunity identified by the SUS team at Amgen was to consider a strategy for consistently grouping inventory-managed material numbers under Raw Material Specifications. In most cases, current practice is to create a new RMS for each new IM Material required. In fact, over 650 of the 700+ single-use RMS had only a

single associated IM Material. However, the 45 RMS with two or more IM materials demonstrates that this framework can be used successfully, albeit with inconsistent grouping criteria.

The advantage of grouping is that a new specification would not be required for each IM material added, saving an average of 35 manhours per IM material. A standardized set of criteria for grouping of IM materials was developed, and is provided in detail in Appendix 2, RMS and IM Material Grouping Manual. These criteria were applied to several categories of SUS assemblies, to gauge the potential decrease in RMS required. The results are shown in Table 4. Notably, the total number of RMS required for these three categories decreased by 46%; considering that Amgen has over 700 RMS and assuming that reduction would hold over all categories, the hypothetical reduction in manhours resulting from fewer RMS exceeds 11,000 hours. In addition, grouping SUS assemblies in this way makes them easier to find, so manufacturing personnel requiring a new assembly are more likely to find one in the existing assembly library.

	Original RMS	RMS with Grouping	% Reduction
Rigid Vessels	13	9	31%
Filters	49	18	63%
Other SUS	27	21	22%
Overall	89	48	46%

Table 4. Application of Grouping Criteria to SUS Assembly Categories

With the grouping criteria in place, the question then became whether it made sense to apply the rules retroactively to existing assemblies, or to only implement the grouping criteria for new designs. A cost-benefit analysis of the two options is presented in Tables 5 and 6. The significant effort required to revise existing documentation, over 3,700 hours estimated, meant that Amgen management elected to apply the grouping criteria only to future SUS designs. However, it is anticipated that this change will decrease the required manhours by over 1,100 per year.

Apply New Grouping Rules to Current and Future RMS		
Cost	Total Time (hr)	
284 specification revisions	3,700	
425 material number tables added	70	
	3,770	One-time effort
Benefit		
40 fewer RMS created per year	1,120	
Increased searchability	142	
	1,260	Annual savings
"Pay-back period"	3	Years

Table 5. Manhour Cost-Benefit Analysis of Applying Grouping Rules Retroactively

Apply New Grouping Rules to Future RMS		
Cost	Total Time (hr)	
None	-	
Benefit		
40 fewer RMS created per year	1,120	
	1,120	Annual savings
"Pay-back period"	0	Years

Table 6. Manhour Cost-Benefit Analysis of Applying Grouping Rules to Future Designs

2. Adoption of Genderless Connectors

Early aseptic connectors used in SUS were *gendered*, meaning a distinct male and female piece connect together to form the sterile connection. Amgen and its peers typically designed single-use processes based on an arbitrary convention, i.e. the upstream connection on an assembly is male, and the downstream connection is female. Consider for example a 'wye' transfer assembly with one upstream male connector and two downstream female connectors. If this assembly was otherwise ideal for a new process that required two upstream connections and a single connector downstream, a different assembly would nevertheless be required. As previously described, gendered connectors require more assembly variants and adapters, hindering modularity and increasing the size and cost of the SUS supply chain.

In more recent years, SUS suppliers have been working to develop *genderless* connectors. While similar in appearance to gendered connectors, genderless connectors are notable in that any connector can attach to any other like connector, sometimes even across tubing sizes. The implications for modular design are obvious. In addition, the author's research found that on average, genderless connectors tend to be 30-40% cheaper than their gendered counterparts.

This study considered whether it would be advantageous to Amgen to adopt genderless connectors across its range of transfer assemblies in the 3/8"-¾" ID range. There are three perceived advantages to genderless connectors, which are discussed in detail below:

1. Cost
2. Connection Time
3. Reduced Number of Assemblies Required

Cost

Amgen occasionally orders loose aseptic connectors for on-site assembly of single-use assemblies. This allows for direct observation of pricing for two leading aseptic connectors, one gendered (Connector X), and the genderless (Connector Y). Table 7 below shows the results of this comparison. For the 3/8" size, each Connector Y connection (comprised of two connectors) is 26.5% cheaper than a corresponding Connector X connection. The difference is even more pronounced at the ¾" size, where we find that the Connector Y is 34.2% cheaper than its competitor. When coupled with the failure rate data for these respective connectors (see Table 3) the genderless Connector Y is a compelling option.

Aseptic Connector	PricePer Unit	Price Per Connection
3/8" Connector X Male	$46	
3/8" Connector X Female	$45	$91
3/8" Connector Y	$33.46	$66.92
3/4" Connector X Male	$51.70	
3/4" Connector X Female	$51.70	$103.40
3/4" Connector Y	$34.02	$68.04

Table 7. Cost Comparison of Loose Sterile Connectors

Connection Time

Connection time is difficult to measure, especially since it can vary widely by the individual technician, size, and location of connection. In addition, individual manufacturing sites typically will favor one type of connector over others, making same-technician comparisons impossible. Therefore, the most reliable source of data for connection times was from Building 23 in Thousand Oaks, which houses a clinical manufacturing facility. Due to the nature of clinical manufacturing, "B23" has produced many Amgen products, and so its technicians must maintain competency with both sterile welding and a variety of connector types. Their technical team report the following times as typical:

Connection Type	Connection Time (min)
Connector X	2
Tri-Clamp	2
Connector Y	1.5
Sterile Weld	3

Table 8. Time Required for Various Single-Use Connection Types

Therefore, the genderless Connector Y is estimated to provide a 25%-time savings (30 seconds) per connection. With over 100 connections required per manufacturing lot in some processes, switching to genderless connectors may provide a substantial reduction in setup time, reducing personnel expenses and allowing the facility to manufacture more product each year.

Reduced Number of Assemblies Required

At the time of writing, Amgen has 57 ¾" transfer assembly single-use specifications in its library. As discussed in Table 2, each of these assembly specifications required, on average, $9,200 and 50 hours to develop. Assuming a hypothetical process which uses each assembly exactly once, a conservative estimate of total reduction of assemblies due to modular design principles (emphasizing genderless connectors) was conducted. The result is a reduction in number of unique assemblies from 57 to 33, a 42% reduction. The method of this exercise is discussed further in Case Study #3, when the same approach is used on an actual manufacturing process.

3. Welding Irradiated Tubing Spools Instead of Straight Extensions with Aseptic Connectors

The visual transfer assembly library (Appendix A) demonstrates that many of the single-use transfer assemblies used by Amgen are simple straight extensions: a length of tubing with a connector on each end. Like other assemblies, straight extensions are purchased from integrators, who charge a price based on the labor to assemble, gamma irradiation, individual double bagging, and shipping. We identified an opportunity to replace these assemblies with gamma-irradiated tubing spools. Instead of purchasing individual, pre-cut assemblies, lengths of these spools can be cut as required, preserving the sterility of the spool, and the cut tubing section can then be sterile welded to the adjoining assemblies. Each time a cut is made, the welding blade used to make the cut must be replaced, ensuring sterility for the next time the welding machine is used.

Quotes for gamma-irradiated tubing spools were obtained for three sizes of a common TPE tubing formulation. The 3/8" and ½" tubing comes on spools of 4200 inches and 3000 inches respectively, while ¾" tubing is sold in 180-inch lengths due to its thickness. The prices per inch for the three diameters are as follows:

Tubing ID	$ per inch
3/8"	0.28
1/2"	0.36
3/4"	1.49

Table 9. TPE Tubing Prices Per Inch (quotes obtained June 2017)

Along with the price to Amgen per weld blade ($12.21), this information allows for the calculation of the variable cost of a welded straight extension assembly. These prices were then compared to 14 existing Amgen straight extension TPE assemblies across the three sizes. The results are in Table 10, and demonstrate that for this subset of assemblies (representing less than 10% of Amgen transfer assemblies) savings from switching to irradiated spools and sterile welding exceed $200,000 annually.

3/8"	Avg Annual Qty	Cost Per Unit	Current Annual Cost	Spool/Welded Cost
Assembly 1	48	$ 303	$ 14,561	$ 1,617
Assembly 2	115	$ 292	$ 33,608	$ 7,747
Assembly 3	20	$ 474	$ 9,486	$ 2,021
Assembly 4	172	$ 59	$ 10,084	$ 6,952
			$ 67,739	$ 18,336

1/2"	Avg Annual Qty	Cost Per Unit	Current Annual Cost	Spool/Welded Cost
Assembly 5	85	$ 243	$ 20,621	$ 93
Assembly 6	60	$ 267	$ 16,046	$ 2,614
Assembly 7	145	$ 427	$ 61,864	$ 6,316
Assembly 8	55	$ 333	$ 18,321	$ 4,791
Assembly 9	220	$ 74	$ 16,355	$ 11,500
			$ 133,207	$ 25,313

3/4"	Avg Annual Qty	Cost Per Unit	Current Annual Cost	Spool/Welded Cost
Assembly 10	20	$ 253	$ 5,051	$ 119
Assembly 11	38	$ 546	$ 20,761	$ 3,400
Assembly 12	39	$ 416	$ 16,231	$ 6,978
Assembly 13	110	$ 480	$ 52,809	$ 39,365
Assembly 14	106	$ 620	$ 65,682	$ 56,901
			$ 160,533	$ 106,764

Total Current Cost	Total With Spools
$ 361,480	$ 150,413
Total Annual Savings	**$ 211,067**

Table 10. Annual Savings from Welding Gamma-Irradiated Tubing Instead of Purchasing Pre-Fabricated Straight Extension Assemblies

Cost savings are not the only implication of switching to welding. Aseptic connectors are often favored by technicians on the manufacturing floor, due to their relative ease of use, and no requirement to position a bulky welder to perform the weld. For these reasons, the time to complete each weld must also be considered. The cost and time tradeoffs were combined into a simple spreadsheet "Weld or Buy Calculator," represented in Figure 9. In the example shown, the calculator takes several known or easy-to-calculate inputs for both the gamma-irradiated spool and pre-cut assembly options. It compares the cost of the materials (lengths of tubing and disposable weld blades vs. the prefabricated assembly), as well as the additional time required to complete the weld as opposed to aseptic connections. With this tool, the Amgen engineering team can quickly estimate whether a new transfer assembly should be purchased from an integrator as a completed assembly, or if it is worthwhile to buy gamma-irradiated tubing spools and perform welds instead.

Weld or Buy Calculator

Inputs	
Inner Diameter:	3/8"
Length Required (in):	150
Number of Welds:	2
Cost Per Prefab Assembly:	$ 250
Cost per Weld Blade	$ 12
Time to complete one weld (min):	3
Time to connect one connection (min):	2
Outputs	
Variable cost of welded tubing:	$ 66
Time to complete welds (min):	6
Welding savings per assembly:	$ 184
Additional time per assembly (min):	2

Figure 9. Weld or Buy Calculator with 3/8" Assembly Example

4. Pooling of Safety Stock

Another potential advantage of enhanced modularity is the ability to pool safety stock between manufacturing sites. Although SAP grants visibility of global SUS stocks to all users with the prerequisite permissions, individual Amgen sites manage their own inventory. Therefore, each site is responsible for maintaining adequate levels of safety stock and cycle stock. In certain circumstances, one site has shipped SUS assemblies to another, but this is done on an ad hoc basis. Purchasing and holding SUS inventory is a significant expense to Amgen, as shown in Figure 10, and one which is certain to continue rising as SUS usage expands.

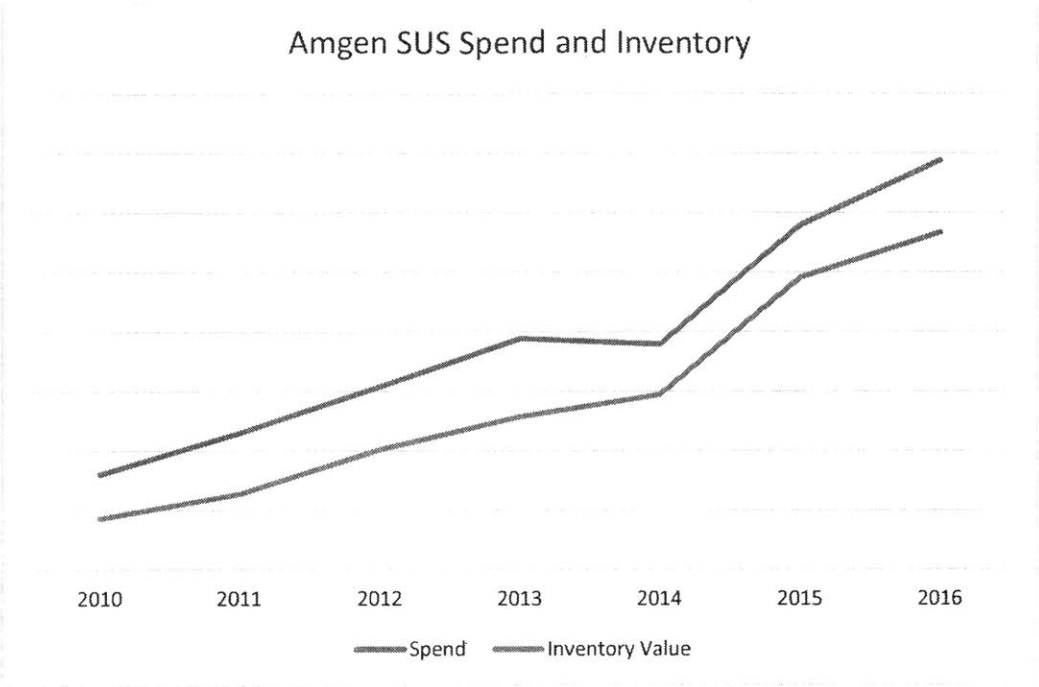


Figure 10. Growth of Amgen SUS Spending and Inventory, 2010-2016

Under the base stock inventory model, the expected inventory level B of a given item is set as

$$B = \frac{r\mu}{2} + z\sigma\sqrt{r + L}$$

Where $\frac{r\mu}{2}$ is cycle stock and $z\sigma\sqrt{r + L}$ is safety stock. The variables are defined as follows:

$$r = periodic\ review\ time$$

$$\mu = mean\ demand\ of\ item$$

$$z = normsinv(service\ level\ \%)$$

$$\sigma = demand\ standard\ deviation$$

$$L = lead\ time$$

This analysis focuses on the safety stock portion of total inventory levels. Among the transfer assemblies in use at Amgen, 23 were chosen (across all six manufacturing sites) which meet at least one of the following criteria:

1. The assembly becomes redundant with an assembly at another site if genderless connectors are used
2. There is an insignificant length difference between two assemblies used at different sites
3. The assembly is identical to one used at a different site, but they have different material numbers

These 23 assemblies were consolidated into 12 assemblies after applying the criteria above. For each assembly, an annual mean and standard deviation of usage at each site was estimated using historical data. The periodic review time of Amgen's Enterprise Resource Planning (ERP) system, SAP, is one week. Lead times vary between assemblies based largely on complexity, but an average of 10 weeks was assumed. Using these inputs, Expected Safety Stock (ESS) levels were calculated both with current practice (individual sites) and in a hypothetical scenario where sites pooled safety stock of common assemblies. The results are presented in Table 11, with a reduction in safety stock of 24%, and an overall working capital savings of nearly $100,000. These assemblies comprise less than 3% of all Amgen SUS, so if the analysis were extended, savings could easily exceed $1 million. There is a past history of sharing SUS inventory when needed across Amgen manufacturing, so formalizing this process and taking credit for it (in addition to further modularizing the assembly design) results in clear operational savings.

Assembly	Unpooled ESS	Pooled ESS	% Savings	Cost per Unit	Working Capital Savings
#1	119	80	33%	$526	$20,409
#2	17	12	27%	$400	$1,809
#3	359	353	2%	$90	$496
#4	123	83	33%	$290	$11,630
#5	155	108	30%	$420	$19,908
#7	100	90	10%	$467	$4,662
#8	631	404	36%	$42	$9,523
#9	33	23	32%	$592	$6,193
#10	35	25	29%	$355	$3,614
#11	12	7	41%	$113	$556
#12	131	79	40%	$338	$17,522
#13	206	197	4%	$126	$1,094
Totals	**1920**	**1461**	**24%**	**$313**	**$97,418**

Table 11. Results of Pooling Safety Stock Analysis

5. Inventory Reduction Through Shorter Lead Times

By inspecting the base stock equation shown above, it becomes apparent that reducing the value of L will have the effect of reducing the amount of safety stock required. Anecdotal evidence from interviews with Amgen's strategic SUS suppliers suggest that by utilizing their standardized, off-the-shelf assemblies in lieu of Amgen custom assemblies, lead times fall by up to 50%. To understand the effect that this would have on reducing inventory, the base stock model is again used. Table 12 shows an inventory calculation for a hypothetical reduction of an actual single-use assembly from 10 weeks to five weeks. In this scenario, total inventory of the assembly is reduced by 21%, with no cost to Amgen. Savings such as these are not obvious when engineers are making SUS design decisions, but should not be understated considering the amount of SUS inventory Amgen holds.

	Ordering a Custom Assembly			Ordering an Off-the-Shelf Assembly		
Time Between Order Placement	r	1.00	weeks	r	1.00	weeks
Demand Average	μ	10.58	per week	μ	10.58	per week
Service Level		99%			99%	
Normsinv (Service Level %)	z	2.33		z	2.33	
Demand Standard Deviation	σ	2.64	per week	σ	2.64	per week
Lead Time	L	**10.00**	weeks	L	**5.00**	weeks
Safety stock	20.40	zσ*sqrt(r+L)		15.07	zσ*sqrt(r+L)	
Cycle Stock	5.29	rμ/2		5.29	rμ/2	
Total Inventory On Hand	25.69	Units		20.36	Units	
				21%	Reduction in Total Inventory	

Table 12. Hypothetical Inventory Reduction Based on Shorter Lead Times of Modularized SUS

Case Studies

#1: Design and Procurement of Continuous Manufacturing SUS

Historical narrative

In 2016 and 2017, Amgen initiated a continuous manufacturing pilot project at one of its clinical manufacturing facilities. The process was to utilize as much single-use equipment as possible; however, because the process called for smaller tubing than typical for commercial-scale biomanufacturing, very few of Amgen's existing SUS assemblies were suitable for the new process. The Drug Substance Manufacturing Technologies (DSMT) team was called upon to design an entirely new SUS process for this project. This case study examines two weldable tee assemblies designed as part of this process.

The two tee assemblies are identical, except that one uses 1/8" tubing and the other has ¼" tubing. In December 2016, the process design was set and included only the 1/8" tee. The decision was made to request a quote and drawing from "Supplier X", one of Amgen's primary SUS suppliers, as part of a 27-assembly order. Supplier X was selected based on their relatively fast turnaround of engineering drawings and willingness to work closely with Amgen engineers to ensure the design meets user requirements. They have also provided very competitive prices when anecdotally compared to Amgen's other Supplier Relationship Excellence (SRE) suppliers. Finally, Supplier X has a large qualified component library, which ensures that Amgen's requirements can be met without custom or special-ordered components.

Supplier X provided an engineering drawing 38 days after the design was requested, which was considered reasonable since that time included the holiday period at the end of the year. Amgen did not approve the drawing until 34 days later, and minor changes to the design were made in the meantime. The Raw Material Specification took 40 days to be generated by the SQM team, and was present in Amgen's GMP document repository only 16 days prior to delivery of the first shipment. The entire process took 128 days from first request to delivery, even for a relatively simple assembly.

After the RMS specification was generated but prior to delivery of the 1/8" tee, the Amgen team realized that the design also required a ¼" tee. Supplier X provided a drawing only 18 days after the initial request, and Amgen approved it the day after receiving it. RMS generation took 27 days, and the first shipment was received 23 days later, for a total time of only 69 days, just over half the time it took to for the 1/8" tee.

Hypothetical differences with proposed framework

This example provides several lessons. First, for a custom design, even a supplier with a reputation for speed can take over five weeks to generate a design drawing. The time was shortened considerably for the second tee, but recognizing that the changes to the drawing were very minor (part numbers and diameters) it likely could have been completed much more quickly. Off-the-shelf equivalents of these tees would have required no time for the design drawing, and quite possibly would have been in stock with a supplier.

Second, though Amgen was able to add the ¼" tee to the RMS specification of the 1/8" tee, it still took nearly a month to re-issue the revised RMS. Anecdotally, delays such as this have caused material to be received by the facility, but unusable because the paperwork is not in place to permit use. Instead, Amgen should expand the practice of grouping RMS specifications (as previously discussed) and prioritize these changes over the much more labor-intensive process of new specification generation.

Finally, neither of these designs were competitively sourced, meaning Amgen accepted Supplier X's cost and lead time without checking to see what other suppliers could provide. If another supplier had these simple tees in a standard library, it's possible that Amgen would have realized both time and cost savings. This opportunity will be discussed in more detail in Case Study #2.

#2: Second sourcing an existing assembly through the SDD framework

PM Group's Standardization of Disposable Design (SDD) initiative, described previously, presented an opportunity to investigate the potential benefits of competitively sourcing single-use assemblies. With modular design, second-sourcing becomes easier due to the ability to match simple assemblies to supplier off-the-shelf offerings. SDD designs are particularly compelling because several suppliers have committed to providing SDD designs, facilitating an easy competitive quote process. The goal of this study was to determine whether significant price and/or lead time advantages could be gained by soliciting multiple quotes on SUS.

The first step of this process was to identify SDD assemblies which closely match assemblies that Amgen currently purchases as custom designs. The study was restricted to transfer assemblies, since more complicated equipment types (bags, filters, etc.) have many attributes that are challenging to align. Ultimately, four assemblies were found which are very close or identical to Amgen assemblies (Figure 11).

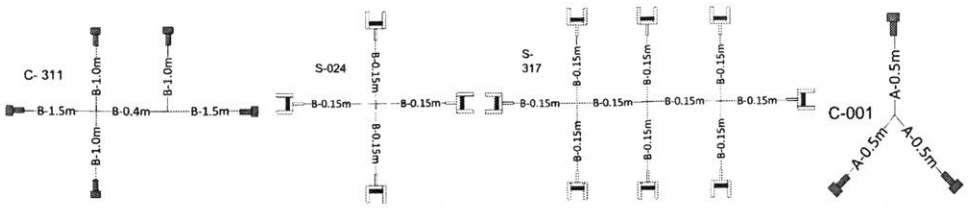


Figure 11. The Four SDD Transfer Assemblies Resembling Amgen SUS Assemblies

For each of the assemblies, the current price and lead time experienced by Amgen was obtained from SAP. Then, three SDD suppliers were contacted in order to obtain formal quotes on each of the assemblies. The results are shown in Table 13. Several observations can be made. First, with the exception of C-001, superior prices and lead times are available from at least one SDD supplier. Second, there are significant variations in price; this suggests either that there is a wide spectrum of supplier purchasing power and efficiency, and/or that some suppliers are used to non-competitive environments with healthy profit margins. Third, lead times tend to be much shorter with at least one SDD supplier as well. When multiple quotes are solicited from equally reputable suppliers, market dynamics suggest that the supplier with excess capacity (i.e. wants the business the most) will provide the most favorable terms. When materials are sole-sourced, the end-user loses all visibility of this potential benefit, instead hoping that the incumbent supplier is not overloaded and is incentivized to provide a competitive market price for its product.

Assembly	**C-311**	**S-024**	**S-317**	**C-001**
Current Price	$123	$426	$873	$32
Current Lead Time	11 weeks	12 weeks	12 weeks	4 weeks
Last Order Quantity	20	100	10	10
SDD Supplier #1 Price	$123	$213	$419	$65
SDD Supplier #2 Price	$191	$219	$442	$68
SDD Supplier #3 Price	$145	$257	$479	$99
SDD Supplier #1 Lead Time	4-6 weeks	4-6 weeks	4-6 weeks	4-6 weeks
SDD Supplier #2 Lead Time	10 weeks	10 weeks	10 weeks	10 weeks
SDD Supplier #3 Lead Time	6-10 weeks	6-10 weeks	6-10 weeks	6-10 weeks

Table 13. Comparison of Three SDD Supplier Quotes to Current Amgen Supplier

If Amgen had obtained competitive quotes on these four assemblies prior to the last order of each, the cost and lead time savings would have been substantial. Table 14 shows the aggregated value of the last orders for the four assemblies discussed above. Amgen paid a total of $132,680 for the last orders of these four assemblies. If they had instead selected the low bidder for each assembly (which includes the incumbent for C-001), they would have saved over $66,000, with the lead times cut in half. With annual spend on SUS on track to exceed $35 million in 2017 as per Figure 10, the potential COGS savings of this enhanced procurement strategy are apparent. In addition to increasing security of supply, the reduced lead times allow Amgen to reduce the working capital invested in SUS inventory, further expanding the economic advantages to obtaining competitive quotes on standardized assemblies.

Total Cost and Lead Time: Last Orders Only	**Cost**	**Lead Time (Average Weeks)**
Amgen Sole Supplier	$132,680	9.5
Competitive Quotes Through SDC	$65,980	4.75
Savings	$66,700	4.75
Savings %	49.7%	50.0%

Table 14. Analysis of Competitive Quote Effect on Last Orders of Four Assemblies

#3: The application of various modularity frameworks to an existing Amgen manufacturing process

One way to test the effectiveness of different approaches to modularity is to apply them to an existing process. The different strategies can then be ranked based on the number of unique assemblies required, total number of assemblies, connection time, variable cost per lot, and net present value. A relatively new, all-SUS process was selected, and five different levels of modularity were applied to all transfer assemblies, as follows:

Case 1, "Low Modularity": This is the base case, present scenario where nearly all assemblies are custom designed.

Case 2, "Medium Modularity": Switch to genderless connectors.

Case 3, "Medium Modularity with Increased Sterile Welding": Switch to genderless connectors, and implement sterile welding instead of connectors on certain assemblies.

Case 4, "High Modularity": Switch to genderless connectors, adopt standard tubing lengths, accept length variations of +/- 20% from current, build larger assemblies from smaller ones where possible, and accept some geometries as interchangeable (for example, tees and wyes).

Case 5, "High Modularity with Increased Sterile Welding": Switch to genderless connectors, adopt standard tubing lengths, accept length variations of +/- 20% from current, build larger assemblies from smaller ones where possible, and accept some geometries as interchangeable (for example, tees and wyes), and implement sterile welding instead of connectors on certain assemblies.

To conduct this study, the single-use diagrams (similar to piping & instrumentation diagrams (P&IDs) in traditional chemical engineering) were used to determine the type and quantity of transfer assemblies used per manufacturing lot of drug substance. From this data, the number and type of aseptic connections utilized was extracted, and the cost per assembly was obtained from SAP. Then, the modularity rules above were applied to the set of transfer assemblies. Some adapter assemblies became unnecessary with the switch to genderless connectors; the prior process had utilized various sizes of gendered connectors. In other cases, a similar assembly could be used in place of the incumbent with no impact on the process, eliminating more unique assemblies. In the scenarios with increased welding, straight extensions and other simple assemblies used the "weld or buy" calculator in Figure 9 to determine whether it would be advantageous to switch to welding in place of aseptic connectors. In cases with significant cost savings and acceptable impact to connection times, welding was substituted.

Several key assumptions also needed to be made. Consistent with the results of the aseptic connector failure rate study described previously, it was assumed that 1 out of every 215 aseptic connectors would fail and require a nonconformance report. This is a realistic penalty for highly modular systems, since they can require considerably more connectors. In addition, it was assumed that it takes two minutes to complete a gendered aseptic connection, and only 1.5 minutes for genderless. This is consistent with feedback received from Amgen's clinical manufacturing team. A sterile weld was assumed to take three minutes. Consistent with Table 2, an estimate of 92 hours to create a new raw material specification was used to calculate total manhours required. With all of the data and assumptions made, the variable cost per lot could be calculated as

$$Variable\ Cost\ Per\ Lot = Material\ Cost + Labor\ Cost + Nonconformance\ Cost$$

Since personnel time required (irrespective of labor cost) is also a key metric, assembly time and time spend on nonconformances was also calculated for each scenario. The results are shown below in Table 15.

	Unique Assemblies	Total Qty	Variable Cost	Assembly Time (hr)	NC Time (hr)	5-yr NPV vs. base case
Low Modularity (Base Case)	53	160	$ 64,100	6.8	55.7	$0
Medium Modularity (Welding)	49	152	$ 53,900	5.4	53.5	$3,100,000
Medium Modularity (No Welding)	52	157	$ 55,400	5.0	54.9	$2,660,000
High Modularity (No Welding)	37	229	$ 85,000	6.8	74.6	($6,340,000)
High Modularity (Welding)	34	153	$ 59,600	12.5	53.8	$1,360,000

Table 15. Results of Modularity Study of an Existing Amgen Process

This exercise results in a number of useful conclusions. Perhaps the most striking is that maximum modularity, while minimizing the number of unique assemblies, comes with significant disadvantages to assembly time required and total cost due mostly to the higher number of aseptic connectors and associated nonconformances. On the other hand, a moderate shift toward greater modularity provides the greatest financial benefit with only a small increase in fabrication time. Clearly, genderless connectors and targeted increases to sterile welding can have tangible benefits, but existing processes (such as this one) would have to consider whether these long-term benefits would outweigh the short-term difficulty of substantial design changes to a commercial manufacturing process. Finally, it should be emphasized that these frameworks were only applied to one part of a single Amgen process; were they adopted as guiding design principles across the company, positive effects could be substantially greater.

Discussion

Achieving the optimal level of SUS modularity – which undoubtedly means adopting more modular design principles than the status quo – has been shown to offer a variety of compelling advantages versus the highly customized design in use today. These can be summarized as follows:

Technical advantages

Perhaps the principal technical advantage of increased modularity is the opportunity to achieve higher quality oversight of SUS components and assemblies. By eliminating unusual or one-off components, Amgen can focus its quality oversight program on fewer suppliers. Instead of using assemblies from 30+ manufacturers with components from many more sub-suppliers, concentrating on SRE suppliers with a second tier of lower-volume, critical vendors gives Amgen the ability to conduct more frequent quality audits and establish closer working relationships.

A secondary technical advantage arises with increased sterile tube welding. Since welds are known anecdotally to leak at a reduced rate as compared to aseptic connectors, becoming more proficient at welding and adopting it as standard practice on a larger scale suggests that SUS processes would become more robust.

Balancing the technical advantages are the risks inherent to the tradeoff between exactly satisfying user requirements (as in a fully customized design paradigm) versus conforming the process to existing, off-the-shelf, or otherwise more modular assemblies. The Amgen teams responsible for SUS design – principally Engineering and Drug Substance Technologies – will need to ensure that shifting toward more modular assemblies doesn't compromise the requirements of each individual process.

Economic advantages

The economic advantages of shifting toward optimal modularity are even greater than the technical ones. One of the easiest cost-savings measures to implement is grouping of multiple IM material numbers under a single RMS. The RMS lifecycle requires a substantial amount of work from a diverse team of Amgen employees who have other core responsibilities. By combining multiple material numbers into a single specification and reducing the number of unique assemblies utilized, this process will become more efficient and has the potential to reduce headcount or allow participants to add value in other ways.

The second clear economic advantage to greater modularity is in reduction of inventory. As demonstrated in the cost-benefit analyses, pooling of safety stock of common assemblies between Amgen sites reduces overall

inventory requirements, potentially saving millions of dollars of working capital. In addition, the shorter lead times inherent to off-the-shelf assemblies further reduce inventory requirements.

Finally, by standardizing purchasing across Amgen manufacturing sites, and especially by adopting supplier standard assemblies, Amgen can realize a substantial reduction in its material costs related to SUS. This is especially true in situations where assemblies can be competitively bid to multiple suppliers.

Case Study #3 shows that taking modularity too far carries economic risk. By creating smaller, more generic assemblies, designers risk adding many more expensive aseptic connectors to the overall system, which increases both material cost and assembly time. Therefore, a balance must be struck between creating assemblies that are standardized enough to be used in multiple applications, but not so small that many more unique assemblies and connection points are required.

Strategic advantages

Increasing modularity also carries with it strategic advantages for Amgen manufacturing. In addition to the economic advantages previously discussed, sharing more common assemblies between sites provides greater assurance that quality concerns, storage issues, or supplier disruptions do not adversely impact commercial manufacturing. This makes it easier to uphold Amgen's flawless track record of providing their medicines to "every patient, every time."

Optimally modular SUS will enable faster startup of new facilities and expansion projects. SUS already enable more agile manufacturing by allowing facilities to quickly adapt to the size and configuration requirements of new processes while minimizing the purchase of new capital equipment. However, debottlenecking the SUS design and procurement process would decrease the time required to design and startup a facility by months. Then, utilization of off-the-shelf, standardized components and assemblies will decrease lead times for all orders of SUS going forward.

Finally, with fewer unique components, new technicians will have a reduced number of procedures for which they will need to achieve proficiency. This is especially true with aseptic connectors, for which operator aptitude is critical to maintaining integrity of the system. Since some processes have hundreds of new connections to make, preventing technicians from needing to switch between several types repeatedly should save substantial time.

Implementation Challenges

Making the transition from early-stage, exploratory SUS implementation to a more scalable, modular framework is difficult, particularly for large organizations like Amgen and its peers. While the benefits are clear, there are challenges ahead, including the following:

1. Implementing more modular SUS designs retroactively: the development of Amgen's existing, largely custom SUS assemblies is a sunk cost. Modifying these in any way will require more manhours to process change requests, especially from the SQM, Materials Science, and Manufacturing teams. There are also potential risks and delays to commercial manufacturing, which may outweigh the future benefits. If Amgen chooses only to implement more modular design practices moving forward, it will be easier in the short term, but some advantages (such as pooling between sites) won't be fully realized across the company.
2. Industry standardization on assemblies and common user requirements: SUS suppliers aren't incentivized to standardize assemblies with their competitors, which would commoditize their offerings and jeopardize exclusive supply agreements with end users like Amgen. While some suppliers are expanding their catalogued, standard offerings, these are still unique to each supplier. Therefore, the drive toward industry-wide modularity must come from the end users, and it is difficult to achieve the necessary collaboration on a large scale. One promising effort is the BioPhorum Operations Group (BPOG), which released a "Biomanufacturing Technology Roadmap" in 2017. This collaboration of many biotechnology and pharmaceutical companies came to the following conclusion:

   Modular manufacturing techniques have the potential to address several key issues facing the industry, such as the large capital expenditures required well in advance of demand, high inventory levels, long cycle times, the high cost of goods and the lack of flexibility in modifying facilities or adopting new technologies.[34]

   Having thus recognized the problem and benefits, hopefully BPOG will be able to influence industry-wide adoption of modular SUS design, to the advantage of all participants.
3. Maintaining material traceability with interchangeability: by making components (and even assemblies) more interchangeable, a risk is introduced that quality investigations will be more difficult to complete. For example, if two tubing formulations are deemed interchangeable and a supplier uses both to construct assemblies, isolating defects in one formulation may be difficult or impossible through Amgen's SAP system. Amgen is attempting to pre-empt this by introducing lot number traceability into PLM, but full implementation could be challenging.

4. Regulatory Limitations: The U.S. FDA and its counterparts around the world require regulatory filings with varying levels of specificity with respect to the equipment used to manufacture biologic drugs. For drugs currently in production, some filings call out single-use components by manufacturer and model number, usually for critical items such as bioreactor bags and filters. However, any system-wide attempt at modularity will have to ensure that the filings contain enough flexibility with respect to the components of interest that the changes can be made without an expensive and time-consuming filing amendment.

Conclusions

Single-use systems hold great promise for Amgen and the entire biopharmaceutical industry. Ultimately, shareholders and patients alike will benefit from the reduced cost of manufacturing and flexibility that they provide. Other industries have been challenged to successfully integrate innovative new technologies into their operations, and it is no different with SUS. As Amgen and its suppliers become more adept at manufacturing and utilizing SUS, usage will expand and understanding of best practices will no doubt mature. Attaining a more modular design framework is one of the most important milestones for SUS in the coming years.

This project assessed the current state of SUS manufacturing at Amgen in 2017, including identification of the root causes of the design proliferation that the company has experienced. After proposing changes to the various processes affecting the SUS lifecycle – including engineering design, supply chain, and manufacturing – these changes were tested using cost benefit analyses and case studies to determine their effectiveness at reducing material costs and manhours, while maintaining critical functionality. This holistic approach to SUS usage at Amgen leads to recommendations across five categories.

Recommendations

See also Appendix 3: Amgen Single-Use Systems Modularity Enablers Responsibility Matrix.

Design Process

1. Standardize single use diagrams across Amgen: There is no standard single-use diagram template and symbology at Amgen as of the time of writing. While one is being developed, various manufacturing sites still use their own versions. These diagrams are critical to allowing engineers to understand the available SUS across the Amgen network, including how they are utilized in other processes.
2. Require native, searchable PDFs of supplier drawings in EDMQ: At present, supplier drawings of SUS assemblies and components are typically manually scanned and not searchable. This makes the process of gathering detailed technical data about assemblies (especially for the purposes of evaluating suitability for another application) especially difficult. Amgen's procurement team should require suppliers to provide native, searchable PDF files as part of each Request for Proposal (RFP).
3. Modify the Single Use Design Guidelines to allow flexibility in design requirements: Currently, design requirements sent to vendors specify exact tubing lengths required. They also give no guidance on whether the supplier is permitted to replicate the functionality of the requested assembly with an off-

the-shelf equivalent or combination of off-the-shelf assemblies. Instead, allowing small length variations (for example, +/- 20%) and other small-scale changes gives suppliers enough leeway to possibly supply a standard assembly.

4. Appoint a project management role for each new SUS assembly: The Amgen SUS design and procurement process consists of responsibility handoffs between individuals and teams, without anyone ultimately accountable for ensuring that the lowest-cost, fastest, and highest-quality assembly has been procured. Appointing a single owner could lead to better results for these key performance indicators.

Genderless Connectors

1. Consider adopting a platform genderless connector for new Amgen SUS processes: genderless connectors proved more difficult to design in the early years of SUS, but have rapidly caught up and surpassed gendered connectors in terms of price and versatility. Adopting a platform genderless connector across several manufacturing sites will result in lower material costs, greater ability to share assemblies between sites, and simplify personnel training. It may also give Amgen more leverage over connector suppliers. This is perhaps the single most important enabler of greater SUS modularity.
2. Track failure rates of all aseptic connectors at Amgen: this is done inconsistently across the company, and better data in this area would help technical management select optimal platform connector(s) for new processes and to retrofit old processes.

Supply Chain

1. Require competitive sourcing when proprietary components aren't involved: many Amgen SUS assemblies are single-sourced at the discretion of the engineer, manufacturing site, or procurement team. Having recognized that Amgen is not price-sensitive, this give suppliers power to set prices much higher than their marginal cost. Losing a few bids on new assemblies should help establish within the marketplace that Amgen seeks to lower its material costs by leveraging the abilities of multiple trusted suppliers to provide similar or identical versions of many common assemblies.
2. Optimize global inventory requirements: this includes pooling safety stock of SUS between manufacturing sites and ordering more off-the-shelf assemblies to reduce lead times. The benefits of these strategies have been discussed in detail in cost/benefit analyses #4 and #5 as well as case study #2.

Sterile Welding

1. Recognize sterile welding excellence as a manufacturing goal: Amgen is already compelled to sterile weld some assemblies for a variety of reasons, but it is not considered a primary connectivity strategy. In addition, there is a spectrum of proficiency in welding across Amgen; some sites are fast and efficient with it, while others report large delays versus aseptic connectors, as well as doubts about weld integrity. Rolling out a program to increase welding skills across the company will provide future optionality to use sterile welding on a more widespread basis.
2. Trial the usage of gamma-irradiated tubing spools at a pilot plant: At least one of Amgen's peers routinely utilizes gamma-irradiated tubing spools and sterile welding in place of pre-cut assemblies with aseptic connectors. This strategy could save millions of dollars per year across the company. However, it is not without risks, and proper practice and procedures should be developed outside of a commercial setting.
3. Evaluate dissimilar welds between TPE formulations: At time of writing, no welds were routinely permitted between dissimilar TPE formulations. While ideally Amgen would reduce the number of unique formulations utilized, in the short term it would be easier to technically establish whether welds between various combinations are acceptable. This would likely require third-party testing and verification, but would give Amgen valuable perspective moving forward about this modularity-increasing option.
4. Track weld failure rates: Weld failures are not tracked as a dedicated category within the nonconformance system. More data on failures – leading to a deeper understanding of the causes – is required to enable continuous improvement in this area.

PLM

1. Populate PLM with bill of material and unit operation data: the early instances of PLM did not include any information about which manufacturing processes and unit operations utilize each assembly. For traceability and compatibility searching purposes, it is important that this functionality be developed.
2. Integrate PLM with supplier standard catalog offerings: As suppliers expand their off-the-shelf offerings, the best way for them to gain visibility with Amgen's design requestors and engineers is to periodically load them into Amgen's PLM system. That way, when searching for a suitable existing assembly within the Amgen network, Amgen technical staff may see that a new-to-Amgen but off-the-shelf option is available, instead of going through the customized design process. This should immediately result in time and cost savings.

Bibliography

1. Amgen. 2017 Form 10-K. 2017.
2. Springham DG. *Biotechnology: The Science and the Business*. 2nd ed. CRC Press; 1999.
3. American Chemical Society. Discovery and Development of Penicillin. https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html. Published 1999. Accessed July 20, 2005.
4. United States Supreme Court. Diamond v. Chakrabarty, 447 U.S. 303. 1980:No. 79-139. http://caselaw.findlaw.com/us-supreme-court/447/303.html.
5. Charles Schwab. Biotechnology Industry Summary. http://www.schwab.com. Published 2017. Accessed July 20, 2005.
6. Schiestl M, Zabransky M, Sörgel F. Ten years of biosimilars in Europe: Development and evolution of the regulatory pathways. *Drug Des Devel Ther*. 2017;11:1509-1515. doi:10.2147/DDDT.S130318.
7. Jacquemart R, Vandersluis M, Zhao M, Sukhija K, Sidhu N, Stout J. A Single-use Strategy to Enable Manufacturing of Affordable Biologics. *Comput Struct Biotechnol J*. 2016;14:309-318. doi:10.1016/j.csbj.2016.06.007.
8. Amgen Inc. The Shape of Drugs to Come. https://www.amgenscience.com/the-shape-of-drugs-to-come/. Published 2017. Accessed July 20, 2012.
9. Amgen. Good manufacturing practice for large molecules and small molecule medicines. http://www.amgenbiotech.com/resources/Good_Manufacturing_Practice_Infographic.pdf. Accessed August 1, 2017.
10. Eibl D, Eibl R, Löffelholz C, et al. *Disposable Bioreactors II.*; 2014. doi:10.1007/978-3-642-45158-4.
11. Martin J. A Brief History of Single-Use Manufacturing. 2017:209087. http://www.biopharminternational.com/brief-history-single-use-manufacturing.
12. Novais JL, Titchener-Hooker NJ, Hoare M. Economic comparison between conventional and disposables-based technology for the production of biopharmaceuticals. *Biotechnol Bioeng*. 2001;75(2):143-153. doi:10.1002/bit.1182.
13. Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States. *Jama*. 2016;316(8):858. doi:10.1001/jama.2016.11237.
14. Yeo D. Amgen unveils next-generation biomanufacturing facility in Singapore. Future Ready Singapore. https://www.futurereadysingapore.com/2014/amgen-unveils-next-generation-biomanufacturing-facility-in-singapore.html. Published 2014. Accessed June 1, 2017.
15. Niazi SK. Environmental Concerns. In: *Disposable Bioprocessing Systems*. CRC Press; 2011:203-236. doi:doi:10.1201/b11472-13.
16. Cox S, Lim J, Leveen L, Sinclair A, Monge M. The Environmental Impact of Disposable Technologies. *BioPharm Int*. 2008. http://www.biopharminternational.com/environmental-impact-disposable-technologies?id=&pageID=1&sk=&date=.

17. Sartorius Stedim Biotech. *Environmental Impact of Single-Use Technologies*. https://www.sartorius.com/mediafile/Broch_Environmental_Impact_S--1508-e.pdf.

18. Colder Products. AseptiQuik G. https://www.cpcworldwide.com/Product-List/Series/111. Published 2017.

19. Sartorius Stedim Biotech. OPTA SFT. http://microsite.sartorius.com/single-use-technology/products/opta-sft.html. Published 2017.

20. GE Life Sciences. Xcellerex XDR-50 to 2000 Single-Use Bioreactor. www.gelifesciences.com. Published 2017. Accessed June 1, 2017.

21. Nordlund M, Kim S-G, Tate D, Lee T, Oh L. Axiomatic Design: Making the Abstract Concrete. In: Elsevier B.V.; 2016.

22. Ulrich K. The role of product architecture in the manufacturing firm. *Res Policy*. 1995;24(3):419-440. doi:10.1016/0048-7333(94)00775-3.

23. Starr MK. Modular Production - A New Concept. *Harv Bus Rev*. 1965;43(November-December):131-142.

24. Tung K. MODULARITY AND COMPONENT SHARING AS A PRODUCT DESIGN. 1991.

25. Nuffort MR. Managing Subsystem Commonality. 2001.

26. Callahan S, Heisserman BJ. A Product Representation to Support Process Automation.

27. ASTM. E3051-16: Standard Guide for Specification , Design , and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and. 2009;i:1-5. doi:10.1520/E3051-16.

28. Repetto R. *Technical Report No. 66: Application of Single-Use Systems in Pharmaceutical Manufacturing.*; 2014.

29. Vogel JD, Eustis M. The Single-Use Watering Hole: Where Innovation Needs Harmonization, Collaboration, and Standardization. *Bioprocess Int*. 2015;13(1):1-12.

30. Wolton D, Heaven L, McFeaters S, Kodilkar M. Standardization of Disposables Design: The Path Forward for a Potential Game Changer. 2015;13(11):21-23.

31. Andrews T. The standardization of single-use components for bioprocessing. 2017;(Whitepaper 7003). https://content.cpcworldwide.com/Portals/0/Library/Resources/Literature/WhitePapers/Documents/CPC_WhitePaper_standardization_of_single-use_components.pdf.

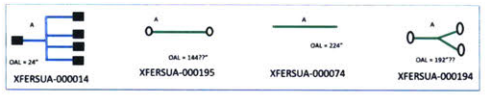
32. Alfano EJ. Reducing Complexity in Biomanufacturing Operations Through Single-Use Assemblies. 2012.

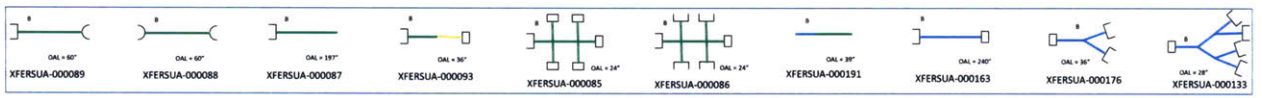
33. Kress DE. Modeling and Economic Evaluation of Early Stage Clinical Monoclonal Antibody Manufacturing Using Single Use Technology. 2015.

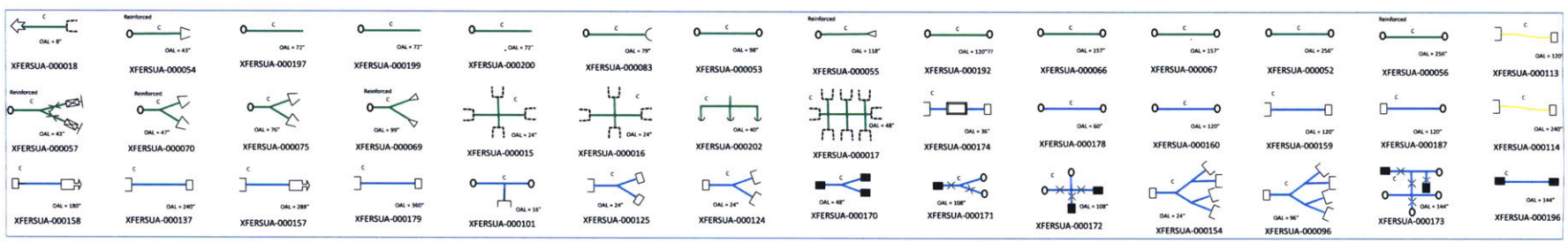
34. BioPhorum Operations Group. *Biomanufacturing Technology Roadmap.*; 2017. https://www.biophorum.com/wp-content/uploads/2017/06/Executive-Summary.pdf.

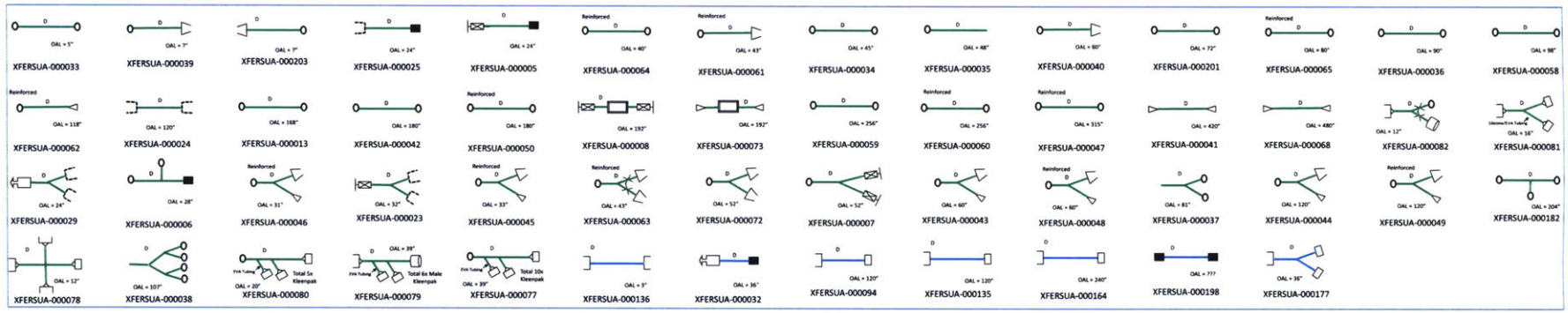
Appendix 1: Transfer Assembly Visual Library

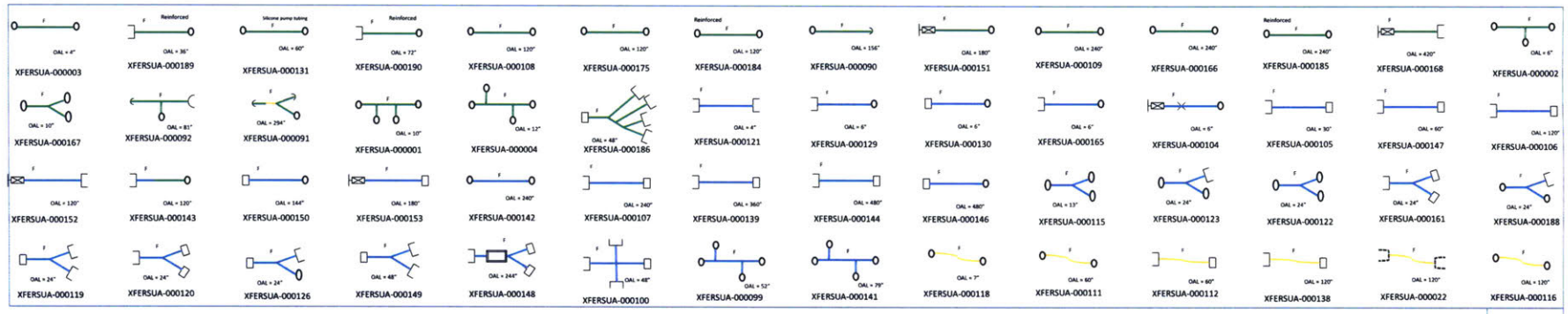
Appendix 1


XFERSUA-000014
XFERSUA-000195
XFERSUA-000074
XFERSUA-000194

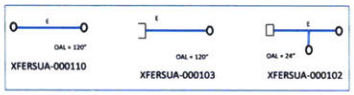

XFERSUA-000089
XFERSUA-000088
XFERSUA-000087
XFERSUA-000093
XFERSUA-000085
XFERSUA-000086
XFERSUA-000191
XFERSUA-000163
XFERSUA-000176
XFERSUA-000133

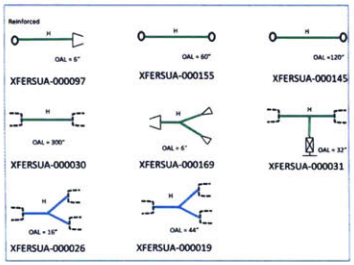

XFERSUA-000018
XFERSUA-000054
XFERSUA-000197
XFERSUA-000199
XFERSUA-000200
XFERSUA-000083
XFERSUA-000053
XFERSUA-000055
XFERSUA-000192
XFERSUA-000066
XFERSUA-000067
XFERSUA-000052
XFERSUA-000056
XFERSUA-000113
XFERSUA-000057
XFERSUA-000070
XFERSUA-000075
XFERSUA-000069
XFERSUA-000015
XFERSUA-000016
XFERSUA-000202
XFERSUA-000017
XFERSUA-000174
XFERSUA-000178
XFERSUA-000160
XFERSUA-000159
XFERSUA-000187
XFERSUA-000114
XFERSUA-000158
XFERSUA-000137
XFERSUA-000157
XFERSUA-000179
XFERSUA-000101
XFERSUA-000125
XFERSUA-000124
XFERSUA-000170
XFERSUA-000171
XFERSUA-000172
XFERSUA-000154
XFERSUA-000096
XFERSUA-000173
XFERSUA-000196

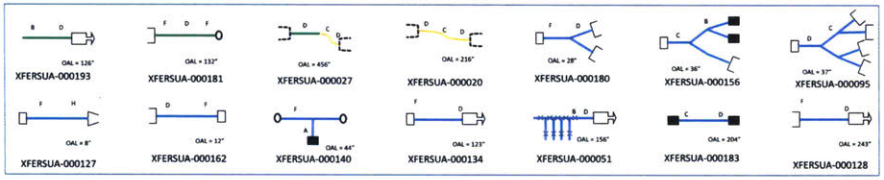

XFERSUA-000033
XFERSUA-000039
XFERSUA-000203
XFERSUA-000025
XFERSUA-000005
XFERSUA-000064
XFERSUA-000061
XFERSUA-000034
XFERSUA-000035
XFERSUA-000040
XFERSUA-000201
XFERSUA-000065
XFERSUA-000036
XFERSUA-000058
XFERSUA-000062
XFERSUA-000024
XFERSUA-000013
XFERSUA-000042
XFERSUA-000050
XFERSUA-000008
XFERSUA-000073
XFERSUA-000059
XFERSUA-000060
XFERSUA-000047
XFERSUA-000041
XFERSUA-000068
XFERSUA-000082
XFERSUA-000081
XFERSUA-000029
XFERSUA-000006
XFERSUA-000046
XFERSUA-000023
XFERSUA-000045
XFERSUA-000063
XFERSUA-000072
XFERSUA-000007
XFERSUA-000043
XFERSUA-000048
XFERSUA-000037
XFERSUA-000044
XFERSUA-000049
XFERSUA-000182
XFERSUA-000078
XFERSUA-000038
XFERSUA-000080
XFERSUA-000079
XFERSUA-000077
XFERSUA-000136
XFERSUA-000032
XFERSUA-000094
XFERSUA-000135
XFERSUA-000164
XFERSUA-000198
XFERSUA-000177


XFERSUA-000003
XFERSUA-000189
XFERSUA-000131
XFERSUA-000190
XFERSUA-000108
XFERSUA-000175
XFERSUA-000184
XFERSUA-000090
XFERSUA-000151
XFERSUA-000109
XFERSUA-000166
XFERSUA-000185
XFERSUA-000168
XFERSUA-000002
XFERSUA-000167
XFERSUA-000092
XFERSUA-000091
XFERSUA-000001
XFERSUA-000004
XFERSUA-000186
XFERSUA-000121
XFERSUA-000129
XFERSUA-000130
XFERSUA-000165
XFERSUA-000104
XFERSUA-000105
XFERSUA-000147
XFERSUA-000106
XFERSUA-000152
XFERSUA-000143
XFERSUA-000150
XFERSUA-000153
XFERSUA-000142
XFERSUA-000107
XFERSUA-000139
XFERSUA-000144
XFERSUA-000146
XFERSUA-000115
XFERSUA-000123
XFERSUA-000122
XFERSUA-000161
XFERSUA-000188
XFERSUA-000119
XFERSUA-000120
XFERSUA-000126
XFERSUA-000149
XFERSUA-000148
XFERSUA-000100
XFERSUA-000099
XFERSUA-000141
XFERSUA-000118
XFERSUA-000111
XFERSUA-000112
XFERSUA-000138
XFERSUA-000022
XFERSUA-000116

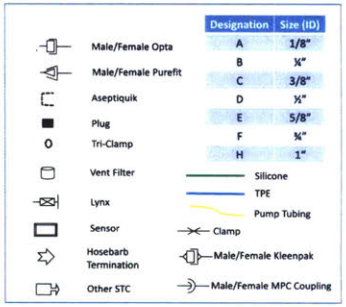

XFERSUA-000117


XFERSUA-000110
XFERSUA-000103
XFERSUA-000102


XFERSUA-000097
XFERSUA-000155
XFERSUA-000145
XFERSUA-000030
XFERSUA-000169
XFERSUA-000031
XFERSUA-000026
XFERSUA-000019


XFERSUA-000193
XFERSUA-000181
XFERSUA-000027
XFERSUA-000020
XFERSUA-000180
XFERSUA-000156
XFERSUA-000095
XFERSUA-000127
XFERSUA-000162
XFERSUA-000140
XFERSUA-000134
XFERSUA-000051
XFERSUA-000183
XFERSUA-000128


XFERSUA-000076
XFERSUA-000028


Male/Female Opta
Male/Female Purefit
Aseptiquik
Plug
Tri-Clamp
Vent Filter
Lynx
Sensor
Hosebarb Termination
Other STC
Silicone
TPE
Pump Tubing
Clamp
Male/Female Kleenpak
Male/Female MPC Coupling
Designation
Size (ID)
A 1/8"
B ¼"
C 3/8"
D ½"
E 5/8"
F ¾"
H 1"

Appendix 2: Raw Material Specification and Inventory-Managed Material Grouping Manual

PURPOSE

This manual is part of Amgen's Single-Use Systems (SUS) Design Management program. It provides guidance to the SUS design triage team for proposing grouping single-use, inventory-managed raw materials (IM Materials) under Raw Material Specifications (RMS). RMS define Amgen's requirements for the material, and are maintained in the Electronic Data Management – Quality (EDMQ) system, a Good Manufacturing Practice (GMP) information management system. An IM material is directly purchased from a supplier by Amgen, and purchase orders and inventory are maintained in the SAP system. The most specific identifier of each material is the ZHE1 number; this corresponds 1:1 with a manufacturer part number, and in cases of functional equivalence, two or more ZHE1 numbers can share a single IM number.

The SUS design triage team meets weekly, and for each new raw material, the team should reference this document to determine whether a new specification should be recommended. During specification development, the Supplier Quality Management (SQM) team will review the grouping recommendation of the SUS design triage team and will decide whether to accept it. Proper application of inventory-managed material grouping should minimize RMS proliferation, maximize SUS library searchability, and enable efficient supply chain strategies such as dual sourcing.

ROLES

Role	Responsibility
SUS Design Triage Reviewer	• Advise on decision to create a new RMS or classify the new IM material under an existing RMS • Determine functional equivalence of two different assemblies
Supplier Quality Management (SQM)	• Review IM Material specification grouping recommendation from SUS design triage team and decided whether to accept or reject

RESOURCES

The following internal documents provide additional information about the Manual's business process/topic:

Document	Title
FORM-105442	Single-Use System (SUS) Design Requirements
FORM-105443	Single-Use Design Review Report
MAN-003635	Early Engagement Process
SOP-001212	Material Classification
SOP-001449	Raw Material Specification Lifecycle: Creation, Revision & Obsoletion
STND-001417	Single-Use System (SUS) Design Process

GENERAL INFORMATION

Definitions

Term	Definition
IM Material Number	Unique identifier for materials purchased from vendors. Assigned by SAP. If a single-use item has an IM Material Number, it must be classified as a SUA in PLM, not an SUC.
Raw Material Specification (RMS)	GMP document stored in EDMQ which contains information about one or more IM Material Numbers.

Abbreviations

Abbreviation	Definition
BOM	Bill of Materials
EDMQ	Electronic Data Management - Quality
ETA	Engineering Technical Authority
GMP	Good Manufacturing Practice
PLM	Product Lifecycle Management
RMS	Raw Material Specification
SAP	Systems Applications and Products
SKU	Stock Keeping Unit
SQM	Supplier Quality Management
SUA	Single-Use Assembly
SUC	Single-Use Component
SUS	Single-Use System(s)

TABLE OF CONTENTS

MANUAL

IM MATERIAL GROUPING – BY PLM SUBCATEGORY

1. Bag Assemblies

1.1 Grouping Criteria

1.1.1 Same bag film and/or configuration

1.2 Attributes Allowed to Vary Within an RMS

1.2.1 Size / bag volume

1.2.2 Connector Type

1.2.3 Assembly and/or Bag Manufacturer

1.2.4 Tubing Type

1.3 Attributes Requiring Separate RMS

1.3.1 Different quality requirements

1.3.2 Different hardware compatibility (bag holder, mixer)

2. Transfer Assemblies

2.1 Grouping Criteria

2.1.1 For Tubing, Same Internal Diameter / External Diameter

2.1.2 Same Geometry Type (Wye/Cross/Tee etc.)

2.2 Attributes Allowed to Vary Within an RMS

2.2.1 Tubing Length

2.2.2 Manufacturer

2.2.3 Connection Types

2.2.4 Silicone Tubing Formulation

2.3 Attributes Requiring Separate RMS

2.3.1 Different quality requirements

2.3.2 Different TPE Formulations

2.3.3 Different Tubing Reinforcement

3. Filter Assemblies

3.1 Grouping Criteria

3.1.1 Same Primary Membrane Pore Size

3.2 Attributes Allowed to Vary Within an RMS

3.2.1 Filter Length

3.2.2 Connector Type

3.2.3 Filter Type (if functional equivalence is established)

3.2.4 Prefiltration

3.2.5 Filter Model

3.3 Attributes Requiring Separate RMS

3.3.1 Different quality requirements

4. Rigid Vessel Assemblies

4.1 Grouping Criteria

4.1.1 Container Material

4.1.2 Container Type (Bottle, Carboy, etc.)

4.2 Attributes Allowed to Vary Within an RMS

4.2.1 Container Size

4.2.2 Connector Type

4.2.3 Manufacturer

4.2.4 Tubing Length

4.2.5 Tubing Type

4.3 Attributes Requiring Separate RMS

4.3.1 Different quality requirements

5. Sampling Assemblies

5.1 Grouping Criteria

5.1.1 Sampling Method Type

5.1.2 Sampling Container Type

5.2 Attributes Allowed to Vary Within an RMS

5.2.1 Needle Size

5.2.2 Bag Size

5.2.3 Number of Containers

5.3 Attributes Requiring Separate RMS

5.3.1 Different quality requirements – these are especially important for sampling assemblies due to their ability to affect testing outcomes

5.3.2 Material of Construction

6. Filling Assemblies

6.1 Grouping Criteria

6.1.1 Same Manufacturer

6.2 Attributes Allowed to Vary Within an RMS

6.2.1 Number of Filling Lines

6.2.2 Surge Bag Volume

6.2.3 ID/OD of Needle

6.3 Attributes Requiring Separate RMS

6.3.1 Different quality requirements

7. Other Assemblies

7.1 Grouping Criteria

7.1.1 Provide Justification

7.1.2 Same Item Type and Manufacturer are candidate for grouping

7.2 Attributes Allowed to Vary Within an RMS

7.2.1 Size

7.3 Attributes Requiring Separate RMS

7.3.1 Different quality requirements

SINGLE-USE COMPONENT GROUPING – FOR BULKSUC ITEMS

1. Bulk Components

1.1 Connectors

1.1.1 Grouping Criteria

1.1.1.1 Same Manufacturer

1.1.1.2 Same Connector Model

1.1.2 Attributes Allowed to Vary Within an RMS

1.1.2.1 Gender

1.1.2.2 Size

1.1.2.3 Hosebarb Connector Geometry

1.1.3 Attributes Requiring Separate RMS

1.1.3.1 Different Quality Requirements

1.2 Filters

1.2.1 Grouping Criteria

1.2.1.1 Same Manufacturer

1.2.1.2 Same Filter Format

1.2.1.3 Same Pore Size

1.2.2 Attributes Allowed to Vary Within an RMS

1.2.2.1 Filter Size

1.2.3 Attributes Requiring Separate RMS

1.2.3.1 Different Quality requirements

1.3 Needles

1.3.1 Grouping Criteria

1.3.1.1 Same Quality Requirements

1.3.2 Attributes Allowed to Vary Within an RMS

1.3.2.1 Size

1.3.3 Attributes Requiring Separate RMS

1.3.3.1 Different Quality Requirements

1.4 Sensors

1.4.1 Grouping Criteria

1.4.1.1 Same Manufacturer

1.4.1.2 Same Type of Measurement

1.4.2 Attributes Allowed to Vary Within an RMS

1.4.2.1 Flow Path Size (Internal Diameter)

1.4.2.2 Measurement Range

1.4.3 Attributes Requiring Separate RMS

1.4.3.1 Different Quality Requirements

1.5 Tubing

1.5.1 Grouping Criteria

1.5.1.1 Same Formulation/Durometer

1.5.2 Attributes Allowed to Vary Within an RMS

1.5.2.1 Length,

1.5.2.2 Inner Diameter

1.5.2.3 Outer Diameter

1.5.3 Attributes Requiring Separate RMS

1.5.3.1 Different Quality Requirements

1.6 Rigid Vessels

1.6.1 Grouping Criteria

1.6.1.1 Same Type

1.6.1.2 Same Material of Construction

1.6.2 Attributes Allowed to Vary Within an RMS

1.6.2.1 Size

1.6.3 Attributes Requiring Separate RMS

1.6.3.1 Different Quality Requirements

1.7 Components with No Grouping Criteria

1.7.1 Bag Chambers

1.7.2 Ports

1.7.3 Tubing Retainers/Clamps

1.7.4 Overmolded/welding Subassemblies

1.8 Attributes Requiring Separate RMS

1.8.1 Different quality requirements

CHANGE SUMMARY

Change	Justification
Document creation	Guidance required for SUS Triage team to consistently group IM materials under Raw Material Specifications.

Appendix 3: Single-Use Systems Modularity Enablers Responsibility Matrix

Appendix 3: SUS Modularity Enablers Responsibility Matrix

	Responsibility								
Change	**SQM**	**Mat. Sci.**	**ETA**	**DS Tech**	**Mfg**	**OLT**	**GSS**	**RMD**	**PLM**
Design Process									
Standardize Single Use Diagrams Across Amgen			X	X	X				
Require native, searchable PDFs of supplier drawings for EDMQ	X								
Modify Single Use Design Guide to consider whether requested assembly can be constructed from a combination of existing custom and/or off-the-shelf designs			X						
Modify Single Use Design Guide to recommend accepting a length difference of +/- 20% from the initially proposed length if it allows use of an existing assembly in place of a new one			X						
Update SUS Design Requirements to indicate preference for off-the-shelf SUS when available			X						
Use Trackwise workflow capabilities to rigorously manage spec development process	X								
Take a "project management" type of role in SUS design/procurement, leading the process from start to finish and integrating all of the various and sometimes competing priorities (user requirements, competitive bidding, lead time and urgency, ensuring timely spec development, etc.). Use PLM as project management tool (dashboard, metrics etc)								X	
Genderless Connectors									
Commit to switching one or more processes to genderless connectors			X		X				
Review SUDs and identify impacted assemblies				X	X				
Initiate all required change requests	X				X				
Provide training from connector vendor to Amgen manufacturing staff					X			X	
Track connector failure data and continuously review pain points. Explore opportunities to automate - integration with SAP inventory mgmt.	X				X			X	
Supply Chain									
Require design request submission to minimum of three suppliers unless a proprietary component is involved							X	X	
Optimize global inventory requirements								X	
Sterile Welding									
Recognize sterile welding excellence as a manufacturing goal					X				
Create internal Amgen welding working group to share best practices across sites			X		X				
Trial gamma-irradiated tubing spools at pilot plant		X	X	X					
Evaluate C-Flex/Pharmed/Pureweld dissimilar welds to enhance modularity		X							
Perform cost-benefit analyses of individual TPE assemblies to determine welding viability				X					
Standardize tube welder preventative maintenance					X				
PLM									
Populate PLM with BOM / Unit Operation Data				X					X
Integrate PLM with vendor standard catalog SUS offerings									X
Create ability to export visual library of SUS assemblies for searchability									X