Facilitating Adoption of Continuous Manufacturing Platforms in the Pharmaceutical Industry

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Submitted to the System Design and Management Program in partial fulfillment of the requirements for the degree of

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Abstract

Continuous manufacturing (CM) of pharmaceutical products has gained a great deal of interest over the past decade. CM promises multiple benefits to all pharmaceutical industry stakeholders; however, pharmaceutical manufacturers generally have been slow to invest in the technology and even slower to transition their manufacturing operations from batch even when a CM process would make the most sense. This thesis intends to drive the implementation of CM to augment batch manufacturing, allowing for a wider array of manufacturing tools in the pharmaceutical manufacturing enterprise by using a system-focused approach in developing a change system for small molecule pharmaceutical manufacturing, with the emergent property of an actionable framework based on systems architectural design that manufacturers can use. This research will employ the Architecting Innovative Enterprise Strategy (ARIES) Framework[1] to illustrate the current and future landscapes of the pharmaceutical manufacturing enterprise. First, the problem space, specifically the environment that impacts the pharmaceutical manufacturing enterprise including stakeholders and governing agencies, will be described. Second, the envisioned future for the drug manufacturing enterprise in which the enterprise adopts CM as a dominant manufacturing process as opposed to solely batch manufacturing is examined. Finally, a framework is synthesized for the transition to CM in the pharmaceutical manufacturing enterprise derived from ARIES elements (strategy, process, organization, knowledge, products, services, information, infrastructure) nested in the previously described ecosystem and stakeholders. This framework will not be prescriptive, but also is intended to be adapted for each company's unique business model and operational circumstances.

Thesis Supervisor: Timothy F. Jamison

Title: Robert R. Taylor Professor of Chemistry

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Chapter 1 Introduction

This chapter contains background on the motivation behind propelling the technology transition of continuous flow chemical synthesis (a subset of continuous manufacturing (CM)) to the pharmaceutical manufacturing enterprise with the goal of revolutionizing and eventually democratizing drug manufacturing. First, the research questions to be answered are addressed, and the intended approach to answering those questions is described. Next, the scope of the research and intended body of knowledge contribution is laid out. Finally, the overall structure of the thesis is summarized to help guide the reader in the evolution of the research project.

1.1 Motivation and Intent

The motivation of this research is to facilitate and hasten the adoption of continuous flow chemical synthesis, or continuous manufacturing (CM) (used interchangeably throughout this text) by pharmaceutical manufacturers as a means to realize the multiple stakeholder benefits CM offers. The implementation of CM introduces a number of externalities from safety and efficacy concerns, to supply chain protection, reduced cost of goods sold (COGS), or enhanced compliance with corporate social responsibility (CSR) principles, and through categorizing these emergent functions, the impacts of ubiquitous CM can be better understood. This would require a paradigm shift for the pharmaceutical manufacturing enterprise.

Ultimately, ubiquitous implementation of CM in pharmaceutical production will lay the groundwork for a revolution in drug access. This thesis defines the pharmaceutical manufacturing industry as an enterprise and will apply systems and enterprise architecting techniques to deliver CM technology adoption strategies in

the form of a socio-technical system. This thesis will construct a future enterprise architecture that facilitates pharmaceutical manufacturers to transition their batch production operations to CM should CM make the most sense for the product production. As such, this thesis will focus on the following objectives:

1. Investigate the current state of CM through multiple perspectives and how it can translate to the pharmaceutical manufacturing enterprise.
2. Analyze the barriers to adoption of CM within the current pharmaceutical industry enterprise.
3. Develop a framework for pharmaceutical industry CM implementation using system architecture.

1.2 Research Questions

This thesis is focused on a single research question, but that question can be further decomposed as seen below:

How can we bridge the gap between continuous manufacturing technology and adoption in the pharmaceutical industry?

1. What need does this technology provide for the beneficiaries?
2. How can CM platforms fit into the FDA regulatory framework so that there is a comprehensive process that allows for future enterprise innovation in manufacturing?
3. Are there risk reduction strategies the CM platform manufacturers and/or the government can employ to reduce enterprise hesitation on technology adoption?

1.3 Research Approach

Implementing CM in pharmaceutical manufacturing has been challenging, because drug companies are hesitant to switch from a technology that has a century of proven reliability to a new technology that brings with it uncertainty in profitability and regulatory considerations. However, it is well established that CM implementation can improve efficiency, agility, and flexibility of pharmaceutical manufacturing.[2] The best way to help facilitate adoption would be to reduce ambiguity in the implementation of this technology, and an actionable framework will be the method used to achieve this outcome. This framework will be constructed as a sociotechnical system using systems and enterprise architecture techniques.

This thesis will devise an adaptable framework for adoption of CM by pharmaceutical manufacturers. Architecting Innovative Enterprise Strategy (ARIES) Framework is used to understand the current and probable pharmaceutical manufacturing enterprise environment, and a concept of operations is developed based on the ARIES principles. To develop the framework, systems architecture will be employed in various forms. First, the sociotechnical system (adoption framework) is defined, and a system problem statement is crafted to help structure the research space i.e., the intended technology transition system. Next, system architecture techniques are used to build the technology transition framework. Finally, systems thinking techniques are used to produce the emergent function—actionable methods aimed at pharmaceutical companies to begin to adopt CM in drug manufacturing. These techniques include a sociotechnical systems approach involving literature

review, organization structure and stakeholder analysis, CONOPS, and eventually a relevant corporate strategy using upstream and downstream influences.

1.4 Research Scope

The scope of this thesis is focused on a strategic roadmap to facilitate the adoption of continuous flow chemical synthesis into the pharmaceutical manufacturing enterprise. This work will focus on CM for small molecule products. While the pharmaceutical industry is steadily moving toward increasing amounts of biologically derived medicines, the CM processes, particularly the Process Analytical Technology (PAT) required, is beyond the scope of this thesis. The scope will therefore touch on the FDA approval process of small molecule drug approvals (NDA or ANDA) with a focus on if the approval process can be more adaptive to future pharmaceutical manufacturing innovations. This work will attempt to address gaps in the approval process that pigeonhole drug manufacturing technology to a single concept of good manufacturing processes in the hopes of eventually democratizing the drug manufacturing process. This work will not encompass personalized or broadly decentralized CM operations as this thesis hopes to be a first step towards that eventual realization.

Because a handful of CM produced small molecules have been given FDA approval,[3] this work is intended to build on their momentum and learn from their example by treating their adoption model as a legacy element to build a CM adoption sociotechnical system off of. Also, the scope will include how the flow synthesis platform manufacturers can help facilitate the transfer using a risk reduction strategy to enable a more forceful technology push. This will also require a deep dive

into technology transition techniques and investigation of the technology readiness level of flow synthesis particularly for drug manufacturing. Additionally, this work will focus on utilizing the regulatory willingness in conjunction with the technology push from platform manufacturers to frame an adoption strategy pharmaceutical companies can use to make the business case for CM implementation. Finally, this work will examine the educational skills gap that exists in the synthetic process design and operation of flow platforms, and how this could be used as a lever to achieve the ultimate goal of this work- facilitate adoption of CM by pharmaceutical manufacturers.

1.5 Research Contribution

This thesis contributes to the management research on technology transition by developing a framework that the pharmaceutical industry can employ to begin to adopt continuous flow synthetic capabilities into their drug manufacturing processes. The contributions of this research will be twofold. First, the main goal is to provide an actionable roadmap for pharmaceutical manufacturers to transition their processes given the numerous benefits of CM. Second, the thesis will build on the body of technology transition and adoption knowledge to help propel new technology adoption and minimize stagnation in a multitude of industries.

1.6 Thesis Structure

The pharmaceutical manufacturing enterprise and continuous manufacturing, specifically flow synthesis, is examined via literature review. This is followed by a market analysis of CM in pharmaceutical manufacturing, barriers to technology adoption, and potential benefits. Culminating in a framework built through systems

architecture techniques to address CM adoption issues in the pharmaceutical industry and provide a vision for a new pharmaceutical manufacturing enterprise.

1.6.1 Thesis outline

Chapter 1: Introduction- Describes background research, objectives, motivation, and approach.

Chapter 2: Literature Review- Introduces continuous flow synthesis, pharmaceutical manufacturing enterprise, and how CM technologies would benefit multiple pharmaceutical industry stakeholders. A specific barrier to CM adoption-flow synthesis education/skills gap-is discussed.

Chapter 3: Research Methodology- Discusses the systems thinking and design techniques to be utilized in the construction of the technology transfer framework. Gives a detailed description of ARIES framework and how it will be the tool used to construct the socio-technical system of the technology transfer framework.

Chapter 4: Enterprise Background, Landscape, and Stakeholder Analysis- Draws on systems thinking techniques to develop an architecture of the technology transition from bulk to continuous flow pharmaceutical manufacturing.

Chapter 5: Current and Intended Future Enterprise Architecture: Transitions from information gathering to deriving a solution for CM adoption.

Chapter 6: Technology Transition Framework- Based on the ARIES framework, the sociotechnical system of a technology transition framework for CM is described. Describes the new enterprise architecture that would facilitate CM adoption. Highlights the strategies for CM adoption via the new architecture.

Chapter 7: Overview of how the system has generated the new architecture along with implementation strategies. Discussion of future research opportunities to continue to implement CM in the pharmaceutical manufacturing enterprise.

Chapter 2: Literature Review

In this chapter, the terms enterprise and enterprise strategy are defined along with the introduction of the ARIES process model. The history of continuous flow synthesis is discussed, and how continuous flow synthesis would be beneficial to pharmaceutical manufacturing. A brief description of the current pharmaceutical manufacturing industry is reviewed along with the regulatory framework the industry is required to adhere to. Finally, the education and training gap that exists in flow synthesis design and operation is highlighted.

2.1 Enterprise Definition and Description

An enterprise is defined by Nightingale and Rhodes as an entity that exhibits the following characteristics: people who **generate value** through production for others; a system that **has a purpose**; a system that **benefits** as part of a larger system network; and a system that will periodically **undergo change**.[1] This definition fits the pharmaceutical manufacturing industry well, because the drug products generated by the industry are intended to **benefit health and wellbeing**; the pharmaceutical manufacturer's **purpose is to produce and sell drug products**; the manufacturers **benefit from the larger pharmaceutical industry** in that the industry designs, develops, and improves existing drug products; and the manufacturing enterprise has seen **many changes** from small molecule production to extensively engineered macromolecules such as monoclonal antibodies. Therefore, the enterprise described

in this work will be in reference to the pharmaceutical manufacturing industry. Specifically, when required for the ARIES model, a generic pharmaceutical company will be used as a proxy to illustrate a path for specific manufacturing companies.

An enterprise is a complex system of systems, and to fully understand a particular enterprise it must be analyzed piece-by-piece. Therefore, throughout this thesis, the pharmaceutical manufacturing enterprise will be examined through multiple lenses as laid out in the ARIES framework.[1] The ten element model used by the ARIES framework (**Figure 1**) is an excellent method for reducing the complexity of the enterprise and providing a systematic way to generate a wholistic view of the current and future enterprise. However, merely identifying and describing these elements for an enterprise will not provide the fully developed landscape for the enterprise. Many elements can be intertwined, and these entanglements need to be understood to grasp the full picture of the enterprise and subsequently develop the enterprise strategy.

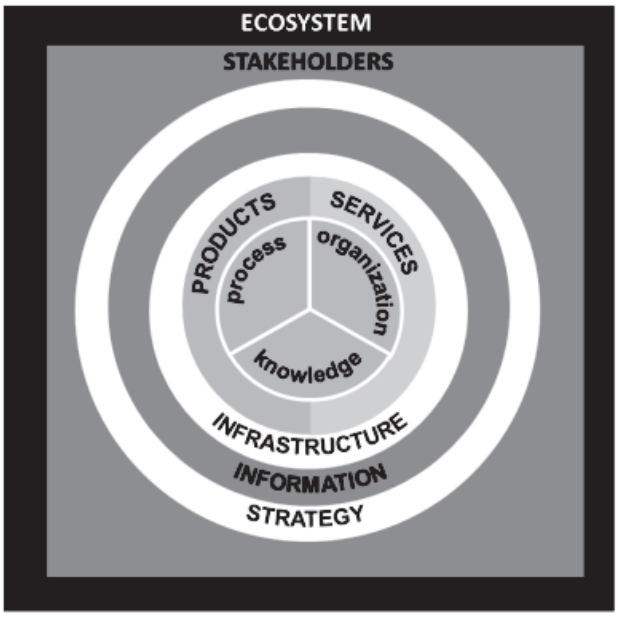

Figure 1 *Ten elements used to evaluate an enterprise using the ARIES model. Reprinted from" Architecting the Future Enterprise"*

Enterprise strategy is, quite simply, "the overarching strategy of the enterprise."[1] As with all strategies, the enterprise strategy guides the enterprise through current and future endeavors and frames what the enterprise ultimately embodies day in and day out. For example, the Department of Defense (DoD) publishes the National Security Strategy (NSS) annually which lays out what the president sees as the future of the DoD—where the DoD needs to be, how it can be achieved, and why this future is crucial to national security. As an enterprise, the DoD is guided by the NSS to deliver value to its stakeholders, American Citizens. The DoD delivers this value by utilizing its inherent capabilities as an enterprise and contributing to the security and safety of the nation. Implementing a new or

updating a current enterprise strategy can be accomplished through the ARIES process model.

Nightingale and Rhodes eloquently state "processes are strategy at work." The process for architecting a new enterprise strategy (**Figure 2**) begins and ends with the enterprise strategy. Attempting to change the enterprise strategy requires the process of understanding the current enterprise landscape, analyzing stakeholders, and defining the enterprise architecture as it currently stands. This leads to the ability to articulate a vision of the future enterprise. Once the future enterprise is envisaged, alternative architectures can be imagined, followed by landing on an appropriate architecture and devising a plan to make that architecture a reality. New enterprise strategies are required for an enterprise to transform, and a common driver for enterprise transformation is the emergence of a significant enterprise threat such as what happened to the pharmaceutical industry supply chain during the COVID-19 pandemic. Drug shortages resulted from the inability to import certain drugs that have been outsourced for cost savings,[4] reduction in manufacturing capabilities due to social distancing requirements, and an overall surge in demand.[5] Threats like this can catalyze enterprise transformation, and therefore can be a deliberate and intentional onramp for a disruptive technology.

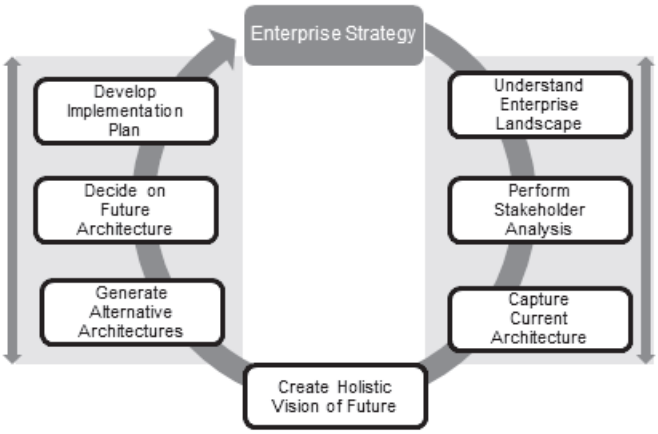

Figure 2 *Seven activities in architecting an enterprise strategy. Reprinted from "Architecting the Future Enterprise"*

2.2 Continuous Flow Synthesis

For decades synthetic chemists and biologists have been constrained to performing reactions in glassware staples such as round bottom flasks. These types of reactions are commonly referred to as 'bulk' or 'batch' reactions because the reagents are loaded into the reaction vessel simultaneously, and the totality of the product is collected simultaneously. The use of these synthetic tools in the pursuit of scientific innovations has remained relatively unchanged, therefore batch chemistry has remained the state of the art for chemical and biological synthesis. Because scientists have been hamstrung by batch reaction methods, innovations in chemical transformations and synthetic processes have been stymied by the pace batch chemistry lends itself.[6–12] Additionally, many useful chemical reactions have been shelved over the years due to inherent safety concerns with their reaction conditions stemming from high pressures, high temperatures, or highly reactive reagents, intermediates, and/or catalysts.[7,11,12] And even more potentially beneficial synthetic

techniques have been seen as impractical such as photochemical or electrochemical transformations due to their difficult execution in bulk.[12] For example, uniform and effective light penetration for photochemical reactions is difficult to ensure in bulk reactions, so this technique is often discarded in favor of more controllable reaction parameters. But photochemical reactions can be exceptionally more atom economical than alternative synthetic routes, thus rendering electrochemical reactions greener and more efficient.

In the late 1990s and early 2000s continuous flow chemistry, chemistry in which reactions are conducted in a constant flow of reagents within small diameter connective tubes, began to emerge as a disruptive technology.[7] This technology sprang from the desire to augment traditional batch chemistry by unlocking reactions that could be performed more safely, efficiently, and/or expeditiously in flow. Eventually, researchers began to see the ability of flow chemistry to decentralize large-scale chemical production by moving chemical transformations to small portable reactors[12,13] while still maintaining the ability to produce scalable amounts of material simply by increasing the flow rate and runtime of the reactors.[14]

2.2.1 Continuous Flow Apparatus

The basic structure of a continuous flow apparatus (**Figure 3**) consists of a modular setup of reactors, separation units, pressure regulators, various sensors such as temperature and flow, and analytical instrumentation, specifically process analytical technology (PAT), to ensure product purity.[15] Reagents are introduced into the reactor and circulated using different pumping techniques (syringe, peristaltic, piston).[9] The modules are connected via small diameter tubing, typically 10 mL in

volume. The tubing is comprised of different materials but typically consists of PTFA,

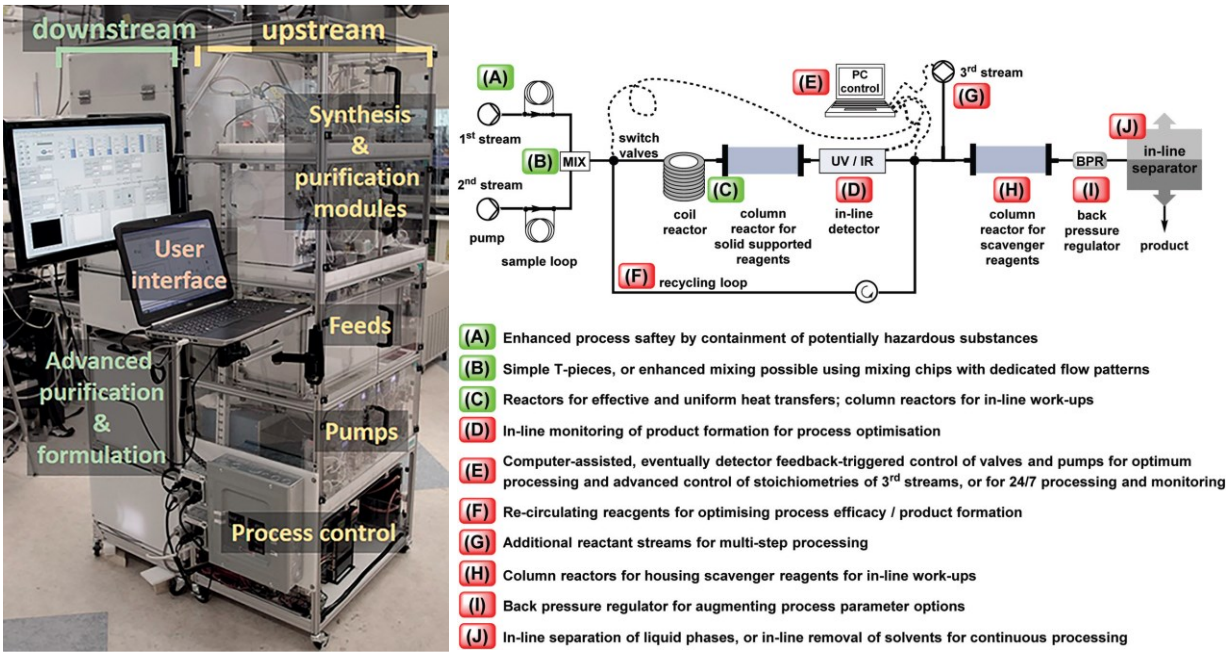

Figure 3 *(left) Photograph of MIT's pharmacy on demand production device. Reprinted from "Continuous Production of Five Active Pharmaceutical Ingredients in Flexible Plug-and-Play Modules: A Demonstration Campaign" (Right) Typical flow synthesis diagram. Reprinted from "Flow Synthesis Approaches to Privileged Scaffolds – Recent Routes Reviewed for Green and Sustainable Aspects"*

stainless steel, or PEEK.[9] Flow synthesis takes advantage of the low surface to volume ratio within the reactor to achieve more efficient mixing and temperature and pressure control.[8]

2.2.2 Benefits of Continuous Flow Synthesis

Historically, multistep synthesis has been tedious in batch chemistry mainly due to the need to work up each intermediate step through purification only to then use that intermediate in the next step, and on and on. These repeated steps can result in a large amount of material loss throughout the synthetic process and thus relatively low final product yields. Notably, nature doesn't do this in the synthesis of complex molecules,[13] hence flow chemistry is essentially looking to nature for inspiration on effective and efficient synthetic techniques. Consequently, this technology can

expedite total synthesis of complex products through the removal of intermediate work-up and analytical steps. Additionally, telescoping of the flow apparatus opens the aperture to more efficiently produced and increasingly intricate moieties to be constructed.

Flow chemistry has been adopted readily in energetic materials manufacturing, oil and gas refineries, green chemistry initiatives, specialty chemical synthesis, and academic R&D laboratories[7,9] to replace batch chemistry, because it is inherently safer and more efficient than batch processes. Flow chemistry unlocks previously unused chemical transformations due to their safety concerns when conducted in bulk.[6] Thus, flow synthesis has put many lesser used, to downright verboten chemistries, back on the table. The modest volume of reagents needed are used over a longer pathway/time interval thus eliminating most of the dangers associated with highly unstable/reactive species. The small scale of the reaction pathway allows for high temperature and pressure steps to be confined to smaller containers, drastically reducing the threat of explosions and fire. The small volumes also lend themselves to efficient heat transfer, reduced headspace, and ability to control any kind of runaway reaction safely when compared to bulk reactions.[7] Multiple reaction parameters can be readily manipulated in flow chemistry without the need for continual teardown and setup such as temperature, pressure, concentration, and energy source.[7] Due to this ease of tunability, reaction conditions can be optimized to eliminate hazardous conditions, byproducts, and other barriers typically encountered in bulk reactions.[7,16] For example, the previously mentioned class of photochemical transformations constitute another category of reactions that are typically shied away from in bulk

because of inefficiencies in light penetration. Flow synthesis has given resurgence to this particular arrow in the chemist's quiver because the flow path is so small thus allowing for efficient photochemical reactions.[12]

Over the last decade, flow synthesis technology has progressed from a primarily chemistry centered technique toward the need for engineering advancements.[9] Most, if not all, chemical transformations that scientists have attempted to harness through flow synthesis have been achieved. Even those that seemed initially impossible due to inline precipitation or fowling have been achieved through engineering and synthetic creativity.[7,9] Currently, the technology is progressing toward more facile utilization in multi-step total synthesis with the goal of end-to-end automation sans the need for any human interaction.[12,17,18] The real challenge now lies in the engineering decisions to determine how to make flow chemistry more accessible, dynamic, and consistent with Current Good Manufacturing Practices (CGMP).[8,9]

2.3 Food and Drug Administration (FDA)

The mission of the FDA includes ensuring patient access to safe and effective medications.[19] The FDA is responsible for protecting patients and prescribers from harm caused by dangerous drug products that were intended as a beneficial therapy. To do so, the agency has adopted rigorous standards in their risk-based regulatory strategy. The agency has emphasized the concept of Quality by Design (QbD) in pharmaceutical development and manufacturing; recognizing that manufacturers cannot test their way to quality products. Quality must be built into the product from start to finish.[20] QbD is focused less on downstream corrective action and more on

upstream process strategy. The key elements in QbD are[20] 1. Development of a quality target product profile (QTPP) to determine the critical quality attributes (CQAs) of the intended product. 2. Identification of the critical material attributes (CMAs). 3. Determining the critical process parameters (CPPs) required for product manufacturing. CPPs take into account the CMAs and CPPs and translate them to the CQAs by identifying the input material attributes (e.g., particle size), the process parameters (e.g., type/geometry of mixer) to link to the quality attributes (e.g., blend uniformity). 4. Codify a control strategy considering the stepwise manufacturing process to include all finished product components (e.g., APIs and excipients). 5. Lifecycle management through continuous process improvement. Key tools used to facilitate QbD are prior knowledge (e.g., company specific IP), risk management, Design of Experiments (DoE), and PAT. The ultimate goal of QbD being to reduce product flaws and improve manufacturing efficiencies while still maintaining regulatory standards.[20]

The FDA has extensive and exhaustive regulations regarding how medications are developed, tested, manufactured, and distributed. Thus, the total time to market for a new drug is typically around 12-15 years (**Figure 4**). However, the agency must balance the need to protect the public with the need to ensure access to medications. To strike this balance, the FDA has multiple partnerships and initiatives.

Duration (year)	2.5	1.0	1.5	2.5	2.5	1.5
Cost ($M USD)	4	15	16	42	158	48

Figure 4 *Typical drug development timeline. Reprinted from "Fundamentals of Drug Development, 1st ed"*

The FDA has partnered with multiple countries—mainly Japan and the EU—in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) with the goal of a unified body to guide global pharmaceutical development efforts. The ICH has taken a lead role in defining and implementing QbD principles throughout the global pharmaceutical manufacturing industry. The ICH is focused on reducing duplicate efforts in clinical trials, standardizing the development of new medicines, streamlining the registration and observation of new medications, and the reduction of animal testing while maintaining safety.[2] In other words, medications developed on one continent should adhere to the same standards as medications developed on any other continent, giving consumers confidence in pharmaceutical products regardless of geography. The guidance set forth by ICH are accepted in any ICH participating country, and therefore ensure rigorous pharmaceutical development standards are adhered to internationally. The ICH has published multiple guidance documents pertaining to safety, quality, and efficacy to establish common global pharmaceutical development standards. Specifically, the set of quality guidelines (Q1-14) are focused on facilitating

CGMP while incorporating flexible manufacturing capabilities and maintaining safety, and the FDA has mirrored this focus.

Internally, the FDA's Center for Drug Evaluation and Research (CDER) has a hand in cultivating drug manufacturing innovations that could lead to supply chain protection and subsequently broader access to critical medications.[21] The FDA has expressed a goal of an "agile, flexible pharmaceutical manufacturing sector that can produce high-quality drugs reliably without extensive regulatory oversight.[21]" And CDER has identified platform technologies such as flow synthesis as a candidate for progressing pharmaceutical manufacturing towards achieving this goal.[21,22] Because CDER has no oversight on innovative technologies when not considering them as part of a drug product application, the office instituted the Emerging Technology Program and Team (ETT) to collaborate with manufacturers who are interested in implementing new manufacturing technologies.[21] This team aims to be a liaison between the manufacturers who are interested in implementing innovative technology and the FDA with a goal of demystifying possible regulatory issues that could arise in the planning of a new process. In 2002 the FDA launched "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach" with the goal to alleviate pharmaceutical manufacturer's concerns centered around adopting innovations in manufacturing practices.[22] The initiative intended to achieve a more science-based and synergistic inspection and approval process.

Additionally, the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Chief Scientist of the FDA is working to facilitate innovative technology adoption in the pharmaceutical manufacturing arena by developing new

regulatory science tools.[23] Specifically, OCET seeks to understand and improve the safety and evaluation criteria of manufacturing technologies that could be deployed to facilitate disaster response and supply chain fortification.[24] Another key OCET initiative is to bolster FDA exposure to advanced manufacturing technologies[24] with the intent of improving regulator understanding of emerging technologies and facilitating a more streamlined product approval process.

2.4 Pharmaceutical Industry Background

The pharmaceutical industry has evolved over the last century from the initial discovery and production of morphine and aspirin to become one of the largest US healthcare industry contributors; an industry that accounts for 18% of the Gross Domestic Product (GDP).[25] And the pharmaceutical industry alone makes up close to 20% of the healthcare segment.[4] Thus, as an integral part of the national healthcare system, the pharmaceutical industry must maintain painstaking oversight over all industrial processes to ensure the highest level of safety and purity of drug products.

Quality risk management (QRM) is a key piece of the pharmaceutical manufacturer's quality assurance strategy, linked to QbD, and is tied directly to patient safety. The goal of QRM is to reduce risk to an acceptable level or introduce processes to effectively manage it.[26] As mentioned previously, QbD processes are instituted to bring the resources necessary for reducing or managing risk to the initial stages of manufacturing development rather than managing concerns as they arise downstream. However, proper and deliberate monitoring of risk ensures essential transparency throughout the drug product lifecycle. For example, any changes to the manufacturing process (e.g. CPPs), be they process control changes, new raw

material specifications (e.g. CMAs), or facility/hardware changes, are evaluated for implications commensurate with the level of risk.[27] These painstaking assessments are digested to determine appropriate strategies to manage or eliminate conditions that may lead to hazardous outcomes. This meticulous control is the price of doing business in a $1.4T industry;[28] enabling agencies to continue to seek and obtain regulatory approval to produce, sell, and distribute pharmaceuticals. Consequently, the pharmaceutical manufacturing industry is exceptionally risk adverse. Even upon achieving regulatory approval for new products, manufacturers are keenly aware that liability lies squarely with them, regardless of documented and certified product safety and efficacy. Therefore, pharmaceutical manufacturers tend to practice risk avoidance at the cost of innovation despite disruptive technologies with the potential of revolutionizing the industry.

Drug companies are interested in gaining a competitive advantage over competitors by improving and building upon their product offerings.[27] Because pharmaceutical companies compete mainly on their portfolios, the industry has begun trending towards outsourcing many of its core functions such as human resources, IT, and manufacturing. Contract manufacturing organizations (CMOs) such as Patheon, Catalent, and Lonza allow pharmaceutical companies to outsource the late stage manufacturing operations, freeing the company up to focus on groundbreaking R&D; the space where the company can expect to best compete for market share.

Manufacturers, be they in-house or contracted, are charged with producing medications that are of the highest quality through consistent engineering and quality

assurance practices. As mentioned previously, QbD and QRM are strategic frameworks to guide manufacturers in the development of processes intended for the production of high-quality pharmaceuticals. Regulators (e.g., FDA) examine manufacturer's processes to determine if the processes and product specifications will deliver safe and consistent products between batches and throughout the product's lifetime. As part of this scrutinization and as a manifestation of QbD and QRM, the Chemistry, Manufacturing, and Controls (CMC) (**Figure 5**) are reviewed in the initial steps in obtaining new drug approval. However, while CMC is crucial in the initial stages of drug development, CMC is a pervasive and active process that is adhered to throughout the lifecycle of a drug.

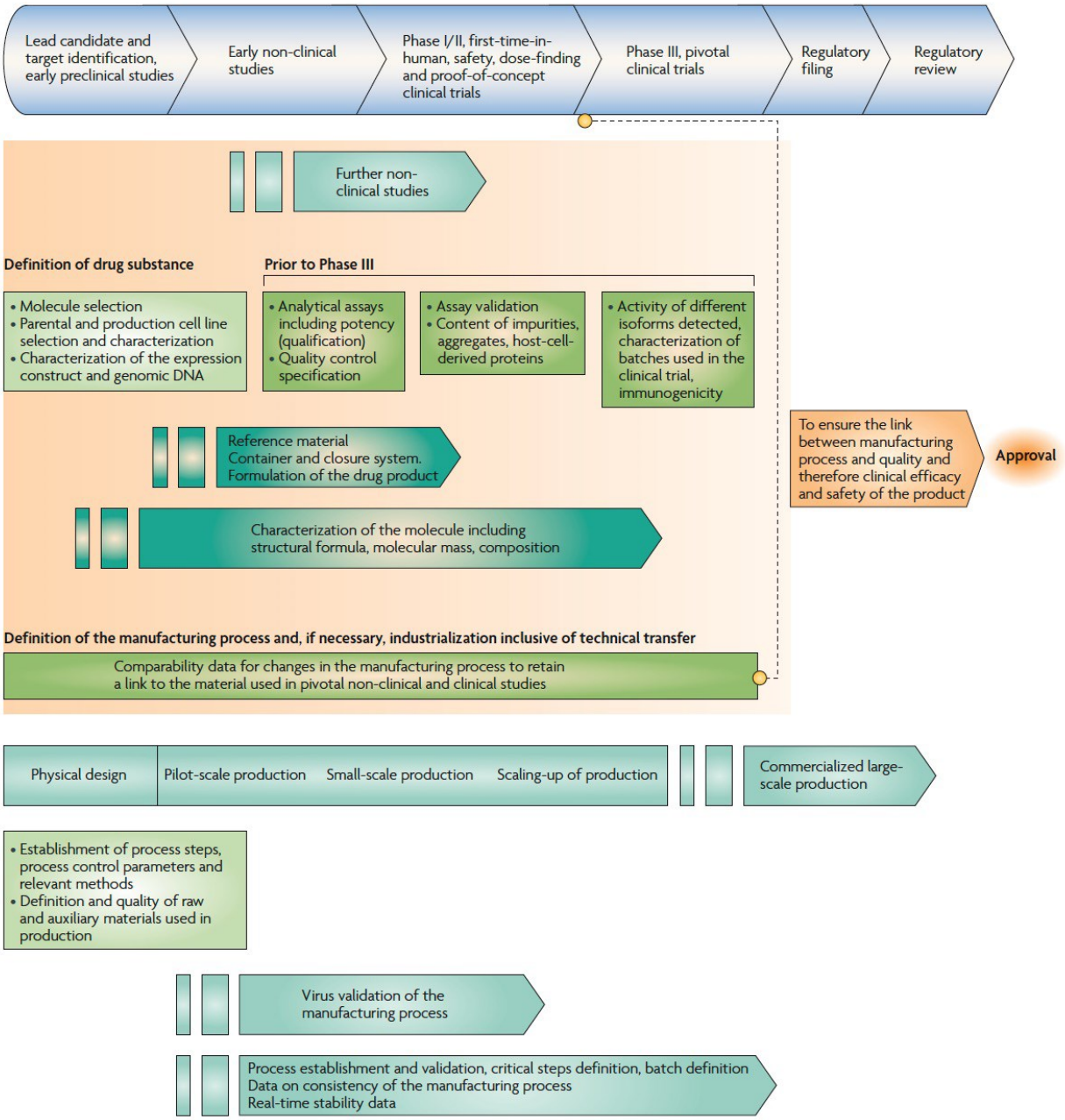

Figure 5 *Steps in the CMC development of pharmaceutical products. Reprinted from "Typical pitfalls in applications for marketing authorization of biotechnological products in Europe."*

CMC not only refers to the drug product but are also applied to the manufacturing facility, and QbD helps ensure appropriate CMC is envisioned early in the process.[29] A cornerstone of the manufacturer's CMC are the analytical methods

engineered into the process to ensure validation of product quality. PAT can actively monitor multiple process variables and product quality attributes.[21] Therefore, the selection of appropriate PAT is critical to effective CMC.

Reproducible, high quality, and effective products are crucial to a successful pharmaceutical manufacturer's business model, and as such, manufacturers actively maintain CMC regulatory compliance consistent with CGMP. CMCs are the set of regulatory principles to guide manufacturers in production, testing, release, and scale up for a particular drug. Throughout any deviations in the manufacturing process or facility, CMC acts a as a guide for the manufacturer to maintain product consistency. Any changes to a manufacturing process are highly scrutinized through the lens of CMC, and thus could require significant documentation, validation, or resubmission of regulatory approval applications.

This commitment to quality and safety has put the US pharmaceutical industry at the pinacol of the global industry. Arguably, the driving force behind the meticulous awareness to deliver a safe and effective product is FDA oversight. The FDA is held as the gold standard for risk-based regulatory processes. And while some criticize the agency for being too risk adverse and too slow to allow products to market,[27] the FDA leads other global regulatory agencies in the number of products approved annually. That volume of approvals is driven, in turn, by the prolific pharmaceutical industry.

Despite its prevalent place in the American economy and infrastructure, the pharmaceutical industry faces many challenges. Two of the most impactful challenges

are timely and equitable access to drug products and environmental hazards caused by current drug manufacturing procedures. While these issues are appropriate for manufacturers to solve, the downstream implications of uneconomical or environmentally insensitive drug manufacturing can harm all stakeholders.

The prevailing cause of drug shortages are typically production-related issues, rather than sales or distribution-related inefficiencies.[30] According to the FDA, causes of drug shortages include quality or manufacturing issues (e.g. contaminants); upstream supply chain interruption (e.g. a necessary ingredient becomes unavailable); scalability limitations (e.g. drug supply needs increase and manufacturers do not have the ability to meet demand); and business decisions of individual firms (e.g. a producer exiting the market resulting in fewer manufacturers).[30] Recently, the COVID-19 pandemic caused a global reallocation of resources focused on developing and manufacturing a safe and effective vaccine intensifying drug shortages on a scale never-before seen.[31] Exacerbating these shortages are the price surges they cause which then lead to further accessibility concerns.

Rising prices of drugs and the inability to access necessary medications can have potentially fatal consequences and can jeopardize national security. From a program management perspective, we can treat drug development from cradle to grave, as a program, and as such, drug manufacturing would be squarely on the critical path. Meaning, if we can reduce the time required for manufacturing, we can reduce the overall program timeline and cut costs. Therefore, if we can reduce the manufacturing time interval, we can economically expedite the delivery of the product to the end user.

2.5 Continuous Manufacturing in the Pharmaceutical Industry

The pharmaceutical industry has begun to embrace flow chemistry as a disruptive technology, because of a push, largely by the FDA, to produce safe and effective products while cutting costs, protecting supply chain, and increasing manufacturing innovation and flexibility.[22] Flow synthesis apparatus can be likened to the Coca Cola™ Freestyle dispenser that allows for personalization of Coca Cola™ beverage flavor without the need to stockpile all possible combinations individually. Similarly, one could envision flow pharmaceutical production consisting of a handful of common reagents or APIs that can be combined in different formulations under different reaction pathways to produce tailored desired drug products. Thus, CM allows for dynamic synthetic capability with a decreased equipment and logistics footprint.

Pharmaceutical manufacturing is classified as a process industry while continuous flow synthesis can be categorized as a process intensifier. The term 'process intensification' describes a manufacturing technique that enables higher yields more efficiently with a smaller footprint, and thus lends itself to a reduction in process costs.[21] In combination with a modular system approach, continuous flow manufacturing systems would allow a single manufacturing facility the ability to adapt to a range of products with varying degrees of product volume flexibly with a reduction in time and cost vs a bespoke manufacturing process (**Figure 6**).

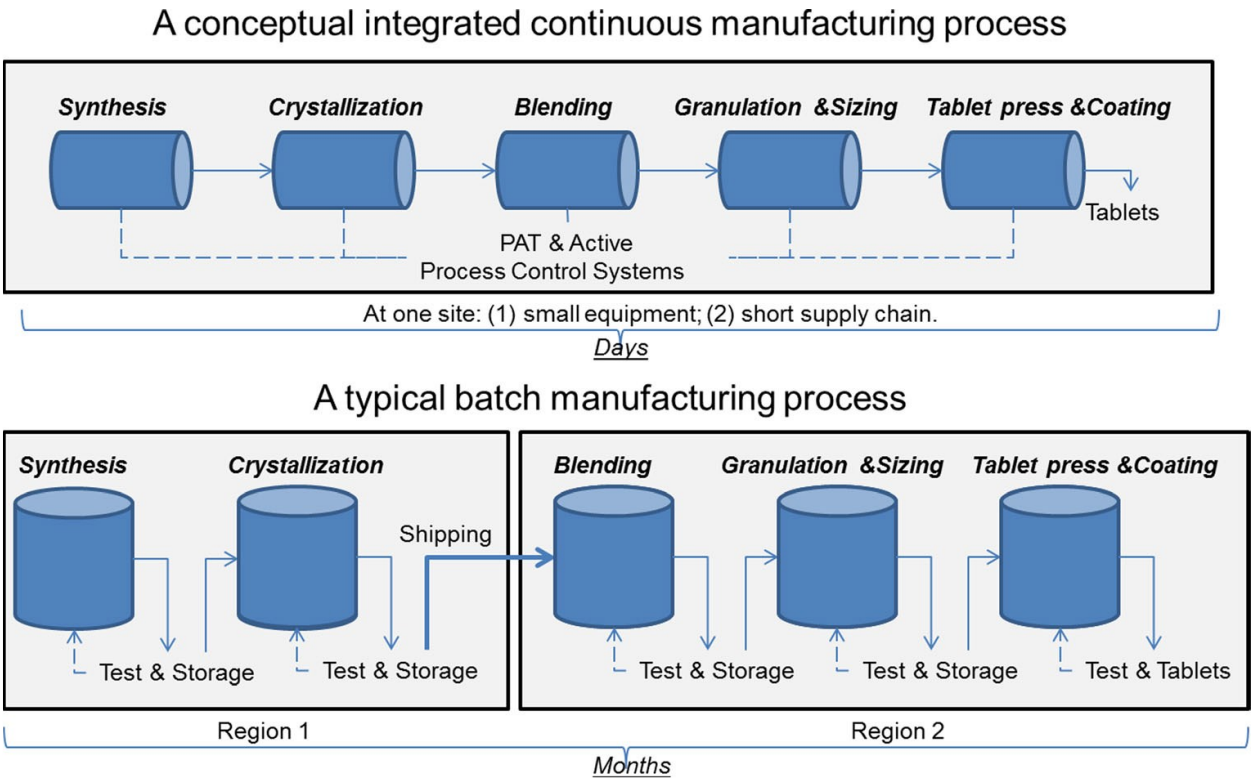

Figure 6 *Continuous manufacturing process compared to the industry standard batch manufacturing process. Reprinted from "The Future of Pharmaceutical Manufacturing Sciences"*

Implementation of CM for pharmaceutical manufacturing requires modification from batch manufacturing process control strategies- "planned set of controls, derived from current product and process understanding, that assures process performance and product quality."[32] CM necessitates a higher level of process design to ensure appropriate system control strategies. When engineering the CM process for a desired drug product, multiple parameters (flow rate, crystallization, synthesis, drying, blending, etc.) can be optimized through adjustment of respective module operations to achieve the desired quality.[33] Unlike bulk manufacturing, the ability to trace mass balance throughout a CM process is a key parameter to be monitored.[21] Again, highlighting the pivotal role appropriate PAT plays in CM

engineering. Batch manufacturing processes do not allow for this level of optimization due to downstream disruption. Imbedded process quality and monitoring systems are essential for CM systems to ensure product uniformity, safety, and efficacy.[21]

2.5.1 Drug accessibility

Flow chemistry can provide APIs and more complex small molecules to globally underserved regions and can be employed to provide critical medications to address regionalized disease outbreaks or natural disaster relief. Additionally, because CM can remove the need for special storage (i.e., low temperatures) of the drugs (they can be made and used immediately), the logistics burden at the point of care is relieved. CM also provides the US the strategic capability of pharmaceutical supply chain protection. For example, many vital generic drugs, which have a very low profit margin,[27] are no longer made in the US because production in the US is cost prohibitive. Moving the manufacture of these drugs back to American soil through a more cost-effective medium such as flow synthesis would ensure supply chain protection.

Adoption of CM by pharmaceutical manufacturers could address drug shortages by allowing for greater scalability and flexibility. As opposed to traditional batch production, continuous flow lends itself to unique scale-up options such as: operating the process for longer durations, utilizing parallel or multiple processing lines, and increasing the flow rate through the system.[33] Also, rather than investing in bespoke processing technology, additional capacity and/or product lines can be added or removed throughout a production center's lifetime, adjusting in real-time to

market demands. In addition, continuous flow synthesis requires a modest volume of reagents, thereby allowing for scaled down production when appropriate, thus the reduction of excess waste.[33]

CM can be leveraged upstream of the full-scale manufacturing process as well to increase medication access through acceleration in the drug development stage. As illustrated in **Figure 7** the drug development process can take upwards of 15 years from concept to market, and the pre-discovery phase can account for almost half that time. Reducing the time for discovery on the front end could be accomplished with CM through rapid synthesis of quick hit target molecules (analogous to rapid prototyping) when probing large chemical libraries.[8,17] Access to preclinical trials of quick hit pharmaceutical candidates could therefore be increased using modular, plug and play, and telescoping flow synthesis. The candidates can also be scaled up for use in clinical trials, or the flow apparatus can be easily modified to produce the next candidate for preclinical trials if further study of the initial candidate is not warranted.

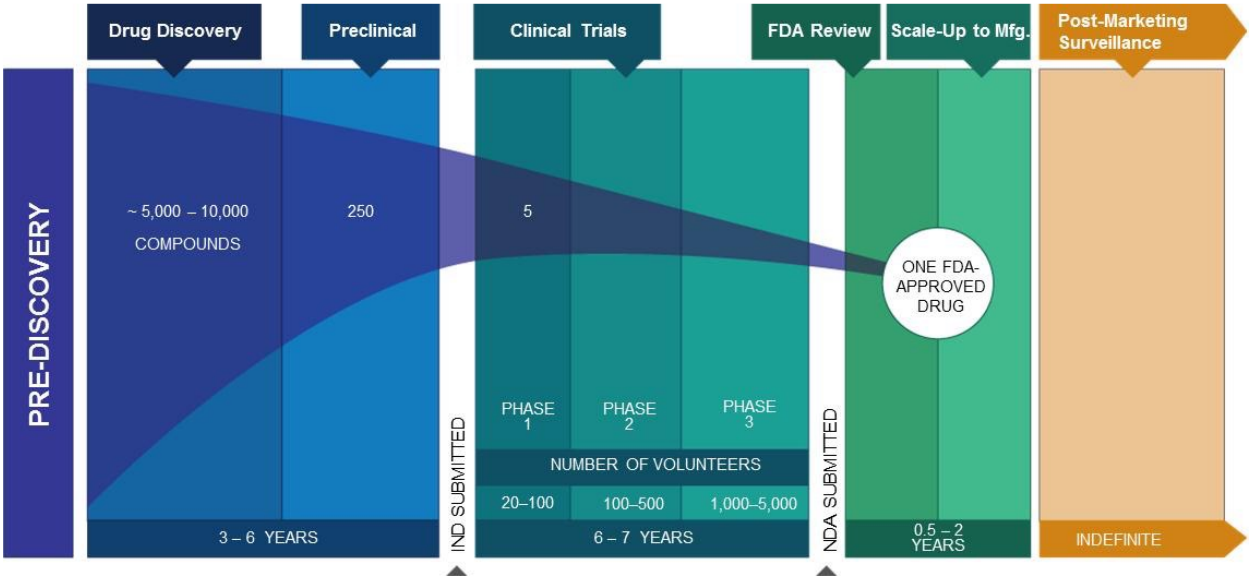

Figure 7 *Timeline for drug discovery process. Reprinted from Pharmaceutical Research and Manufacturers of America, Innovation.org*

2.5.2 Environmentally Sustainable Manufacturing

The push to achieve more ecofriendly pharmaceutical manufacturing processes aims to reduce the amount of material and energy used and waste generated in the production of drug products.[34] Traditional batch manufacturing is responsible for a significant amount of waste, while CM appears to be a candidate mechanism to transition pharmaceutical manufacturing towards green chemistry. For example, according to Dr. Adela Magher, Health Care Without Harm (HCWH) Europe pharmaceuticals policy officer, "The production of both active pharmaceutical ingredients (APIs) and finished dose antibiotics is concentrated in specific locations so the resulting point, source pollution, is in incredibly high concentrations and encourages the development of drug resistance. This practice has a detrimental impact on vulnerable populations living near manufacturing facilities and wastewater treatment plants in these countries."[35] Because CM of pharmaceuticals can result in a

more distributed manufacturing network, such concentrated pollutant streams can be eliminated. Additionally, PAT, process and residence time control, improved heat and mass transfer, increased safety, shorter process intervals, inherent reproducibility, and better product quality contribute to the overall reduction in energy and wasted material when utilizing CM vs batch manufacturing.[36]

Specifically, CM processes can leverage recycling streams which can greatly increase efficiency. Continuous recycling is achieved through engineering recycling loops in the flow apparatus to salvage unreacted starting materials, catalysts, and solvents, which has a profound effect on the overall mass efficiency of a process.[34] Reusing reagents improves yield with minimal wasted precursors—a pervasive problem with batch production. This is particularly valuable with API feedstocks or process intermediates.

2.6 Technology Transition Barriers

Pharmaceutical manufacturers have been slow to embrace universal adoption of continuous flow chemistry. The introduction of a new manufacturing technology requires regulatory approval of that technology for each product manufactured using the technology. This regulatory approval could introduce unforeseen financial obligations due process and synthetic protocol redesign, training requirements, and opportunity costs. Therefore, a manufacturer tends to find that it might make the best business sense in the short term to use established batch manufacturing techniques when developing a new product.[21] However, as mentioned previously, the FDA has instituted multiple initiatives to help assuage the uncertainty in instituting new technologies such as CM in pharmaceutical manufacturing and is working to

codify guidance on how to navigate the regulatory challenges presented by CM (ICH Q13).[2,10] These efforts have borne fruit recently when two drugs, Orkambi (a drug to treat cystic fibrosis) and Prezista (a drug used to treat HIV) were given FDA approval to be manufactured using continuous flow techniques.[12,17,18,37]

Widespread continuous flow pharmaceutical manufacturing adoption requires dynamic and modular reactors to be readily achievable, and a number of companies and government agencies[38–40] have been investing in making accessible CM a reality.[41] In practice, flow chemistry can be tedious because many engineering challenges still have not been solved. For example, precipitation can be a big issue even though there are methods to combat fouling. When reactor tubing becomes clogged, getting the reactor running again is time consuming. A skillful workforce educated in the design, engineering, and operation of flow reactors is an impediment to ubiquitous CM implementation.

2.7 Beyond Small Molecules

Flow synthesis is not limited to small molecule synthesis. Medical therapies are increasingly trending toward specialized, tailored, point of care medicine. For example, cancer treatment has moved toward using the patient's own DNA and the biomarkers of their cancer to personalize treatment. Because only a small amount of this type of medication would be needed, the use of flow synthesis is uniquely suited to production of these types of tailored drugs. Furthermore, proteins and peptide sequences are typically synthesized through biological methods limiting the amino acids that can be incorporated. Flow synthesis can be used to easily add non-naturally occurring amino acids to further adapt proteins to target biological moieties more

precisely.[42] Similarly, orphan drugs, drugs that are FDA approved for only a small patient population due to low disease prevalence, could see a resurgence in both production and development with the widespread adoption of CM in the pharmaceutical industry. If the cost associated with these drugs could be reduced through the beneficial application of CM, the aperture of care would be greatly increased allowing for many more healthy and long lives to be realized. So, as a wider lens is cast on the possibilities for CM in pharmaceutical manufacturing amongst a variety of disciplines, the technology will continue to achieve greater likelihood of advancement toward adoption by the pharmaceutical industry.[7,23,43]

Chapter 3 Research Methodology

In this chapter, the system architecture techniques used in this system are defined. The socio-technical system developed in this thesis—CONTINUES (Continuous Next-gen Unique Pharmaceutical Manufacturing for Enhanced Quality and Efficiency Change System) (**Figure 8**)—is a framework to assist pharmaceutical manufacturers in adopting CM in their manufacturing processes.

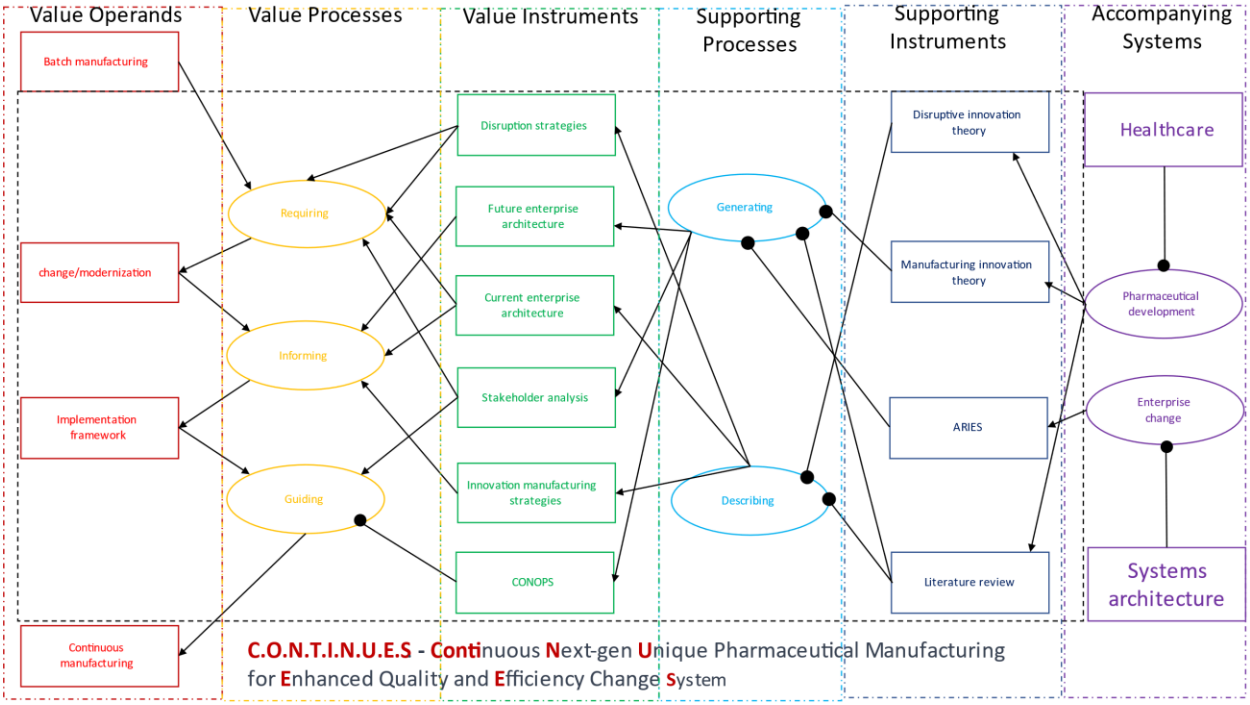

Figure 8 *Object Process Diagram (OPD) for the system being designed in this thesis (CONTINUES)*

The framework will be composed of parts, and the parts are system thinking techniques such as ARIES; business theories such as disruptive innovation theories and manufacturing innovation theories; and the previously accomplished literature review. The role of each of the parts is to deliver the value instruments for the overall system. Each section of this chapter will address one of the supporting instruments of the system (ARIES, disruptive innovation, and manufacturing innovation). Literature review is treated as a supporting instrument, but it was already accomplished in the previous chapter. However, the final section will address how the literature review will contribute to Continuous Next-gen Unique Pharmaceutical Manufacturing for Enhanced Quality and Efficiency Change System.

3.1 Systems Architecture Techniques

The first task in systems architecture is to identify the system, its form, and function. "Form is what has been or is eventually implemented. Form is eventually built, written, composed, manufactured, or assembled.[44]" The form of the system developed in this thesis will be the written/composed tools to be used in the transition of the current pharmaceutical enterprise from an almost exclusively batch manufacturing enterprise to one in which most manufacturing is done in a continuous approach. In other words, the form of the system is this thesis, and the function of the system is delivering is a framework to facilitate CM adoption in the pharmaceutical enterprise, previously defined as CONTINUES. The form of the system is consequential for the function of the system—the form feeds the function. Therefore, the form of this system will be key to the function.

In system architecture, the goal is to map form to function through a concept. Defining the objects of form for a system and the functional aspects contained in the system facilitates this mapping—form and function items are tied together via the architectural concept of the system. The concept of CONTINUES (**Figure 9**) is an actionable roadmap, grounded in proven theory and architecting techniques, that can guide any pharmaceutical manufacturer to adopt CM in their manufacturing processes. Eventually, ubiquitous adoption of CM in manufacturing processes will lead to the democratization of drug product access.

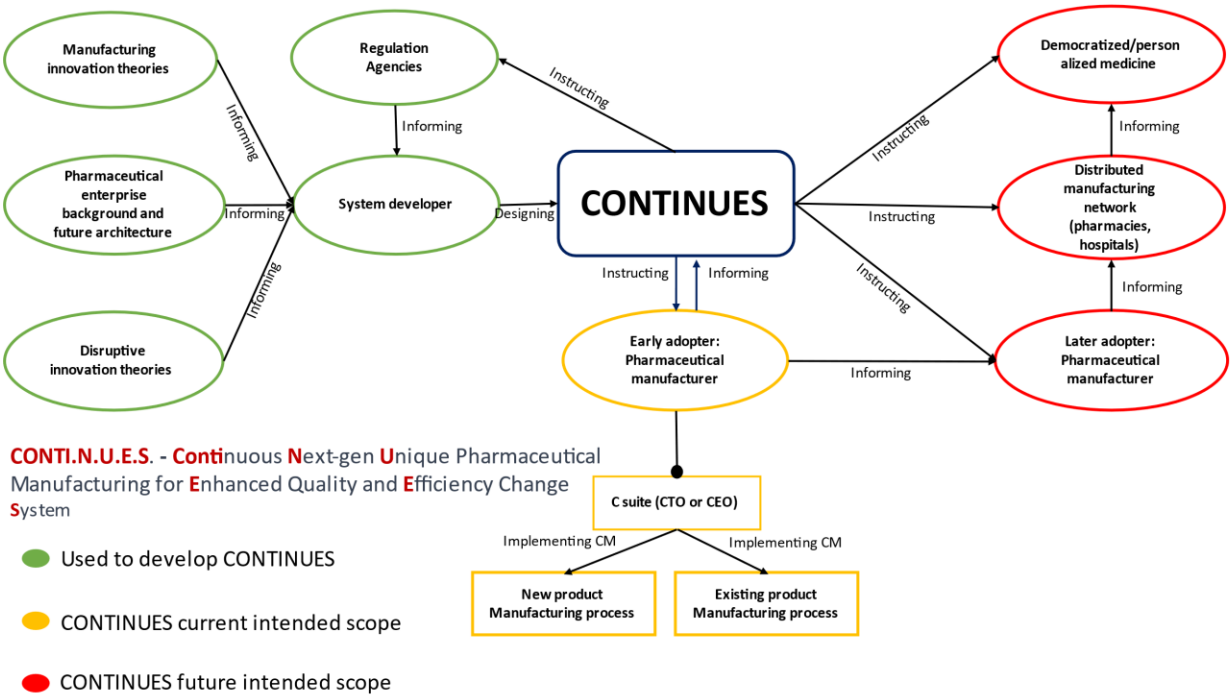

Figure 9 *Concept Map for CONTINUES*

The second task is to identify the entities of the system, their form, and function. The entities of the system being architected in this document are the descriptive and prescriptive change/adoption methods for greater CM adoption in the pharmaceutical enterprise, tools used to derive those methods, and background examination on the current and intended state of the pharmaceutical enterprise including the benefits and barriers to CM adoption. The form of these entities are the synthesized management techniques for technology adoption, system thinking theories, disruptive technology theory, CONOPS, exhaustive literature review, and stakeholder interviews (where possible). The function of these entities will be the reduction of perceived barriers to CM adoption by the pharmaceutical enterprise and

to provide an actionable roadmap for pharmaceutical companies to use to facilitate this transition.

Task three is to determine the relationship between the entities. The relationship of the entities described in task two will be the intermingling of the principles and strategies they deliver to synthesize the CM adoption roadmap. The relationships between the entities will be both formal (how the entities are physically aligned in space) and functional (how the entities interact with and upon one another). The formal relationship of the entities of this system are how the tools are laid out and presented in this thesis. The entities are presented in a particular form to facilitate adaptation of theory into actionable strategy for the pharmaceutical manufacturing enterprise. The functional relationship of this system's entities translates manufacturing, business, and systems architecting theories into convergent guidance for pharmaceutical manufacturers to adopt CM.

Finally, **task four** is defining the emergent function, and as described previously, the emergent function of this system will be transition of the pharmaceutical enterprise from batch manufacturing to CM.

The role of the architect is to reduce ambiguity in the system. Currently, there is no roadmap for CM transition into drug manufacturing. Therefore, the tech transition framework developed in this thesis will act as a socio-technical system and work to reduce the ambiguity that exists in CM adoption by the pharmaceutical industry. Ultimately, this thesis intends to transform the pharmaceutical enterprise from one formal structure (solely bulk pharmaceutical manufacturing) to a new

formal structure (bulk manufacturing augmented by continuous manufacturing) but maintain and improve on the functional capability.

3.2 System Development

The pharmaceutical industry has almost a century of data on how to manufacture drugs safely, effectively, and relatively efficiently. Therefore, the adoption of continuous flow synthesis platforms into their manufacturing operations faces a large barrier to entry despite the promised benefits the technology can provide. This thesis is an attempt to lower that barrier and facilitate the technology transition of CM to pharmaceutical manufacturing by designing a functional architecture for adoption (CONTINUES). If we look at the functional architecture developed in this research as a sociotechnical system, we can use systems architecture to build the system starting with the **system problem statement**, followed by the **system objectives, objects of form, processes, relationships,** and **tools** used.[44] From this definition, we can identify **the emergent function** of the system—CM adoption in pharmaceutical manufacturing.

3.2.1 System Problem Statement

When designing a system—the intended outcome of this thesis (CONTINUES)—the system architect must codify the system problem statement. This is defined as "the statement of the problem that defines the high-level goal and establishes the boundaries of the system.[44]" This statement will be how this thesis intends to accomplish the goal of CM adoption along with the scope of the intended goal. The system problem statement is crafted in the form of '**To-By-Using**'. **To** is the system objectives (the solution neutral function), **By** is the system concept (the

solution specific function), and **Using** is the form of the system.[44] Below is the system problem statement for CONTINUES.

To facilitate the pharmaceutical manufacturing enterprise adoption of CM to augment enterprise means of small molecule drug/drug product manufacturing

By designing an adoption system utilizing system architecting principles, disruptive innovation theories, and innovative manufacturing theories.

Using an adaptable and functional guidance document that pharmaceutical manufacturers can employ.

Going one level deeper from this initial abstraction, a system problem statement can be generated from the enterprise perspective to be used by pharmaceutical manufacturers as they enact CONTINUES:

To manufacture pharmaceuticals efficiently, safely, and profitably while reducing the manufacturing footprint and infrastructure needs

By converting batch manufacturing to CM for current and future pharmaceutical manufacturing processes in cases where CM would be the better manufacturing option

Using CONTINUES

3.2.2 System Objectives

The objectives of this system will be to increase CM adoption in the pharmaceutical manufacturing enterprise. A diagnostic metric to measure this would be the annual increase in FDA approved drugs manufactured using CM. For this metric and throughout this document, CM is defined as an integrated process consisting of two or more steps in sequential unit operations.[43] Currently, there are six FDA approved drugs, so a nominal initial goal of a 15% increase would lead to one to two new drugs manufactured using CM the year following the deployment of CONTINUES. Another objective for this system is to increase funding for CM in the pharmaceutical industry. This metric could be tracked by probing the annual investments made by pharmaceutical manufacturers in CM. An increase of 30% annual funding for CM implementation could be an achievable goal. Finally, a third objective of this system is to decrease the perceived risk—both regulatory and from a product liability standpoint—of CM adoption. This metric would be more qualitative and would be tied directly to increased CM implementation, but if the perceived risk could be cut in half through this CM adoption framework, the system should be considered successful. To measure this, surveys could be used to gauge the industry's perception of transitioning to CM from batch.

The objectives of CONTINUES have been defined, but the pharmaceutical manufacturer who implements this system will be concerned with the objectives of the CM system. To track these objectives, the critical performance trajectory of CM in pharmaceutical manufacturing would be relevant and important information for manufacturers to have, because it details the rate at which CM technology has

improved and is expected to improve.[45] An informative critical performance trajectory for pharmaceutical manufacturing could be the rate at which a manufacturer can fulfil an emerging pharmaceutical need or the speed at which a manufacturing process using CM could be designed, approved, and put on the market. These are the objectives the system is designed to achieve, but properties of the system emerge as the system is fielded called '**ilities**'.

The **ilities** of a system are related to the objectives and are the desired properties of the system—these are the functions that customers want. For the system developed in this thesis, the intended customer is the pharmaceutical manufacturer's decision-making body. The functions these customers would be interested in for CONTINUES are **adaptability** (can this system be used in a variety of processes?), **evolvability** (can this system constructively evolve as more manufacturers use it and provide feedback?), **usability** (is the system easy to use to get the desired emergent function?), **robustness** (does the system maintain its capability and function as external parameters change?), and **scalability** (can the system be used in a range of processes?).

If we go down one level of abstraction and look at an actual CM system a pharmaceutical manufacturer could adapt into their process using this CONTINUES, a wide range of ilities could be important. The system customer at that level could be varied because there could be several different, and sometimes conflicting, stakeholders. For example, a regulator would be interested in quality, safety, and traceability. While a payer would be more interested in affordability, efficiency, or

scalability. These ilities could sometimes be in conflict, thus contributing to the CM adoption barrier that must be overcome by CONTINUES.

3.2.3 Objects of Form, Processes, Relationships, and Instruments

Systems are designed in layers as illustrated in **Figure 8**, starting with the **value related operand** and other operands. Operands are what is being acted upon, changed, or processed in the system. Then, the **value related processes** are defined, followed by the **value instruments**—the tools the value related processes use to carry out their functions. The processes are the actions that act upon, change, or process the operand. The final layers involve incorporating the **supporting processes** facilitated by the **supporting instruments** and defining any **accompanying systems**. The supporting processes act upon the value instruments using the supporting instruments. The supporting instruments are typically affected by accompanying systems.

In CONTINUES, the objects of form are the chapters and their respective contents in this thesis that describe the instruments, relationships, and processes the system uses to execute the **system process**—guiding/convincing/facilitating CM adoptions on the **system operand**—pharmaceutical manufacturing enterprise. The following sections will describe the instruments used in CONTINUES and how they generate the processes and relationships within the system—ARIES, disruptive innovation theories, manufacturing innovation theories, and comprehensive literature review.[1]

[1] See Chapter 2 for comprehensive literature review

3.3 ARIES Framework

One of the instruments used in this sociotechnical system will be the Architecting Innovative Enterprise System (ARIES) framework. ARIES takes the architecture of an enterprise as it stands currently and devises a new architecture based on a series of steps. A key step in this process is imagining alternative architectures. These alternative architectures are then analyzed to determine the most appropriate architecture to produce the desired end state. A description of the ARIES framework was introduced in Chapter 2.[2]

The ARIES framework is a piece of form in this system and is a supporting instrument because it provides value instruments used to transform an enterprise from its current state to a future desirable state. In this thesis, ARIES is a tool for generating (process) the current and future pharmaceutical enterprise architecture along with the stakeholder analysis (operands). These value instruments are then used to inform the implementation framework and guide the change from batch manufacturing to CM.

3.4 Disruptive Technology Theories

Another tool used as a supporting instrument in this system will be Clayton Christensen's disruptive innovation theories supported by Geoffrey Moore's technology adoption model. These theories will be used to describe and generate (process) new enterprise architectures and disruption strategies for pharmaceutical manufacturing (operand) to change the current enterprise from batch to the desired state of ubiquitous CM adoption.

[2] See Chapter 2 for description of ARIES framework.

In 1997, Clayton Christensen published one of the most influential business texts of the 20th century "The Innovator's Dilemma.[46]" This and subsequent publications defined his disruptive innovation theories. In his writings, Christensen described how new market entrants will do what they need to do to survive, while incumbents are usually comfortable knowing they are thriving in the current market. This market security doesn't mean that incumbents thoughtlessly rest on their laurels. Incumbents stay close to their customers and ask, "do the customers want it?" Meaning incumbents tend to focus on the customer base that contributes the largest proportion of their profits—the sophisticated customers.

Christensen states that disruptive innovations aimed at the less sophisticated customers have a better chance of gaining entry into the market segment those customers occupy. For example, in the 1960s mini-mills were developed as a new way to make steel, and instead of aiming at the sophisticated customers in the steel market (sheet steel), the mini-mills aimed at the rebar market—the unsophisticated customers in the market.[46] Once the mini-mills captured the entire rebar segment, they moved up to the next rung on the ladder, and repeated the process until mini-mills dominated the entire steel industry (**Figure 10**).

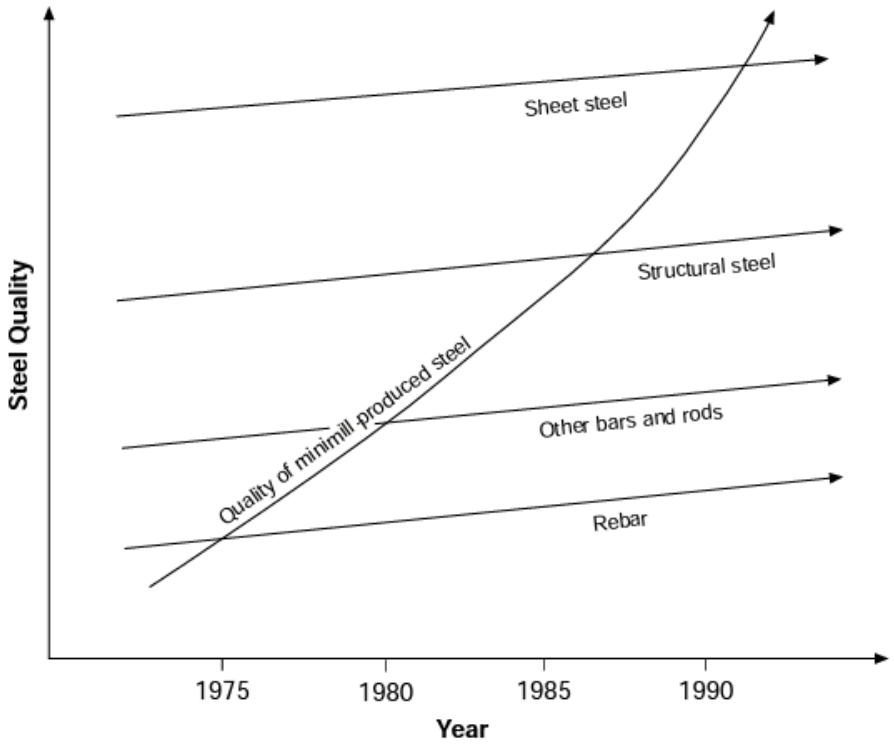

Figure 10 *Progress of Disruptive Mini-mill Steel Technology. Reprinted from "The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail"*

Throughout the next chapters, Clayton Christensen's disruptive innovation theories will be used to describe both the current state of the pharmaceutical manufacturing enterprise and the future of the enterprise. These theories will also be used to show how the current, almost exclusively, batch manufacturing structure of the enterprise requires change as it is clear that CM is on a trajectory to disrupt the industry. Finally, Christensen's theories will inform the implementation framework that will guide pharmaceutical manufacturers to adopt CM.

3.5 Manufacturing Innovation Theories

A third tool used in CONTINUES are the manufacturing innovation theories developed by Harvard Business School professor Willy Shih. This tool will be used to generate (process) current and future enterprise architectures and strategies for

innovative manufacturing (operands). These value operands will then be used to inform the implementation framework that will guide the enterprise to adopt CM as an additional tool to use rather than solely relying on batch manufacturing. In drug development, it has been said that the manufacturing process is the product[47]—a reason biotech companies began turning to manufacturing platform technology.[48] In practice, the manufacturing portion of the drug development process is tied heavily to the innovation/development method requiring close coordination with those who design and those who manufacture.[49] **Figure 11** describes the spectrum of how process and product can be interconnected, and pharmaceutical manufacturing can land anywhere on the left of the figure. Meaning the manufacturing process is heavily connected to the innovation/development process. However, as Shih points out, innovation/development has been steadily drifting away from manufacturing causing ripple effects throughout the US economy.

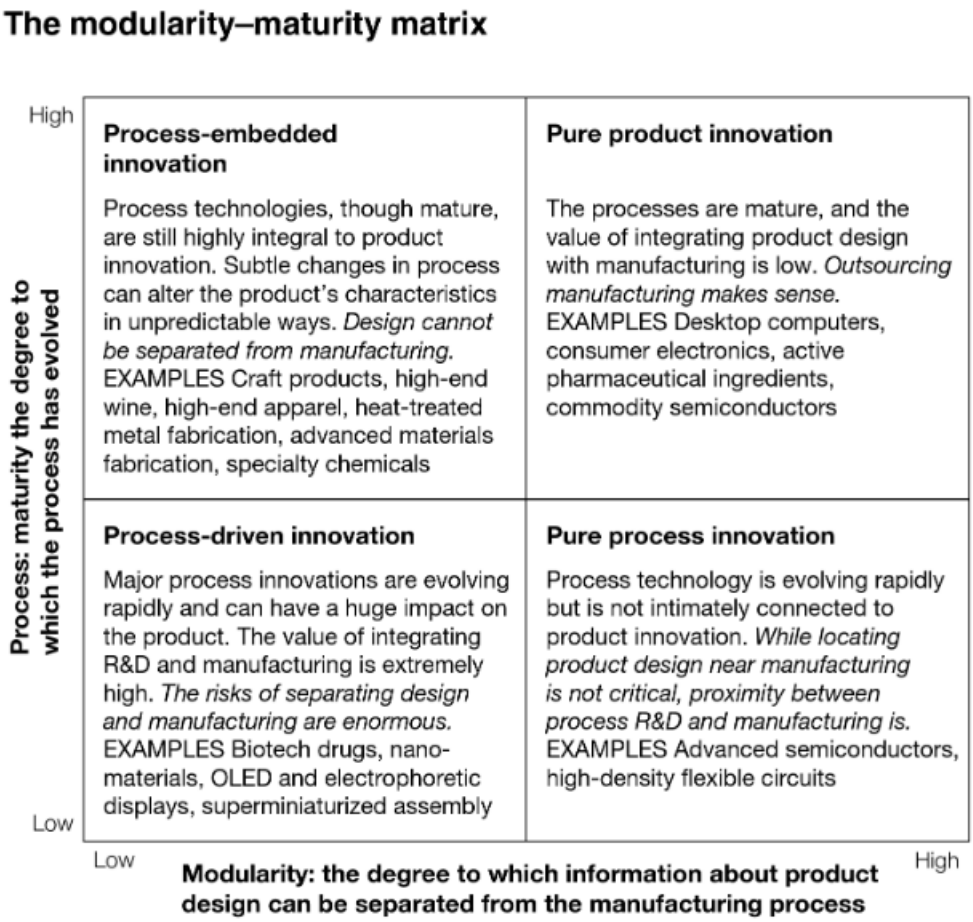

Figure 11 *Reprinted from "Does America Really Need Manufacturing"*

As the US has steadily progressed toward a more technologically complex ecosystem thanks in part to the exponential progression of IT and R&D, the country's manufacturing sector has declined by nearly 40% since the 1950s.[49] Many welcomed this decline in manufacturing as an opportunity to focus on more prosperous and innovative knowledge-based endeavors, but the two are not mutually exclusive. Manufacturing is often perceived as a low-skilled occupation with little value added when compared to economic sectors like R&D, but if manufacturing and innovation are separable, then how would one account for the manufacturing capabilities required to produce items required for biotech, semiconductors, aircraft

systems, and any number of complex systems and materials required for innovation progression?[49]

Clearly, the manufacturing sector suffers from a PR problem, because innovation relies heavily on manufacturing to bring new technologies to market. If innovation relies on manufacturing and the US is making big bets in entrepreneurship, then the US needs to be invested in manufacturing to the extent that the manufacturing investment has a reciprocal relationship with the innovations requiring advanced manufacturing. However, many still believe that the US can forgo manufacturing capabilities in pursuit of innovation development. Shih describes how the two—manufacturing and innovation—are intertwined in his explanation of the industrial commons.

Industrial commons are the network of operational capabilities, special skills, and knowhow shared by the industrial ecosystem both intrinsically and extrinsically.[49] Shih explains that the industrial commons is a key piece of industrial infrastructure, because it maintains an industrial competency level required for future ventures and innovations. In the absence of industrial commons, a knowledge gap opens and expands, leading to reduced or eliminated capabilities. Additionally, industrial commons are local phenomena meaning they tend to benefit those enterprises that are centrally located and the proximal benefit tends to decrease the farther away from the epicenter of the commons the enterprise drifts.[49] One needs look no further than the lack of a skilled additive manufacturing workforce to illustrate this inevitabilty.[50] Because manufacturing has become deemphasized in the US, the adoption and

utilization of additive manufacturing technology has missed the highwater mark that was originally predicted for its industrial transformative potential.

As manufacturing capabilities are outsourced to other countries, the suppliers that depended on the manufacturers find it more difficult to stay in business because they have lost their proximity to the industrial epicenter. As these support functions are then forced to outsource to stay profitable, the entrepreneurial agencies find it increasingly difficult and less profitable to invest in technology development and workforce education.[49] This cycle repeats as the outsourcing of manufacturing continues to erode innovation capabilities in a process of unintended consequences. Investing in the industrial commons in the US is not a patriotic decision; it is a good business decision,[49] and this framework uses this strategy as a value related process to produce the emergent function of the CM technology transition/adoption system.

Shih argues that a combination of management decisions and governmental policies bore the rise of science and technology (S&T) dominance in the US after World War II, driving the emerging technologies that defined the US as an entrepreneurial leader. Therefore, these same forces can and should be used to break the cycle of manufacturing outsourcing. "Government can create the right conditions, but ultimately, management decisions will determine what happens.[49]" In this document, the role of the government and the role of management are laid out both in their current state and their future envisioned state regarding CM adoption in the pharmaceutical manufacturing industry.

3.6 Role of the Literature Review

In CONTINUES the literature review that was accomplished in Chapter 2 will be used as a supporting instrument to help describe the current enterprise architecture and generate the future enterprise architecture. These value instruments will then be used to inform the implementation framework. The literature review will also be used to generate the stakeholder analysis and the CONOPS for the system. These value instruments will be used to guide the implementation framework for CM adoption.

Chapter 4 Enterprise Landscape and Stakeholder Analysis

In this chapter, the pharmaceutical manufacturing enterprise background is revisited briefly to illustrate the foundation for the current landscape. The landscape refers specifically to the ecosystem and the relevant stakeholders that the CONTINUES system will be used in and associated with. Both the enterprise's inner and outer landscape will help generate the stakeholder analysis used in CONTINUES to supplant current batch manufacturing and guide the enterprise to adopt CM.

4.1 Pharmaceutical Manufacturing Landscape

Based on the ARIES view elements described in Chapter 2, the enterprise ecosystem and the stakeholders are the foundation of the enterprise model.[1] They are not necessarily 'view' elements, because they are where the enterprise is housed, while the other eight elements are lenses through which we describe the enterprise. These other elements will be developed in Chapter 5. In this system, the ecosystem will be treated as the outer landscape, and the stakeholders will be treated as the

inner landscape along with the enterprise identity, guiding principles, motivations for change, and capabilities.[1]

The ecosystem (outer landscape) is the surrounding entities that envelope the enterprise. Importantly, the ecosystem is largely made of entities that the enterprise can influence but not control. The enterprise must adjust to the changes in the ecosystem, not the other way around. The internal landscape definition and analysis will include the enterprise stakeholders. Stakeholder analysis is used to determine the spectrum of influenced/influencing entities. This analysis is meant to determine how the current enterprise architecture is meeting the stakeholder's needs along with how a future enterprise architecture could influence the value delivered to/by the stakeholders.

4.1.1 Ecosystem

The key constituents, boundary, and scope of the pharmaceutical manufacturing ecosystem were described in Chapter 2. This description laid the foundation for the ecosystem description. In this chapter, the ecosystem definition will be further refined by describing the key uncertainty and influencing factors that affect the pharmaceutical manufacturing enterprise. These are the factors that, if shifts occur, could trigger an enterprise change.[1] The shifts that could influence/be influenced by CM adoption in the enterprise are described for each factor.

1. Regulatory: The enterprise is heavily regulated through multiple agencies, mainly the FDA in the US, to protect consumers. The role of the FDA was visited thoroughly in Chapter 2. As previously discussed, the FDA has shifted to embrace CM, but has stopped short of using more influential levers to increase/expedite adoption

throughout the enterprise. For example, the agency could adopt policies to force a certain percentage of NDAs to use CM.

2. Economic: Manufacturers are financed by investors betting on blockbuster drugs with substantial upfront capital. Because the enterprise is reliant on big investments on the front-end of product development, shifts in the economy could influence the ability for manufacturers to pursue new products. Because CM reduces the COGS, implementation of CM in the enterprise builds resilience against the influence of economic factors.

3. Market: Pharmaceutical manufacturers compete on new product development, IP, and generic (off-patent) formulas. A transition to CM has been shown to reduce the time to market for new products,[51] can help protect IP by moving the manufacturing process inhouse vs contracting it out, and can produce off-patent products locally due to reduced cost.

4. Technology: The technology used to manufacture medicines has evolved over the last two centuries from manual, small batch processing to sophisticated automated bioengineering of personalized drug products.[52] As previously discussed, the pharmaceutical manufacturing enterprise is slow to incorporate innovations, because they are exceedingly risk adverse. CM technology represents a disruptive innovation for the enterprise. Meaning, as CM becomes more pervasive, those manufacturers who are on the tail end of adoption will begin to become obsolete. This will be further explored in upcoming chapters.

5. Environmental: As global citizens increasingly turn their attention toward the planet's finite resources, companies have begun investing in more environmentally

friendly practices and are using these investments to attract and retain customers. Transition from batch to CM reduces waste as described previously. The shift toward an emphasis on corporate social responsibility (CSR) practices[53] will open the door for CM adoption in the pharmaceutical manufacturing enterprise.

6: Political: The enterprise is a sizable contributor to the totality of the American healthcare system and is therefore a vital piece of maintaining national security. The transition to CM will make for a better business case to bring manufacturing back within the US borders, thus eliminating supply chain considerations such as transit impediments, geopolitical turmoil, and localized shortages.

Figure 12 depicts how the above inner and outer landscapes interact along with their topography with relation to the pharmaceutical manufacturing enterprise.

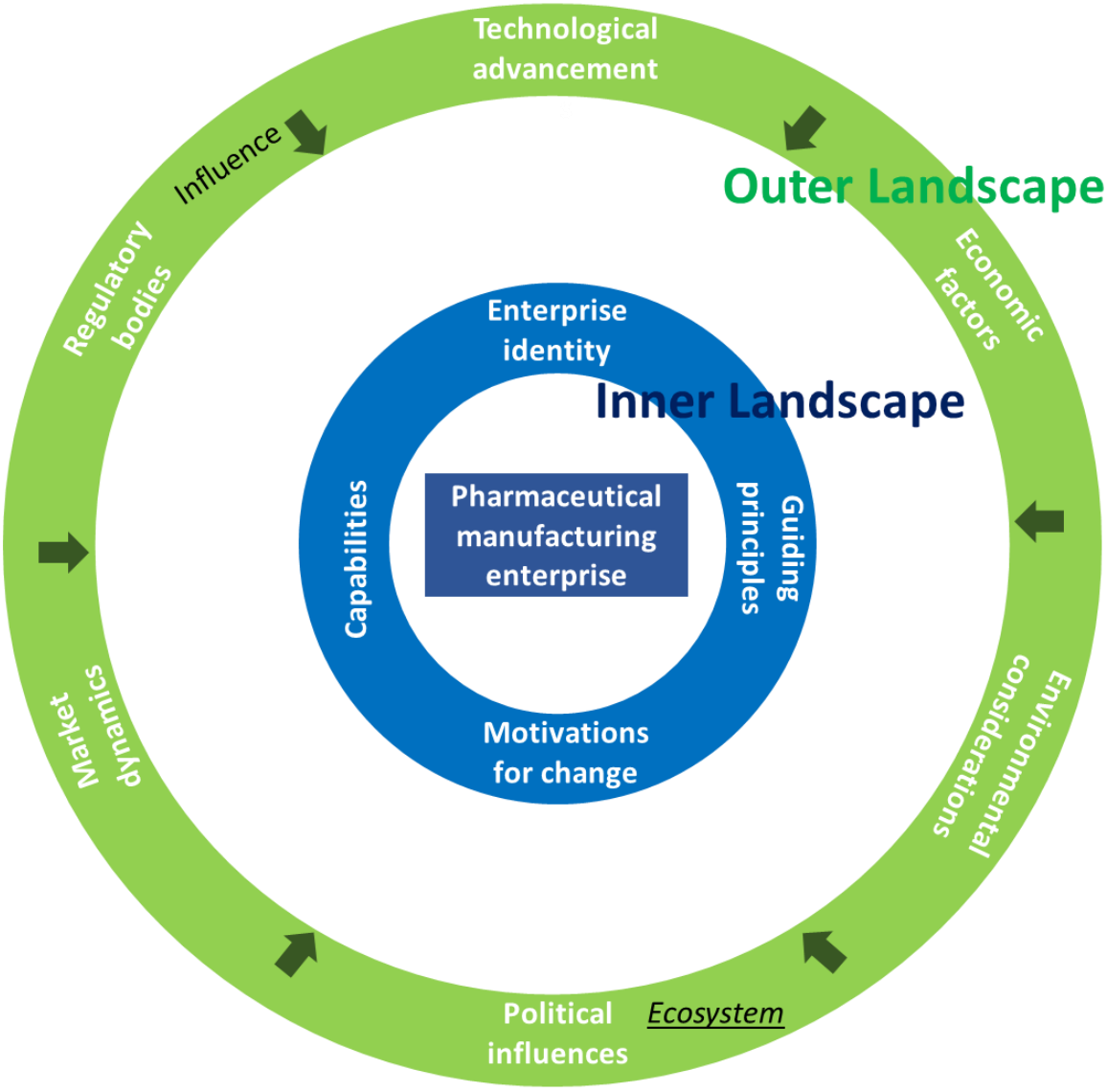

Figure 12 *The pharmaceutical manufacturing enterprise is nested in the inner and outer landscapes.*

4.1.2 Stakeholders

At this point, the internal landscape of the enterprise will be examined using the enterprise identity, guiding principles, motivations for change, and capabilities. This examination leads to an initial description of the stakeholders. First, the pharmaceutical manufacturing enterprise identity and guiding principles are associated with extreme quality standards and a laser-focus on patient safety. These

breed a culture of excessive risk mitigation and strict adherence to well established procedures and regulatory compliance. Next, the enterprise identity and principles have established an enterprise which has little motivation for changing manufacturing techniques, because the enterprise has over a century of data pointing to the quality and safety profile of the status quo batch manufacturing. However, the enterprise is financially motivated to change should the change prove profitable while still maintaining the standard safety profile. Many manufacturers don't see a financial upside for manufacturing changes. Finally, enterprise capabilities include groundbreaking R&D including clinical research, robust regulatory compliance methods, innovative process development, production of lifesaving/changing medications, marketing and sales, IP protection, and investment capital generation. These internal landscape characteristics can now help to generate an initial accounting of the enterprise stakeholders. The term 'stakeholder' refers to parties that touch or are touched by the system/architecture of interest. **Figure 12** explains how the outer landscape from section 4.1.1 and the internal landscape, including the stakeholders, interact to house the pharmaceutical manufacturing enterprise. **Figure 13** builds on this ecosystem model by describing the number and relative importance of each of the stakeholder interactions.

1. Pharmaceutical developers: The companies responsible for researching, developing, manufacturing, and marketing drug products.

2. Patients: The consumers of pharmaceutical products.

3. **Physicians:** Prescribe medications to patients based on their professional judgment of the patient's need.

4. **Collocated residents:** Individuals who reside near a manufacturer's facility.

5. **Regulators:** Government agencies charged with ensuring safety and efficacy standards in the pharmaceutical industry to maintain public trust and industrial fairness.

6. **Payers:** Agencies that pay healthcare costs on behalf of patients.

7. **Investors:** Fund the initial R&D to discover new products.

8. **Distributors:** Responsible for circulating APIs and finished products geographically so they can be sold.

9. **Suppliers:** The companies that provide materials to produce APIs and finished products.

10. **Employees:** Individuals who are employed by pharmaceutical manufacturers.

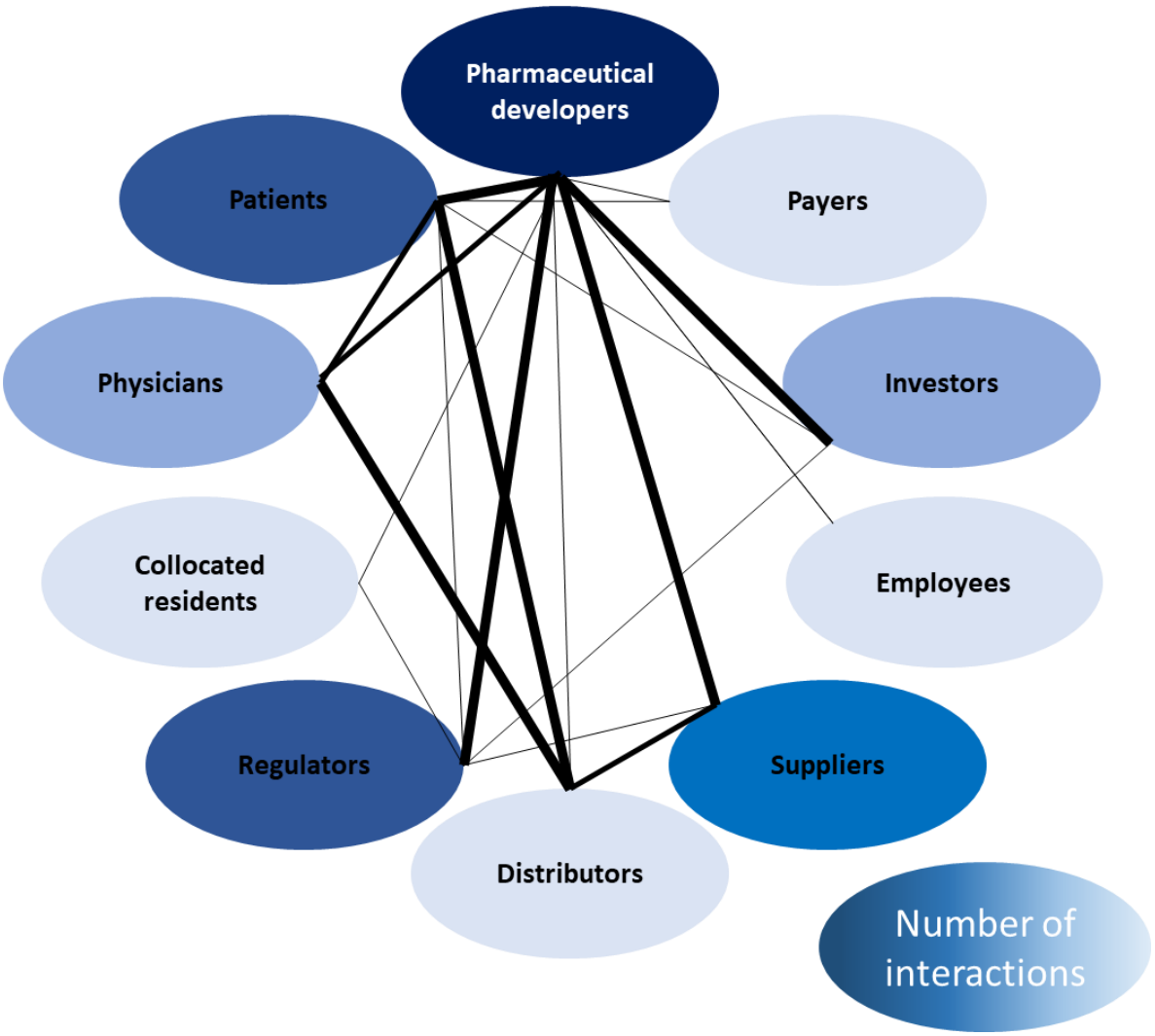

Figure 13 *The pharmaceutical manufacturing enterprise stakeholders have multiple interactions. Note: The stronger or more important interactions have been denoted via gradient line thickness.*

When designing a new enterprise architecture, stakeholders must be considered throughout the lifetime of the intended architecture, not just as a downstream consideration. In CONTINUES, these stakeholders will be considered to help coax the enterprise toward CM adoption by highlighting how CM will provide better value flows upstream and downstream. Additionally, the stakeholder analysis is used to guide the implementation framework toward those that are crucial to CM

execution. Based on the above list of enterprise stakeholders, the pharmaceutical developers stand out as crucial to CM adoption.

Once both models are derived, the entirety of the pharmaceutical manufacturing ecosystem can be modeled to illustrate the different layers and how they interact **Figure 14**.

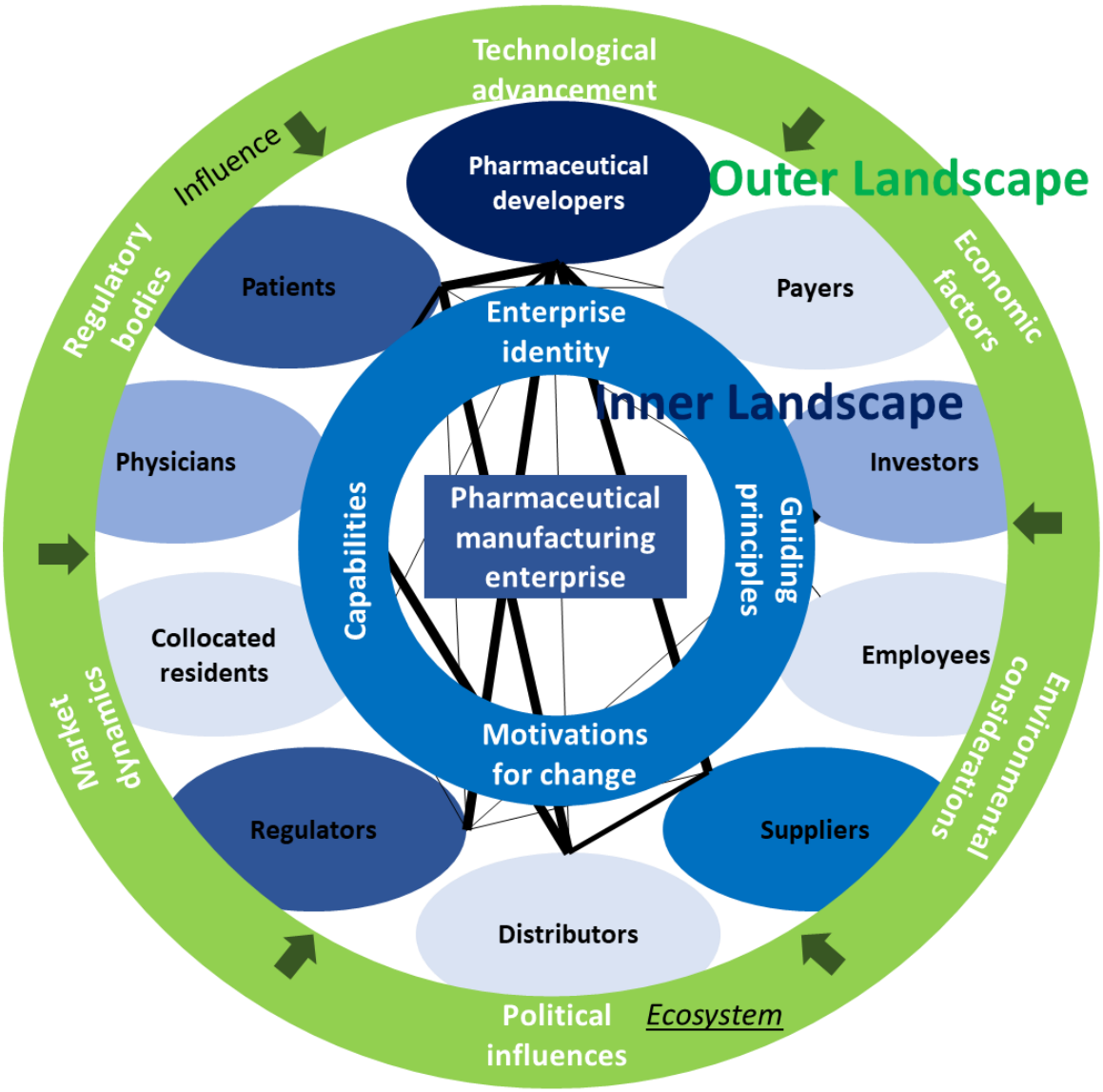

Figure 14 *The pharmaceutical manufacturing enterprise inner and outer landscapes overlayed onto the stakeholders and their relative interactions.*

4.2 Stakeholder Interviews

As part of the enterprise background and stakeholder analysis, and to better understand the perspectives of one of the most important stakeholders for CM adoption, the following questions were used in interviews with three pharmaceutical manufacturers. Each of the manufacturers had at least one FDA approved product produced using CM technology.

1. **What are the most significant challenges you have faced while implementing continuous manufacturing processes in your organization? How have you attempted to overcome these challenges? Can you provide some of the best lessons learned?**

Because the industry has worked in batch for so long, management of change is critical to successfully implementing CM into the manufacturing process. CM introduces such a different way of thinking about the manufacturing process, there can be a lot of resistance in an organization. The human element of the CM implementation becomes the hardest part of the change, because of humans' inherent resistance to change. One manufacture has introduced the idea of a pre-mortem—an effective technique developed by Gary Klein to determine how a project can fail before the project kicks off.[54] They use this technique to identify any and all major risks to CM implementation. Also, it was pointed out that the manufacturer has a tendency to want to exhaust batch manufacturing capacity before tapping into the CM capabilities even though CM adds a unique business benefit.

Another manufacturer pointed out that changing the way the quality department thinks about how to judge and assure batch quality has been challenging. Because

changing from batch to CM requires a different definition of a "batch", there is a need for updated and specific SOPs for CM.

Manufacturers have yet to change the manufacturing processes of established products from batch to CM, but they are increasingly looking to how to make new products using flow techniques. They look for synthetic steps that aren't as efficient in batch to produce in flow such as steps that involve meso mixing, fast reactions regardless of temperature or cryogenic reactions.

To overcome the challenges presented by CM adoption, a pervasive and protracted education campaign is needed to educate all levels of the company as to the benefits of CM and why it should be chosen vs batch. The manufacturers use multiple means of communication to attempt to normalize CM adoption. Because communication and education are key to CM adoption, some think that smaller firms would have an easier path to ubiquitous CM adoption. Finally, companies who use a top-down approach vs a bottom-up effort are having more success in CM incorporation.

2. How do you ensure regulatory compliance during the transition from batch to continuous manufacturing?

The use of the pre-mortem has been key to compliance assurance. Manufacturers are integrated into the regulatory aspect of the CM transition process by participating in the ICH Q13 development and by ensuring that regulators are trained on the use of CM. Additionally, the control strategy for the CM processes are developed to be able to retroactively engineer any possible anomaly in the process back to the cause. This is crucial to FDA approval. However, the FDA is concerned that the product is safe

and that it can be made consistently. Some manufacturers have experienced that the FDA appears to be agnostic to the process (batch vs flow) as long as the manufacturer can define a 'batch'. With batch manufacturing, the definition of a batch is straightforward and well established, but with flow a batch can be defined several ways e.g., the start-up batch, end batch.

3. What steps have you taken to train and develop your workforce to handle the new continuous manufacturing processes?

Manufacturers have implemented deliberate workforce plans for training employees with the new skillsets required for CM implementation. These plans have included upskilling through conferences and partnerships with industry and acidic collaborators. The manufacturers have been able to obtain their skilled workforce through a mix of new hires and upskilling of current employees. These employees are also required to be proficient in automation. Some manufacturers indicated that individuals with chemical engineering backgrounds are well suited for CM processes, so they pair chemical engineers with new hires in an apprentice type workforce development.

4. What do you think would jumpstart the ubiquitous adoption of continuous manufacturing in the pharmaceutical industry? Can you point to a key lever to increasing CM adoption?

It is believed that developing a standardized set of modularized technologies for CM processes in producing both APIs and finished drug products could jumpstart the adoption of CM. The most successful flow platforms are those that most closely

mirror scaleup. Because most people doing CM have their own way of doing it, regulators must learn a new process each time they are faced with an approval using CM. Additionally, standardization ensures a robust talent pool of skilled workers able to design and implement CM in pharmaceutical manufacturing. Currently, the competitive advantage goes to those manufacturers whose platform designs are superior which could help drive standardization. It is estimated that 40-50% of synthetic steps could be performed using a basic set of standardized flow reactors. Therefore, a standard set of platforms would level the playing field. This could be a place the FDA could impart influence.

5. Do you intend to expand continuous manufacturing to other products within your company?

Manufacturers agree that their companies have plans to expand CM to new products, but not to products that are already on the market. If they were to consider changing established products, the COGS would be a driver.

6. How do you see continuous manufacturing evolving in the pharmaceutical industry in the next 5-10 years, and how are you preparing for these changes?

There will always be processes that will be better suited to batch manufacturing, so in the near future it looks like there will be a hybrid between both CM and batch in the industry. Manufacturers are optimistic that standardization of flow equipment will become a reality in the next 5-10 years. This standardization will reduce the current 'firefighting' that the multiple flow platforms cause. Manufacturers are also hopeful that CM used for crystallization and drying will improve.

7. How do you measure the success of the transition from batch to continuous manufacturing in terms of production efficiency, product quality, or profitability?

Manufacturers use sustainability, environmental impacts, COGS, flexibility, and speed of delivery to measure the success of transitioning to CM. For example, a cycle time reduction of 50% is considered a success and a driver for future CM adoption. Or, when batch processing leaves no room for potential delays, flow is an attractive alternative. Additionally, manufacturers are reaching for a net-zero carbon emission standard. Therefore, the environmental benefits of CM have made it increasingly attractive.

8. Do you feel continuous manufacturing provides a strategic advantage over your competitors? How so?

Historically pharmaceutical companies have been bad at predicting the demand for their products. CM allows those who use it to flex with the demand. Also, it's expected that CM will provide increased speed to market through both shrinking the clinical and manufacturing timelines. Furthermore, having CM in the manufacturer's toolkit only increases their capabilities, inducing an inherent advantage over those that don't use CM.

9. How has the implementation of CM affected your supply chain and inventory management?

Currently, manufacturers have found that their supply chain and inventory management have been increasingly complicated by CM because they are maintaining a contingency. It is expected that this complexity will be alleviated as the

technology is more widely adopted. However, some manufacturers reported no clear difference in their ability to manage their supply chain.

10. What are the major cost implications of transitioning from batch to continuous manufacturing?

The cost implications discussed centered on how CM will reduce overall costs, so a smaller footprint and cheaper equipment were the major drivers important to the manufacturers. The costs associated with development and R&D for new flow processes are also considered.

Additionally, three continuous flow apparatus/process manufacturers/process developers were interviewed. The following questions were used to guide the conversation:

1. What types of commercial products have been produced/marketed using your equipment? One of the developers indicated that the commercial products that have been produced using their equipment are largely unknown, because once the equipment is delivered, the manufacturer doesn't necessarily include the system developer in downstream use. Generically, it is known that the CM equipment and accompanying process has been used in a two-step synthesis for an antibiotic. This antibiotic synthesis is much safer and efficient using the CM equipment/process because of the small volume needed in the flow apparatus. On a larger scale, there would be a requirement for much more heat transfer (exothermic quench) and the precise mixing achieved in flow (reaction time on the millisecond time scale) would not be possible. Another commercial application the CM equipment is being used

for is the recovery of enantiomeric impure product. The higher pressures that can be achieved safely in flow contribute to the effectiveness of this reaction.

Another flow process developer indicated that their process has been used to produce an antibody drug conjugate used in the delivery of chemotherapy. If approved by the FDA, it would be the first approved biologic made in flow and could open more doors for CM in biologics. Another flow process developer has filed an ANDA for a critical drug used when a patient requires intubation. There was a shortage of this drug during the COVID-19 pandemic, and approval of this drug, made using CM, could lead to more approvals of products that come with supply chain concerns. Once approved, this drug would be readily available in the US in a 'just add water' type of production scenario. Meaning, all ingredients would be delivered in packaging that would dictate the steps needed to create the finished dose. This medication could be prepared at the point of care and with less waste, because normally, once a vial is opened and a dose is removed, the remainder of the vial normally goes to waste unless used by other patients.

2. How does your equipment differ from traditional batch manufacturing? What are the biggest benefits from using your equipment? The main benefit that was highlighted by all the developers interviewed was the ability to automate the CM equipment and processes developed by these firms. The programmability of the systems provides the agility of CM. Each step can be controlled and isolated, meaning each step has the potential to be used in the next step or to be passed to another process. The automation is facilitated, in part, through extensive characterization of each system platform. The process developers know exactly how each type of

platform will fit into the reaction sequence and all kinetics have been characterized for each reactor type. One developer compared the system to a molecule, and the atoms of the molecule are the different processing steps. The systems can be reconfigured to make different products, just as atoms can be rearranged to create different molecules. While this can be done with batch manufacturing systems, the turnaround time for the system is cut to hours vs. days. Additionally, photochemical transformations were highlighted as a benefit to these flow systems over batch manufacturing.

One flow process developer uses cell-free synthesis to produce biologics in flow, which has the benefit of speed over typical synthetic biology techniques. Additionally, this type of CM technique has reduced maintenance considerations, elimination of cold chain requirements, and can be delivered at the point of care.

3. What kind of support do you provide for implementing continuous manufacturing processes, including process development, equipment validation, and regulatory compliance? Do you provide training? Can you provide onsite operation services?

One process developer indicated they provide support both at the manufacturer and allow the manufacturer to come train in their facility. They assist with Installation Qualifications (IQ) and Operational Qualifications (OQ) at the receiving site. The developers also provide regulatory documentation that will be needed for eventual CMC such as control strategy. For example: if mixing is a critical piece in a reaction step, the firm can provide the control strategy for the mixing piece to show how the mixing is sufficient. The developers indicated they will engage with the FDA. One

developer has a big hand in training the next generation of CM workforce but mentioned that training is typically not a market-driven process. Meaning, if pharmaceutical manufacturers want a skilled workforce, trained in the use of flow/CM, it would be helpful if the manufacturers or government agencies such as NIH provided fellowships.

One developer foot stomped that the chemistry is only about 10% of the process. The purification, isolation, and final dose production is the lion's share of the process. This is where it is important to program both the human and the equipment to achieve agility.

4. Why kinds of PAT are available for your equipment, and how are they used to ensure safety, consistency, and regulatory compliance?

The aim is for sophisticated PAT such as NMR, IR, RAMAN, etc., to be unnecessary beyond clinical development. The process characterization used for the overall control strategy should engineer the PAT out of the process. For example: If the process developers, using initial PAT, determine that a possible impurity is eliminated after washing three times, a wash x3 is added as a control strategy, and the PAT is no longer needed to detect that impurity. The developers use GMP quality control labs to develop this control strategy. One developer is actively working on developing sensors for critical quality attributes of the product.

5. Do you have any data on cost savings when converting batch manufacturing to your equipment? The developers emphasized that flow synthesis should be used only when the synthesis would benefit from it e.g., temperature, mixing, reaction time.

One developer indicated they have delivered continuous alternatives to batch for manufacturers, but it is unknown if they have been implemented. While the firm did not provide the equipment to Vertex to convert their batch process for Orkambi,[55] they did mention that that conversion resulted in cheaper and safer manufacturing of the drug than batch. One developer discussed a possible biologic that could be produced for $10 less a dose, but it has not been submitted to the FDA.

One developer is focused on providing medications as a service and is not focused on changes in cost as much as they are focused on the agility achieved. Ensuring the integrity of America's access to medicine is where this developer is providing value.

4.3 Pharmaceutical Manufacturing Enterprise Stakeholder Analysis

Now that the most relevant stakeholders have been identified, the stakeholders' value proposition is examined. The value proposition is what the stakeholders provide the enterprise, and what the enterprise gives to the stakeholders.[1] **Table 1** describes this value exchange that flows to and from each of the stakeholders.

Table 1 *Pharmaceutical Manufacturer Stakeholder Value Exchange*

Value expected from the enterprise	Stakeholder	Value contributed to the enterprise
Infrastructure and talent capable of developing blockbuster drugs quickly	Pharmaceutical developers	Research and develop new therapies capable of addressing current and emerging health concerns
Safe and rewarding employment	Employees	New ideas, skills, and innovations
Revenue from sales and support	Suppliers	Provide high-quality raw materials when and where they are needed
Provide a pollution-free environment	Collocated residents	Provide a good community to attract high-quality employees
Provide needed products to address current and emerging health concerns	Distributors	Widest dissemination of products for maximum market saturation where therapies are needed
Develop and market safe and effective therapies in an expeditious manner	Patients	Consume products; identify emerging health concerns; participate in clinical trials for new therapies
Safe and effective therapies brought quickly to market to address current and emerging health concerns	Physicians	Prescribe products as needed to address current and emerging health concerns
Lowest achievable cost for therapies	Payers	Reduce out-of-pocket expenses for patients; allow easier access to products
Maximum ROI	Investors	Up-front capital investments used to research potential therapies
Safe and effective therapies. Orderly, verifiable, and comprehensible data	Regulators	Maintenance of high barrier to entry market for therapies; ensure products are safe and effective

From this table, a graphical representation of each of these value flows and how they are contributing to the enterprise architecture can be derived (**Figure 15**).

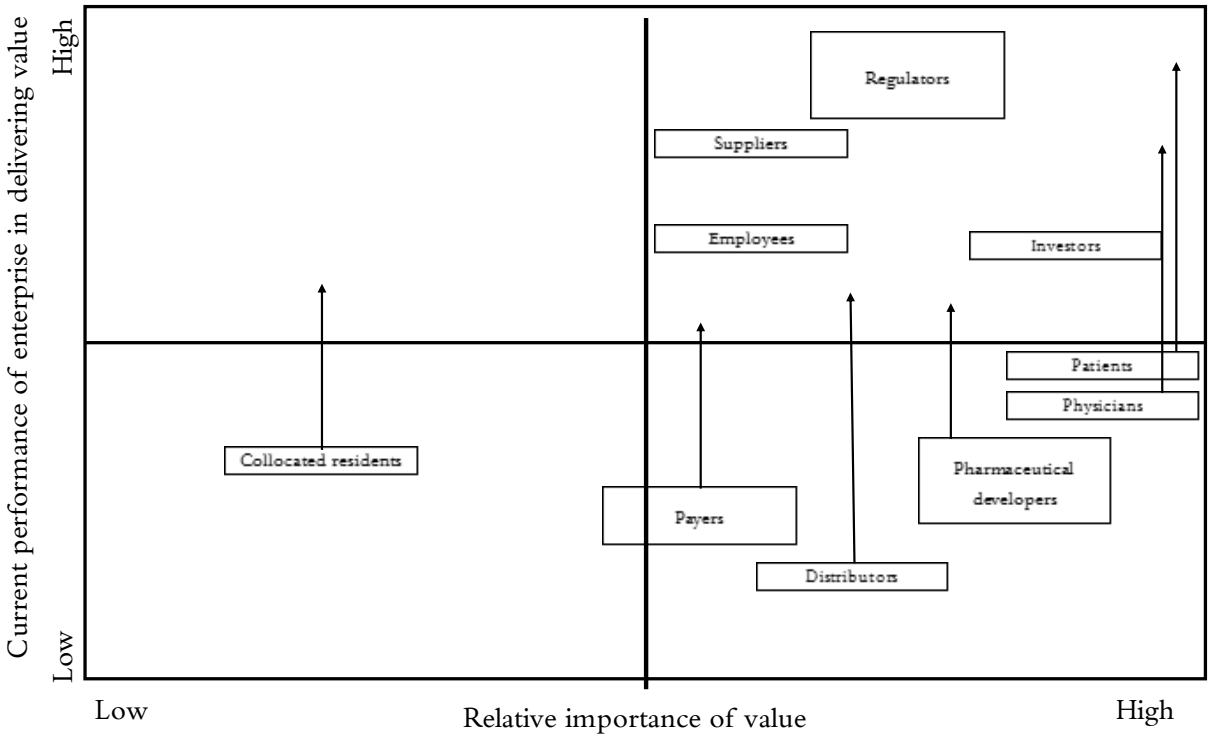

Figure 15 *Consolidated Pharmaceutical Manufacturing Enterprise Stakeholder Value Exchange*

This analysis can help determine which stakeholders are most important, which ones are underserved, and which stakeholders may have similar issues.[1] For the pharmaceutical manufacturing enterprise, based on the previous literature review[3] and interviews with stakeholders, the following high-value stakeholder needs are falling short in value delivered by the enterprise. First, payers (mid-level enterprise importance) are not receiving the lowest cost possible for products, because products could be produced more economically if done in a more efficient manner. Second,

[3] See Chapter 2

distributors (mid to high-level enterprise importance) are not able to consistently access products needed for distribution due to supply chain shortfalls and interruptions. Next, pharmaceutical developers (high-level enterprise importance) could receive improved access to infrastructure capable of providing therapies more expeditiously if slower batch manufacturing processes were updated to more efficient systems. Finally, patients and physicians (highest-level enterprise importance) could receive improved access to therapies if the products were made more quickly so that emergent health needs and/or on-going needs could be addressed expeditiously. Additionally, collocated residents (low-level enterprise importance) could benefit from more ecofriendly processes to ensure less local pollution. While these are lower value stakeholders, improving their enterprise value remains an important part of transforming the enterprise.

Chapter 5 Current and Intended Future Enterprise Architecture

In this chapter, the current enterprise architecture is examined through the lenses of the remaining eight view elements laid out in the ARIES model. The current architecture provides the bedrock upon which to launch the new intended architecture.[1] A SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis for the current pharmaceutical manufacturing enterprise will be synthesized as a culmination of the current architecture description and as a segway into the future architecture. This chapter will then examine the future intended enterprise. For CONTINUES, this change in architecture is a deliberate enterprise transformation intended to improve and propel the enterprise into a new era of manufacturing

capabilities. This intended enterprise architecture will drive the implementation roadmap produced in Chapter 6.

5.1 Current Enterprise Architecture

In the previous chapter, the enterprise **ecosystem** and **stakeholders** were examined. These two elements were highlighted separately because they are the highest priority of the ten view elements when examining the current enterprise architecture and provide the basis upon which to build the remaining view elements. Below, the remaining eight view elements are examined to complete the picture of the current pharmaceutical manufacturing enterprise (**Figure 16**). These elements were examined based on the literature review, manufacturing innovation theories, and the stakeholder interviews. Following these view element definitions, further analysis of the enterprise using disruptive innovation theories will demonstrate which elements, along with ecosystem and stakeholders, are critical in transforming the enterprise based on highlighted gaps.

5.1.1 View Elements

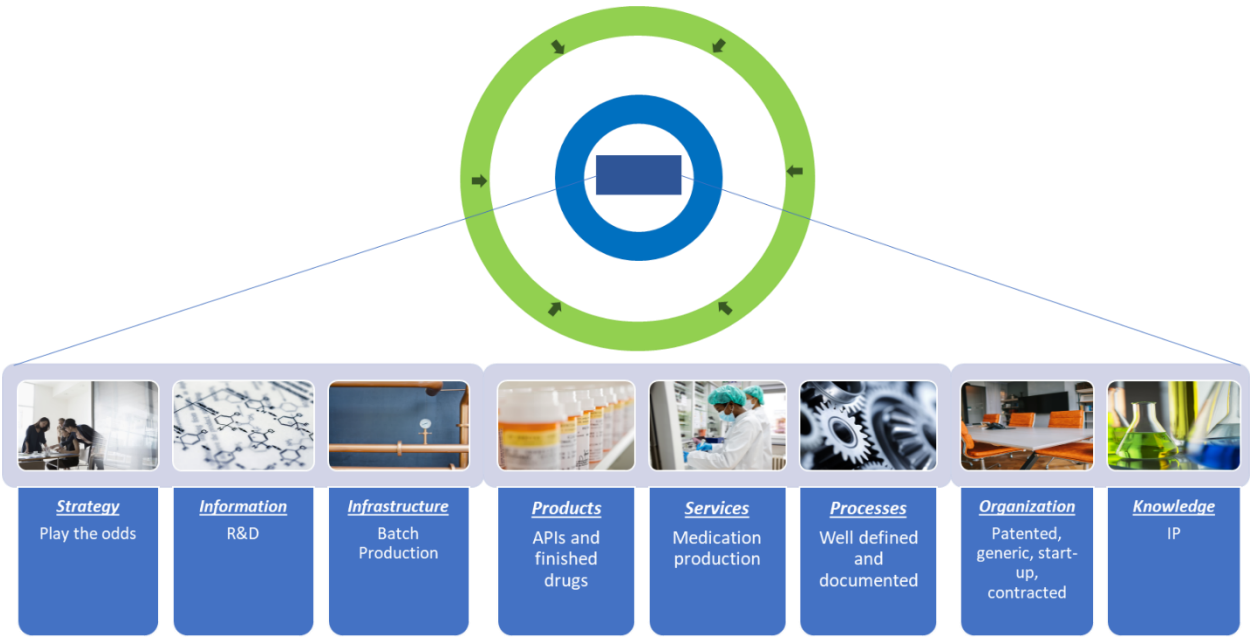

Figure 16 *View Elements Within the Pharmaceutical Manufacturing Enterprise*

Strategy: A typical strategy for a pharmaceutical manufacturing company would be to produce innovative, effective, and safe products while providing maximum profits to investors and maintaining and securing IP. Additionally, many company strategies have become increasingly focused on ensuring environmentally friendly product manufacturing while maintaining efficiency.

The business model for pharmaceutical companies is notably different from that of other industries because the companies rely on significant upfront investment for their R&D—investing in a product that doesn't exist yet. Most drug candidates in the initial phases of R&D never make it into the next phase, let alone all the way to FDA approval. It is estimated that 90% of all compounds investigated for druggable

targets fail.[56] With these dismal odds, investors have to count on developers to play the numbers game when researching potential candidates in order to lessen the uncertainty in the investment. Investors spend a significant amount of upfront capital to investigate enough candidates so that, based on probability, there will be a few that gain FDA approval, reach the market, and pay off.

Information: The information pharmaceutical manufacturers require to accomplish their mission includes emergent medical needs and threats, available technology capabilities, the latest regulatory considerations, industrial capabilities, product landscape, product specifications, and required synthetic process parameters. PAT provides critical process information needed to develop efficient CMCs for production. The enterprise gains information through a heavy investment in R&D. This is how the enterprise determines what druggable targets to pursue, and what possible hit molecules can affect the targets. This is a painstaking process that takes years, but the industry is willing to make significant investments—both time and money—in the information gained from R&D. Because the enterprise invests so heavily in R&D, they also take great care to protect the IP that is generated from it.

Infrastructure: The enterprise requires processing apparatus such as batch mixers and other synthetic capabilities, analytical equipment, a skilled and trained workforce, regulatory communication, and a robust/functional supply chain to receive ingredients and distribute finished products. Larger companies tend to have sizable and diverse portfolios which carries with it a large infrastructure requirement. While smaller organizations regularly anchor their firm to a unique chemical modality or technology.[27]

Currently, there is tension between the impending partial obsolescence of pharmaceutical batch manufacturing and the process innovation that is pharmaceutical CM. While batch manufacturing has been the norm for pharmaceutical manufacturing, batch manufacturing facilities will eventually need to be decommissioned to upgrade or replace equipment which presents a key opportunity for the manufacturer to pivot to CM technology.

A barrier to adoption by the pharmaceutical manufacturers is that converting the manufacturing process to CM makes the current batch capital stock outmoded, and many firms have capital stock that is not fully depreciated. However, CM dramatically changes economies of scale for pharmaceutical production and thus capital costs. Prior to conversion of infrastructure, these firms need to compare the competitive cost benefits from upgrading their facilities to accommodate this process innovation with cost avoidance.

Products: The products the pharmaceutical manufacturers make (APIs and finished pharmaceuticals) are therapies designed to prevent, treat, or alleviate health conditions. These products include prescription drugs (both brand name and generic), over-the-counter medications, dietary supplements, and vaccines. These products can be classified broadly on the spectrum of small molecules through biologics.

Services: The services provided by the enterprise include the production of medications using strict regulatory standards and CGMP. Additionally, manufacturers can deliver specialized production services in collaboration with pharmaceutical

developers to share expertise critical for innovative product development. Manufacturers can also provide patient support such as product information and pricing adjustments.

Process: The key processes where pharmaceutical manufacturers create value for stakeholders is through strategic planning, innovation, and risk management (QRM), quality assurance and process management—to include scale up, supply chain management, and IT management. Because the enterprise is heavily regulated, processes are well defined and documented thoroughly.

Organization: The current pharmaceutical industry can be segmented into five categories:[21] 1. Expansive, global R&D focused organizations that are responsible for bringing typical patented drug products to market. 2. Generic drug companies. 3. A wide array of start-up and medium-size organizations, responsible for the development of cutting-edge treatments and drug delivery systems. 4. Contract services that provide development and manufacturing facilities for categories 1-3. 5. Technology production companies that deliver process equipment, PAT, data/information technology, and related supportive services. Pharmaceutical manufacturers would ideally be integrated with the development processes so that the commercial scale production of the product would be able to produce the same product used at clinical scales. Some contracted manufacturers are not integrated, but this organizational structure is common when the product and the manufacturing process is well known and not novel. From **Figure 11**, Shih outlines that pharmaceuticals are on the low end of modularity capability meaning that the manufacturing process and the product are highly coupled. Additionally, he states

that the pharmaceutical development process has a low degree of maturity, mainly due to the rapid pace of innovation in the field.[49] In other words, pharmaceutical development processes can't be considered to be mature because the development technology is constantly progressing, thus the development process doesn't have an opportunity for homeostasis. This combination of low modularity and low process maturity indicates that the manufacturing process of pharmaceuticals requires a high degree of proximity between the development process and the manufacturing process. However, many pharmaceutical development companies are contracting out the manufacturing process in contrast to this requirement and possibly to the detriment of the development firm's future capabilities. "This strategy runs the risk of diffusing proprietary know-how, and making processes more standardized across the industry and dramatically reducing the role manufacturing can play as a barrier to entry.[49]" Shih also adds that in the case of biotherapeutics, out sourcing the manufacturing may jeopardize the development firm's market share when these relatively new medicines start to come off patent and biosimilars are introduced.

Knowledge: The pharmaceutical manufacturing enterprise hinges on IP from innovations in new products. The IP is centered around the synthesis of novel products that have been investigated for safety and efficacy in regulated clinical trials. The IP does not typically encompass the manufacturing process of the API or the finished product. The enterprise has a common thread of knowledge of how to manufacture products using bulk manufacturing technology, because these same techniques have been used for decades. The workforce is well educated and stable.[57] This leads to a stability in corporate knowledge, but new, talented, young entrants

arrive continuously. Additionally, knowledge flows to the consumer in the form of advertising of products. This allows the consumer to be more informed about possible treatment options. (Discussed further in 5.2).

5.1.2 View Elements Analysis

Pharmaceutical companies compete on **products** and **knowledge**, but have room to compete on their manufacturing **processes**, **infrastructure**, and **strategy**. The above view elements highlight that these five elements, combined with the **ecosystem** and **stakeholders**, have potential levers for CM adoption, because the current architectural design of pharmaceutical manufacturing has reached a limit of improvement capability. In a heavily regulated industry, market entry is closely controlled leading to little innovation. Therefore, the current platform architecture (almost exclusively bulk manufacturing) is primed for a disruption/architecture change to improve capability, and this shift should result in a change in competitive advantage.

Disruptive technology typically does worse on value dimensions at the outset but provides value in another dimensions that consumers, in this case the pharmaceutical companies, would prioritize over existing values. Unfortunately, loss aversion is working against CM adoption. Pharmaceutical manufacturers have been choosing to maintain the design decision of manufacturing drug products using bulk processes, because they are anchored on the technology. This decision space has remained stable for over a century, and this is a huge amount of inertia to attempt to overcome. A disruptive innovation, such as CM, is needed to break this trend and overcome this inaction.

Established pharmaceutical manufacturers are poised to be the leaders in this innovation space, because start-up companies will feel they don't have the resources to invest in flow platforms at the outset unless the risk of the regulatory landscape has been sufficiently codified. Similarly, smaller companies and start-ups may not feel comfortable investing in the use of flow platforms unless they see multiple successful NDAs or ANDAs using flow platforms for product manufacturing. Hence, established pharmaceutical manufacturers would have to play the role of both incumbent and market entrant simultaneously to adopt CM.

Flow synthesis presents an opportunity for pharmaceutical development companies to maintain local/in-house manufacturing, because the adoption of CM will reduce the infrastructure footprint and lead to less expensive manufacturing over the drug lifecycle[58]—two key reasons developers turn to CMOs. Another benefit of moving to a smaller footprint/modular manufacturing set-up would be better IP protection, because the firm can move the manufacturing from contractor facilities to in-house, improving information protection capabilities.

Commercially available flow chemistry systems are designed to be highly modular in nature.[41] The modularity increases the pharmaceutical manufacturing firm's process flexibility and capability by allowing for facile process changes simply by substituting one module for another to achieve an alternative product. This modularity utilization capability is demonstrative of a technology that is relatively mature, yet it is incorporated into a process that is everchanging to keep pace with innovation. This seemingly inconsistent juxtaposition may telegraph a clue to the reasoning behind the pharmaceutical manufacturing industry's hesitance to adopt

CM. The industry is aware of the symbiotic nature of their product design and manufacturing process technology. Therefore, the thought of transitioning a highly coupled manufacturing process to a modular means of production may seem incongruous.

5.1.3 SWOT Analysis

Based on the current enterprise architecture analysis, a SWOT analysis can be synthesized to facilitate the transition to envisioning a future architecture. This analysis will summarize the enterprise strengths, weaknesses, opportunities, and threats, and these will be used to generate an envisioned architecture for widespread CM utilization.

Strengths:

1. Strong regulatory framework to ensure safety and efficacy of products.
2. Significant investments in R&D, leading to innovative and life-saving drugs.
3. Established market presence and brand recognition for globally established pharmaceutical companies.
4. Large network of suppliers and distributors for APIs and finished products.
5. Well established infrastructure capabilities and IT incorporation.
6. Highly skilled, innovative, and trained workforce.

Weaknesses:

1. Reliance on large upfront investments for drug development, making the industry vulnerable to economic shifts.
2. Slow adoption of new manufacturing technologies due to risk aversion and emphasis on quality and safety.

3. Limited financial motivation for manufacturers to adopt new manufacturing techniques.
4. High prices for some drugs leading to affordability concerns for patients.
5. Dependence on foreign sources for raw materials and production, leading to supply chain risks.

Opportunities:

1. Adoption of Continuous Manufacturing (CM) can reduce costs and improve efficiency in drug manufacturing.
2. Advances in automation and AI can drive increased efficiency and lead to breakthrough innovations.
3. Transition to CM can help protect Intellectual Property by moving the manufacturing process in-house.
4. CM can produce off-patent products in a more profitable manner thus allowing the production to move locally, reducing dependence on foreign sources and mitigating supply chain risks.
5. Increasing emphasis on corporate social responsibility (CSR) practices can drive adoption of environmentally friendly practices.
6. Political pressure to bring manufacturing back within the US borders can create a better business case for CM adoption.

Threats:

1. Increasing regulatory scrutiny and requirements may increase costs and limit innovation.
2. Patent expirations and generic competition can erode market share and revenue.
3. Increased public scrutiny and negative perceptions of the industry due to high drug prices, environmentally hazardous, and unethical practices.

4. Global economic uncertainty and instability can impact investment in drug development.
5. Disruptive technologies and new entrants can challenge established companies and disrupt the industry.

5.2 Envisioned Future Architecture

"Most of the world's steel has been made by massive integrated steel companies. The other way to do it is to build a mini mill. In a mini mill, you melt scrap in electric furnaces, and you could easily fit four of them in this room. The most important thing about a mini mill is that you can make steel for twenty per cent lower cost than you can make it in an integrated mill. Now, imagine you're the C.E.O. of a steel company somewhere. In a really good year, your net profit will be two to four per cent. Here is a technology that would reduce the cost of making steel by twenty per cent. Don't you think you'd adopt it? And yet not a single integrated steel company, anywhere in the world, built a mini mill. Today, all but one of the integrated mills have gone bankrupt. So here is why something that makes consummate sense can be impossible for smart people to do.[59] *" Reprinted from speech delivered by Clayton Christensen 2012*

The future state of the pharmaceutical industry is moving towards an increase in distributed networks of regulated products which could lead to an uptick in personalized medicine.[60] As this future becomes more apparent, the traditional batch manufacturing process will begin to give way to more advanced manufacturing processes such as CM.[61] A definition of disruptive technology is a technology that forces adopters to interact with the product differently,[62] and CM would certainly force manufacturers to interact with their production facilities differently. Therefore, employing theories and techniques aimed at making consumers comfortable with adopting disruptive technology is the basis of CONTINUES.

Technology consumers can be separated into innovators, early adopters, early majority, late majority, and laggards on the technology adoption lifecycle.[62] **Figure 17** shows the timeline of adoption relative to the amount of adopters in each category. Also evident are the gaps that exist between each category of consumer. These gaps

are opportunities for the technology adoption to either fail to progress further to the right or continue through the adoption trajectory. The key to full spectrum market

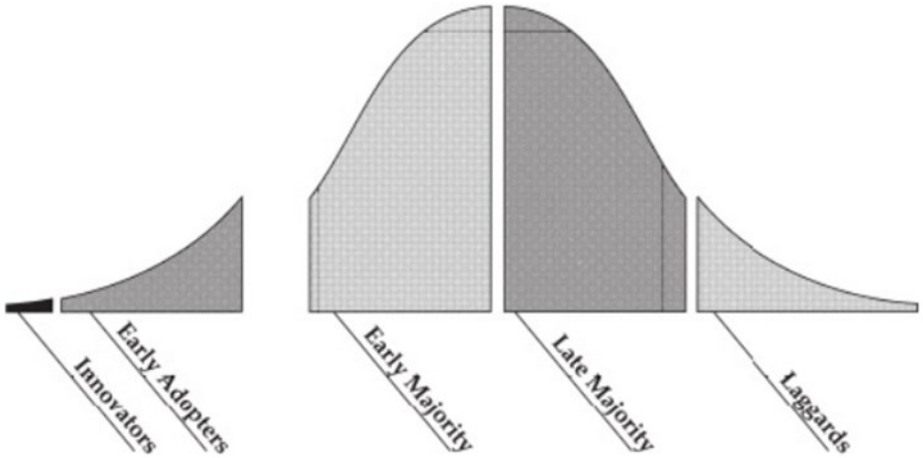

Figure 17 *Illustrates market penetration and the gaps between each for new technologies over time based on the types of consumers it attracts. Reprinted from "Crossing the Chasm."*

adoption/penetration lies in maneuvering through these gaps between consumer categories. For the purposes of CONTINUES, manufacturers are considered consumers of the technology. The nature of CONTINUES requires that it focuses on guiding CM across the small gap between the innovators and the early adopters and the 'chasm', as Moore describes in "Crossing the Chasm"[62] that exists between the early adopters and the early majority.

Consumers as individuals normally fit into one of these categories based on their personality and the relevant technology category. Successful tech companies, interested in selling their products, know how to target each of these types of consumers when launching new products, and the best strategy is to begin with the innovators and early adopters. As consumers from categories to the left adopt a new technology, the rate of adoption progresses into the subsequent categories. However,

it's difficult to pinpoint the specific pharmaceutical manufacturers that might fit into the categories to the left, so strategic targeting may not be the best course of action for CONTINUES.

A key to convincing early adopters and beyond, is first winning over the visionaries who can see the potential of the technology—what the technology can accomplish that hasn't been done before.[62] Based on the current level of CM incorporation in the enterprise, and the existence of programs, championed by forward thinking agencies such as DARPA, aimed at propelling CM technology forward,[38] these visionaries have seen what this technology can provide—democratized, personalized, on-demand medicine. CONTINUES is an attempt to provide the pathway for pharmaceutical manufacturers to become early adopters and beyond.

CM adoption by traditional batch pharmaceutical manufacturers is merely the first step in the process toward fulfilling the future of CM, recognized by enterprise visionaries. From the CONTINUES concept map **Figure 9**, the steppingstone between established manufacturing operations' transition to CM and democratized pharmaceutical facilities is a more distributed network of CM capabilities. This median CM deployment could mean small footprint CM capabilities located in hospitals and pharmacies (possibly replacing compounding pharmacies). But, before this ultimate democratization of pharmaceutical access can be fully realized, the transition of batch manufacturing to CM, where CM would make better sense, by established pharmaceutical manufacturing firms will need to emerge as the dominant enterprise architecture.

These manufacturers need to be the early adopters of the technology in the pharmaceutical enterprise if CM stands a chance of fulfilling its potential for readily available personalized medicine. Interestingly, examining CM adoption from one level of abstraction up from the pharmaceutical manufacturing enterprise, the enterprise, when treated as a consumer, is actually further to the right on the technology adoption spectrum. Because many other industries have already fully

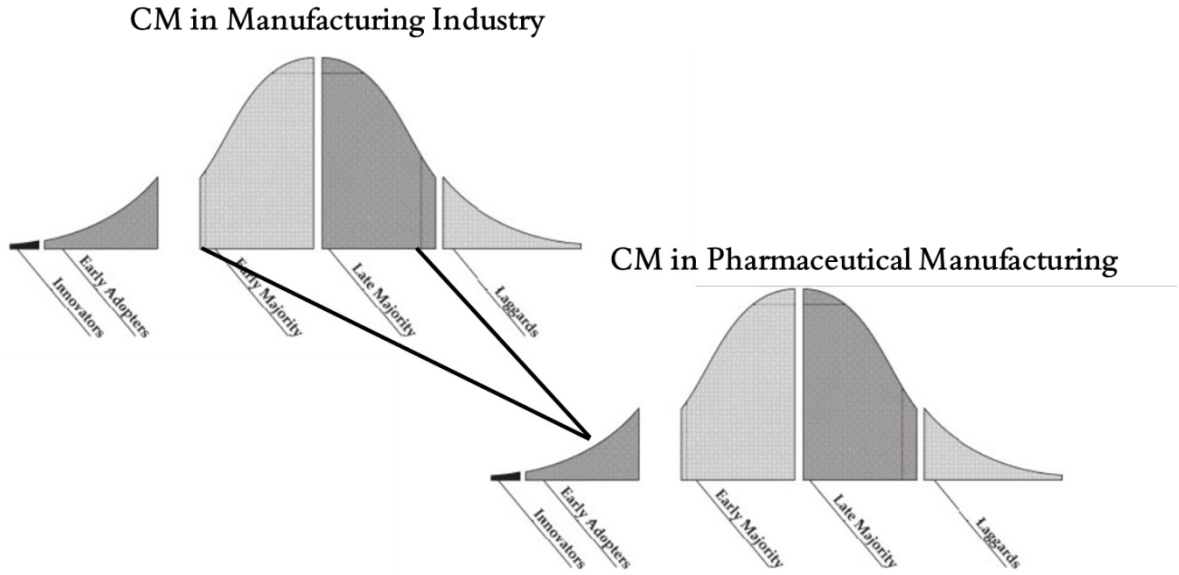

Figure 18 *The manufacturing industry is further along the technology adoption spectrum with respect to CM than the pharmaceutical manufacturing segment.*

embraced CM, such as oil refining, metal smelting, paper production, and even peanut butter,[63] the pharmaceutical manufacturers could be categorized as early or even late majority (**Figure 18**). This provides a greater range of tools to leverage pharmaceutical enterprise-wide adoption, because each "captured" group can be used as a reference to the next category.[62] Analogous industrial success stories, similar to "testimonials" are a good way to build trust in groups to the right of the spectrum.

Continuous casting of steel, or strand casting, is an analogous technology to continuous flow chemistry in that a continuous flow of molten steel is poured into a stream that is then cast into the desired shape using continuous rollers. Prior to this disruptive technology's introduction, the molten steel was poured into pre-formed shapes to solidify—batch manufacturing technology. Adoption of continuous casting led to significant cost savings, increased standardization, and improved process control due to automation capabilities. However, the steel industry was slow to adopt the technology because it didn't provide cost incentives that would compare with the incumbent batch technology.[45]

CM presents a set of attributes that investors may not initially see as desirable. Managers are all-too-often judged upon their ability to make successful bets on future trends. Therefore, managers will typically stick to betting on processes that are well established vs. risking venturing into a potentially disruptive technology. Yet, there is no doubt that CM's attractiveness will become evident to investors, and value will increase at a rapid rate following initial adoption and growth in the industry. Christensen said "When a technology that has the potential for revolutionizing an industry emerges, established companies typically see it as unattractive."[45] Disruptive innovations typically underperform existing technologies at the outset, and are therefore overlooked by enterprises that are hyper-focused on their customer's needs.

Incumbents are inclined to cater to their sophisticated customers while ignoring opportunities to service their less sophisticated customers' needs.[45] In the case of CM, the incumbent would be the established pharmaceutical manufacturing firm, and in Chapter 4, stakeholder analysis revealed what could be considered the

sophisticated and less sophisticated customers for the pharmaceutical manufacturing enterprise (**Figure 15**). This incumbent's sophisticated customer would then be the investors who place very large bets (upwards of $2B) on pharmaceutical development[64] in anticipation of, in the best case, the next blockbuster drug, but will settle for drugs that turn a modest profit.[65] With an average annual profitability rate of ~14% for pharmaceutical companies compared to an ~8% rate in other industries,[66] the pharmaceutical enterprise's investor customer base is highly influential. The pharmaceutical manufacturing enterprise is focused on keeping this customer satisfied by removing risk and increasing speed wherever they can effect change in the process. Because the front end of the investment is so risky, the manufacturers attempt to streamline all other variables to compensate. This way they can continue to maximize ROI for the investors, who will then continue to invest.

In an audit conducted by the FDA published in 2022, the agency looked at data related to some key issues that manufacturers have pointed to as a barrier to adoption of CM: increased regulatory scrutiny leading to increased time to approval and protracted time to market of products and difficulty in post approval changes.[51] While the data set the auditors reviewed was relatively small (only 5 approved drugs made using CM technology) due to the aforementioned sluggishness in CM adoption, their findings may help assuage pharmaceutical manufacturing hesitancy. Of the key takeaways, the most notable is that drugs manufactured using CM were approved three months faster than batch and were brought to market four months sooner resulting in increased patient access and an estimated $171-537M in early revenue access.[51] It is noted that CM products were brought to market faster than

their batch counterparts indicating that the scaleup required to take a product to the commercial market is a factor that weighs on batch processes whereas CM processes are primed to reach consumers more rapidly following approval. Interestingly, the report also noted that the CM applications tended to be subjected to slightly increased scrutiny manifested in pre-approval inspections. The authors postulate that this could be an indication of a difference in focus for regulatory approval between batch and CM. The audit also highlighted that approved batch processes accounted for 100% of the process change requests filed with the FDA following initial approval. This is strong evidence of the increased flexibility a CM process brings vs a batch process. But how does CM realize its potential with its sophisticated customers if they don't give it a chance? The less sophisticated customers could be the key.

Typically, process innovation unseats incumbents similar to continuous steel casting or Christensen's famous example of how mini-mills disrupted US Steel.[59] Eventually, disruptive technologies will gain a foothold in a corner of the market because they can open entirely new markets and begin to outperform old-guard technologies long relied upon. Based on the previous stakeholder analysis, the less sophisticated customers could be categorized as: distributers—the middle-persons between the manufacturers and the pharmacies;[67] payers—the insurance companies or government-sponsored payment plans (e.g. Medicare) responsible for reimbursement of drug expenses;[68] patients—the ones who use the medications; and prescribers—the physicians who determine what medications should be prescribed based on diagnosis, efficacy, and safety. These customers have many needs in common such as safe, inexpensive, targeted, and more accessible therapies. More broadly, these customers

have the need for eco-friendly/responsibly researched and manufactured medications along with national security protection.

The unsophisticated customers don't know if they want CM, because they don't know about it or how it would benefit them. Therefore, if the pharmaceutical manufacturer adheres to being guided by the customer's wants, the customer in this case would lead them to ignore CM technology. This lack of informed consumerism on these stakeholders' part could be compared to the pharmaceutical industry prior to the 1980s when patients/consumers were uninformed about potential treatments/therapies unless provided by their doctor. Now, patients/consumers can gain information about treatments/therapies through advertisements,[69] increasing awareness of possible medical innovations. Many have argued the value this added to the healthcare system, but it undoubtably gave patients/consumers more leverage in the pharmaceutical market. An alternative unsophisticated customer could be the pharmaceutical manufacturers who have chosen to focus solely on the manufacture of generic products. The emphasis placed on maximum profit margins from drug products has caused the expansive, global, R&D focused manufacturers to cede the lower margin market to generic manufacturers. And, as these generic manufacturers struggle to turn a profit on off-patent products, they have overwhelmingly retreated to overseas markets where labor is less expensive. The next chapter will include strategies to leverage these potential unsophisticated customers as part of the enterprise architecture change framework.

5.2.1 Element-Based Future Narrative

When envisioning the future enterprise architecture, it can be helpful to imagine an envisioned scenario based on the view elements. In section 5.2, the envisioned future architecture was described in the abstract, but this exercise can anchor the proposed future architecture in reality.[1] Below is an imagined scenario based on the 'to-be' pharmaceutical manufacturing enterprise architecture.

Future scenario:

Pharmaceutical manufacturing is now employing CM at every opportunity where batch production would be inferior. Batch manufacturing is only used for those transformations and processes that are less efficient in CM, and flow platform technology is enjoying the increased advancements that come with widespread user adoption.

Ecosystem:

Regulatory: Regulatory policies have been overhauled to include seamless CM consideration in NDAs and ANDAs. The FDA and manufacturers speak the same language when it comes to CM processes, leading to improved understanding of possible process control, safety, and efficacy implications. As more manufacturers begin to use CM, the FDA has adopted more influential levers to increase adoption throughout the enterprise, such as incentivizing the use of CM through preferred/expedited applications and encouraging a certain percentage of products be produced using CM. The FDA has become so well versed in CM that they have

begun suggesting, but not mandating, its use when they spot a process that might benefit from CM incorporation over batch.

Economic: The COGS have been reduced for most CM processes, making manufacturers more resilient against economic factors. With reduced COGS, manufacturers can pursue new products with less upfront capital, making them less reliant on blockbuster drugs. This has led to a more diversified product portfolio and a more stable economic position. Drug prices have been reduced.

Market: The reduced time to market for new products has made it easier for manufacturers to compete on new product development. A greater percentage of the manufacturing process has been moved in-house reducing the risk of contracting out to third-party manufacturers. Local production of off-patent products has increased, increasing competition in the market, and lowering generic drug prices even further.

Technology: Manufacturers who were slow to adopt CM have become increasingly marginalized. This has led to a shift in the industry's approach to innovation, with a greater emphasis on incorporating new technologies to remain competitive.

Environmental: Waste from the manufacturing process has been greatly reduced, making the pharmaceutical manufacturing process more environmentally friendly. This has attracted customers/investors who prioritize corporate social responsibility. CM has allowed manufacturers to take advantage of tax incentives put in place to reward reduction in waste.

Political: Manufacturers have transitioned production back within the US borders, reducing supply chain considerations ensuring a stable supply of essential medicines,

even during times of crisis. Manufacturers took advantage of tax incentives aimed at reclaiming American manufacturing, and this has resulted in a reduced cost of local manufacturing sans the initial tax incentives.

Stakeholders:

There is now an additional stakeholder in the enterprise—flow synthesis platform and process developer/designer. This stakeholder is focused on standardizing the industry equipment to improve user experiences and achieve manufacturing goals. The manufacturer receives value from the enterprise through the sale of equipment and process development services. They provide value through the production and servicing of manufacturing equipment. They also provide a standardized set of equipment that the enterprise can rely on in developing processes for new products. Because this stakeholder has tried to standardize flow platforms, the complexity associated with incorporating CM into synthetic processes has been greatly reduced.

Collocated residents are enjoying increased value delivered by the enterprise due to reduced pollution from manufacturing facilities. Payers and patients are receiving greater enterprise value because prices have been reduced. Distributors are receiving improved value because the pharmaceutical supply chain has been stabilized and shortages have been reduced. Pharmaceutical developers have gained increased value because they are enjoying increased revenue. Finally, physicians are receiving greater enterprise value due to an increase in treatment options and a decrease in the need to find alternatives for medications that are unavailable due to shortages. Interestingly, enterprise employees have increased in value to the enterprise because

they now require a new set of skills needed to operate CM platforms and the automation that goes along with them. Although automation has reduced the number of employees required for manufacturing, it has shifted the labor requirement to workers trained in the development, operation, and maintenance of highly automated systems.

Strategy:

There is a noticeable increase in the number of drugs making it to clinical trials and gaining FDA approval. Therefore, profits have increased through an improved economy of scale. Additionally, safety and efficacy profiles have improved due to a decrease in manufacturing complexity and better QA capabilities. Additionally, an increase in customer satisfaction based on an improved environmental impact from the manufacturing processes has led to an uptick in trust in the enterprise resulting in easing of scrutiny and a greater willingness for the public to allow manufacturers to expand operations as needed.

Information:

The enterprise has seen a surge in the emergent medical needs that the industry is attempting to address because the manufacturers can produce and screen candidates more swiftly. As CM technology improves, the manufacturers can incorporate process improvements in real time with improved confidence. The regulatory implications have been well established and the exchange of process information to and from the FDA is efficient. PAT provides critical process information, and advances in PAT have enabled enterprise-wide advancements like digital twins for product safety/efficacy

certification.[70] These digital models have been accepted by the FDA to be used for safety and efficacy certifications.

Infrastructure:

As batch reactors progressed toward the end-of-life, manufacturers replaced many with flow platforms rather than doubling down on batch platforms. Flow platforms have become more standardized, because a dominant design became an industry standout as more manufacturers incorporated CM. Existing analytical equipment has been able to fit into the new processing equipment. While there was an initial gap in the workforce capable of designing and operating flow processes, the steady increase in adoption has created an increase in educational institutions offering flow chemistry as part of their core curriculum. Supply chain management has become less of a burden because ingredients are mainly produced in-house using CM processes to reduce costs. The ingredients that aren't produced in-house are easily found domestically, because with the shift in manufacturing back to the US came an influx of supply chain support.

Products:

The enterprise has increased the number of APIs and finished products produced annually. It has begun producing more generic, over the counter, and dietary supplement products locally, because CM was able to establish a foothold in these lower value markets as it moved to higher priced markets. Similarly, manufacturers have seen an increase in the number of orphan drugs they have been able to produce at lower costs, because the enterprise pursued this class of drug to gain an alternative

market foothold. The enterprise is still focused on employing CM for mainly small molecule products where it makes sense over batch, but manufacturers are investigating where CM would make the most sense for biologics as the technology improves.

Services:

The enterprise can provide a wider variety of price adjustments for its products, because it is enjoying increased profit margins. It is also able to provide a more diverse array of specialized products. Collaboration between drug product developers and CM process engineers is flourishing, leading to efficiency improvements.

Process:

Scale up from pilot to full-scale production has been simplified through CM, thus eliminating many of the time-consuming and costly aspects of traditional batch manufacturing process control and CMC development. Additionally, CM has improved the batch-to-batch consistency eliminating the need for constant batch testing and parameter modifications. Manufacturers' strategic planning initiatives have become more complex because the flow platforms provide an increase in potential products. Therefore, ensuring that the reactors are operating at maximum capacity has become challenging but necessary to build competency and provide supplemental revenue as the CM learning curves are surmounted.

Organization:

Contracted Manufacturing Organizations (CMOs) have largely been absorbed into established manufacturing firms. Manufacturers produce most of their product line in-house. This has led to a decrease in process development rework. Even well-established, off-patent, product lines are produced locally, because these product lines have been used to exercise the CM technology and generate cashflow as other newer product lines are developed.

Knowledge:

IP is more tightly protected, and patent infringement litigation budgets have gone largely unused. With the new CM products, the IP includes the process techniques used in production. The process and the product are coupled. A PR campaign has been successful in informing manufacturers and the public about the numerous benefits these stakeholders can experience when CM technology is widely adopted. As such, the stakeholders have put pressure on agents of change to utilize influence where possible to make adoption of CM a reality.

Chapter 6 Technology Transition Framework

This portion of the system will produce the emergent function—an actionable method for implementation of CM in the pharmaceutical manufacturing enterprise. This chapter focuses on the future architecture implementation plan CONTINUES has derived using and expanding on the tools in the previous steps of the ARIES framework. This plan will be one level of abstraction higher than that of a company-specific plan and should be used to design a plan based on unique company attributes.

6.1 Architectural Options

The pharmaceutical manufacturing enterprise requires a change in architecture allowing for CM to become a normal part of the manufacturer's toolbox when developing the production of a new, and possibly existing, drug products. This architectural change involves shifting the culture of the pharmaceutical manufacturing enterprise to adopt new processes and rethink the value it receives from/provides to its stakeholders. Organizational change is difficult because processes and values are typically hesitant to change. However, when faced with the need to develop new capabilities, resources are the easiest avenue to leverage the change.[45] Therefore, three resourced focused architectural option to catalyze the change from batch to CM are:

1. **Daughter organization**- New organizational units within the company where processes can be adjusted as needed without the requirement to go through traditional channels in the organization.

2. **Spin-off organization-** Create a separate organization from the company where new values and processes can be explored with relatively greater autonomy.

3. **Adoptive organization-** Acquire a new external organization with values and processes desired for the required change to take place.

A common strategy for pharmaceutical manufacturers is to be first to market with therapies, but, based on the previously stated application of disruptive innovation theory, a better strategy for increased CM adoption in a profitable manner might be holding back and being second to market. Letting new start-up

pharmaceutical companies invest in CM technology to try and gain a foothold in the market and observe how they fare would appear to be the safest plan. However, from the previous stakeholder analysis, it is unlikely that new start-ups would be comfortable investing in CM when batch technology has historically delivered profitably and reliably. The investment may seem too great a risk. Christensen states that developing satellite companies within an already established firm could be the answer to this conundrum, because the company would be dual hatted as incumbent and new entrant.

The ROI for the overall change from batch manufacturing to CM has been documented.[51] It has been estimated that the use of CM in pharmaceutical manufacturing can reduce the COGS by 10-30%, but when the process development costs are factored in, only smaller firms with lower production volumes see a cost savings in the implementation of CM.[58] Once the initial investment in equipment and training is recouped, the variable cost savings could be between 40-50%.[61] Remembering that as CM technology progresses and is adopted more readily, the costs associated with it will only decrease, this is further evidence that either satellite/sequestered product lines (for large firms) or smaller startup firms would be the ideal foothold market for CM in pharmaceutical manufacturing. Because CM can give these market areas a fiscal advantage, it would then be able to make its way upmarket as implementation costs decrease so that larger firms would find CM more fiscally attractive. However, as previously stated, it is unlikely that startups would feel comfortable investing in CM without successful models from established

manufacturers. Meaning, established manufacturers need to play the role of the startup.

Currently, most pharmaceutical companies are investing in continuous flow synthetic capabilities, but a majority of these investments have been organized architecturally to be on par with existing product lines that produce higher profit margins. Therefore, the teams focused on incorporating the CM functions into the manufacturing model are competing for resources with segments of the company that are the most profitable. Thus, these CM groups are destined to struggle or fail due to lack of appropriate resources. Sequestering these teams using the three options presented would allow them the space needed to demonstrate the benefits of CM adoption.

6.2 Implementation Strategies

This section will describe strategies to close the gap between the current and future enterprise architecture. To achieve this new enterprise architecture, several levers can be used as evidenced by the view element analysis. These levers should be interpreted not as a forceful implementation of change, but like jujitsu in that a small amount of pressure on any of these levers would affect disproportionate change. Enterprise architecture change doesn't hinge on simply picking one strategy. The more levers used, the greater chance of swift and successful enterprise architecture change. Of note, these levers can be used while maintaining stability of the enterprise. The following strategies are discussed with the pharmaceutical manufacturing enterprise **ecosystem, stakeholders, products, knowledge, processes, infrastructure,** and **strategy** in mind.

6.2.1 Leveraging Government and Management Influence

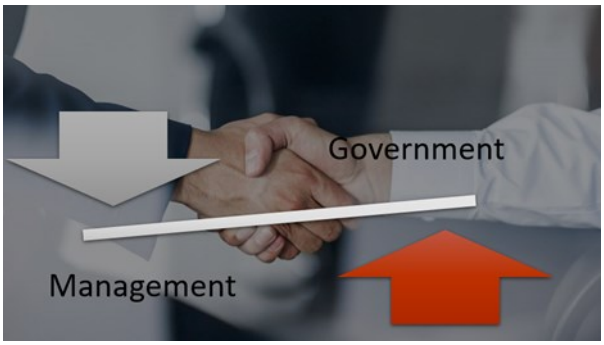

Figure 19 *Enterprise management must utilize government influence to make CM adoption more attractive to the enterprise. In turn, the government can reap the rewards (e.g., increased national security) from increased CM implementation.*

The adoption of CM in the pharmaceutical manufacturing enterprise can be significantly influenced through a collaborative approach between the government and enterprise management (**Figure 19**). This strategy recognizes the important roles played by both entities and emphasizes the need for their cooperation. Historically, the government has demonstrated success in supporting industries by acting as a customer rather than a venture capitalist, thereby contributing more value to the industry.[49] The government acts as a customer in the pharmaceutical manufacturing enterprise in multiple ways: as a payer (e.g., Medicare), through the funding of clinical trials, through public health initiatives (e.g., antiviral medications or vaccines during the pandemic), and as a direct consumer for government personnel (e.g., military members).

In 2022 President Joe Biden signed the Inflation Reduction Act (IRA) which highlights the government's commitment to lowering prescription drug prices for Americans.[71] The executive order allows the government to negotiate for Medicare drug prices, and companies can be financially liable for increases in prescription drug

prices. Hence, pharmaceutical manufacturers face increasing pressure to keep costs low. This governmental pressure can serve as a powerful lever to incentivize CM adoption if manufacturers can demonstrate even marginal cost reductions through its implementation.

However, for this strategy to succeed, enterprise management must also exert influence within the organization. It is crucial for management to convince decision makers, such as the C-suite and investors, that CM is a tool that can effectively address the government's demands to reduce manufacturing costs. Based on stakeholder interviews conducted for CONTINUES, CM adoption initiatives are welcomed more readily and have found greater success when the push comes from an influential position in the firm vs. a grassroots effort.

The argument for collaboration between the government and enterprise management becomes even more compelling when considering national security. Having lifesaving and life-improving medications made in the US is key to a robust national security strategy. Recently, the COVID-19 pandemic has demonstrated what can happen when supply chains are interrupted; leaving the US vulnerable to shortages if the nations we rely on to provide crucial capabilities, such as medications, are unable or unwilling to meet US demands. Clearly, the US needs locally sourced manufacturing to maintain and grow our innovation infrastructure, but not all categories of manufacturing are needed locally to achieve that goal. As Shih points out, the types of manufacturing processes that are closely coupled to innovation and R&D are the categories that are reliant on proximity—rely on the industrial

commons.[49] As mentioned previously, pharmaceutical manufacturing falls into this category.

Countries with emerging economies have been capturing low value added, low wage sectors of manufacturing, in a similar way that disruptive innovations gain a foothold in undervalued markets such as the rebar market for mini-mills.[59] These countries now hold the advantage on a wide variety of high-tech products, and there are even more products that are in jeopardy of succumbing to the same fate. Therefore, restoring the manufacturing industrial commons in the US involves bringing the majority of pharmaceutical manufacturing back to the US. Unfortunately, all forms of manufacturing, including pharmaceuticals, have been caught in the spiral of outsourcing Shih describes as the loss of the industrial commons.[49] The adoption of CM in pharmaceutical manufacturing could be the tipping point to reverse this spiral.

The two historical drivers for the offshoring of pharmaceutical manufacturing are tradability and labor content and cost differentials.[72] Tradability: pharmaceuticals, by in large, can be manufactured far from where they are sold because they are shelf-stable and don't cost much to ship. Labor content and labor cost differentials: the cost of labor in emerging economies were too good to pass up in the early 2000s, therefore manufacturing operations were moved away from the US. However, recent legislation, such as the Infrastructure Investment and Jobs Act (IIJA) and the IRA have introduced a variety of incentives aimed at bridging the margin differential between manufacturing products in these lower cost labor markets and transferring the manufacturing back to the US.

Similar "demand side incentives" could be used to break the tension between pharmaceutical manufacturers' willingness to invest in CM vs their near-term financial incentive in maintaining their bulk manufacturing status quo. If the government wants to bring manufacturing jobs back to America, targeting tax incentives for manufacturers to adopt CM would make the transition a financially viable option. Ultimately, the conversion of US facilities to CM would render the foreign, exclusively bulk, manufacturing facilities less profitable, even after tax incentives have expired, because the CM facilities in the US will be able to build economies of scale. Additionally, the high degree of CM automatization potential leads to a net decrease in the cost of manufacturing, further reducing any advantage foreign labor markets may enjoy. Again, this government influence can't effect change unless enterprise management can make the case for how these incentives will pay off.

Bringing outsourced manufacturing back to the US is a lever the government could use to increase the rate of CM adoption in the pharmaceutical manufacturing enterprise, and biomanufacturing can illustrate how this lever could be used. Continuous flow synthesis can be compared to biomanufacturing in that biomanufacturing can be used to create a wide variety of products from pharmaceuticals to fuel, and as mentioned previously, flow synthesis can be used in the production of a similar variety of products. Additionally, these technologies are both in their relative infancy as a process technology meaning they have heightened potential for scientific advances.[49] Just as the pharmaceutical industry was propelled into the production of next generation breakthrough/blockbuster drugs using

biomanufacturing to unlock chemical transformations previously unavailable to synthetic chemists, so to can flow synthesis harness transformations not available using batch chemistry manufacturing.

Because both techniques are so new, their use brings with them additional costs making their incorporation into existing processes less fiscally attractive. And, in the case of biomanufacturing, this has led manufacturers to shift operations to countries such as India and Singapore in an attempt to buy down this increased price tag.[49] However, Shih argues that would-be advances in biomanufacturing know-how in the US would not only stem the tide of biomanufacturing outsourcing, but could result in an influx of manufacturing to the US from other countries. This is a perfect example of an advancement the government is championing to effect change in US manufacturing—incentivizing biomanufacturing in the US.

In 2022, the Executive Order on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy was signed. This executive order will increase investment and coordination in US biomanufacturing, and is structured to "coordinate a whole-of-government approach to advance biotechnology and biomanufacturing towards innovative solutions in health, climate change, energy, food security, agriculture, supply chain resilience, and national and economic security.[73]" A similar investment in CM should result in analogous anticipated outcomes hastening CM adoption in pharmaceutical manufacturing. Government investment in R&D for the purposes of solving expansive challenges leverage resources and create the foundation for an industrial commons through the development of industrial collaboration and

networks.[49] Therefore, government investment in both manufacturing R&D such as CM technology for pharmaceutical manufacturing, and investment in human capitol such as STEM education and vocational benefits would complement management investment for CM adoption.

The FDA is another government entity that has enormous potential to affect the enterprise adoption of CM. This government lever is reliant on enterprise management as well. The FDA is invested in the transformation of the enterprise (described previously, pg.25). They have facilitated collaboration with the enterprise aimed at increased adoption of CM, with the goal of preventing drug shortages, but have stopped short of any forceful action. If the FDA is committed to CM for pharmaceuticals, the agency could offer incentives such as an accelerated approval process for products manufactured using CM technology. In Thaler and Sunstein's book on human behavior "Nudge" they illustrate that to get people to act in a certain way, the use of a 'nudge' simply makes it easier for them to do what you want them to.[74] Making the NDA or ANDA process simpler when CM is incorporated in the manufacturing process would be a perfect 'nudge' to accelerate adoption.

Additionally, as evidenced by the stakeholder interviews, the absence of standardized flow platforms for CM is a barrier to CM adoption. This is another avenue of influence for the FDA, because as more products are submitted using CM, the agency would be able to judge a dominant platform architecture and steer manufacturers toward a standardized set of platforms. Enterprise management could also influence the standardization of flow platforms through enterprise-wide cooperative initiatives aimed at deciding on a dominant flow platform architecture.

Finally, the government maintains a Strategic National Stockpile (SNS) to allow for rapid response to emergent medical needs caused by natural disasters, malicious attacks, or outbreaks. As part of this SNS, Federal Medical Stations (FMS) "are rapidly deployable caches managed by the Strategic National Stockpile (SNS) that contain beds, supplies, and medicines that can quickly turn a pre-identified building into a temporary medical shelter during a national emergency. The FMS can support healthcare systems anywhere in the United States.[75]" One of the goals of the FMS is to have at least a three day supply of medication available for 50-250 patients. While these medications are relatively shelf stable, they do expire. The government could double down on their investment in CM by mandating that SNS medications be made on demand for these FMS sites. This would be a mutually beneficial investment because it would ultimately save logistics costs for medication upkeep by the government and would help to propel flow chemistry platform technology towards a more personalized medication delivery. This would also force pharmaceutical manufacturers to investigate CM for existing products—a difficult hurdle to clear in the aim of augmenting bulk manufacturing, even when CM would be more beneficial. If medication access is to be truly democratized, existing products produced using batch manufacturing will have to be investigated for CM incorporation.

6.2.2 Leveraging the 'Unsophisticated' Customers as Early Adopters

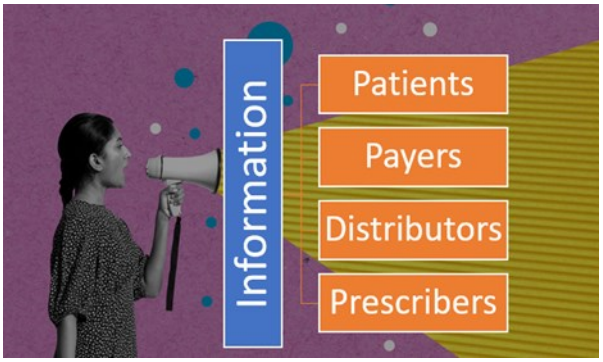

Figure 20 *Exploit early adoption behavior to propel further adoption using the 'unsophisticated' customers. Use information campaign to let these customers know why they want this technology adopted.*

Chapter 5 highlighted the importance of early adopters for new technology penetration.[4] Early adopters would fuel continued innovation in CM leading to increased attractiveness of incorporation, therefore a strategy reliant on incentivizing early adoption could catalyze market penetration through technology improvement. This early adoption push would be most beneficial if aimed at the 'unsophisticated' segment (**Figure 20**) because this customer base is likely to contain an early adopter mindset. Also in Chapter 5, the 'unsophisticated' customers in the pharmaceutical manufacturing enterprise were described: distributors, payers, patients, prescribers.[5]

Because these customers don't know how CM incorporation would benefit them, they don't know to ask for it to be used. Therefore, the sophisticated customer—the investors—are the ones the enterprise caters to, and in doing so, the enterprise will continue to maintain the current batch manufacturing dominated architecture. Convincing the unsophisticated customers that they want CM in the

[4] See page 88
[5] See page 94

enterprise architecture is a lever that could force this change. Again, this lever must be pulled by someone in the enterprise management structure, or in combination with CM platform manufacturers, and will involve significant upfront investment, similar to the pharmaceutical manufacturing enterprise new drug development business model. Similarly, if the upfront investment is successful in convincing these customers they want CM used in the products they buy, it will pay for itself and more.

This strategy would require an information campaign to be launched advising these customers about the benefits CM can provide them, analogous to how pharmaceutical manufacturers advertise products. A successful example of such a strategy is renewable energy systems. Information campaigns and advocacy efforts highlighting the benefits of renewable energy sources, such as solar and wind power, have influenced consumer attitudes and behaviors regarding energy consumption.[76] As consumers have become more informed about the advantages of renewable energy, including cost savings and reduced carbon emissions, they have increasingly demanded access to renewable energy systems. This has caused growth of renewable energy use to double in the US from 2010 to 2020.[77] Commodities such as hybrid vehicles, organic products, and plant-based food alternatives are further examples of similar information campaigns. These products gained recognition after information regarding their potential benefits was aimed at consumers. Their respective industries then began offering more of these products and services as more customers began to demand their promised benefits.

Pharmaceutical manufacturers could include information on CM processes along with their product advertisements, touting the array of benefits these customers stand to gain from its use. These customers would then be empowered to begin asking for their products, for example, to contain a certain percentage of CM (like organic or free-trade products). These advertising campaigns would be intended to convince payers and patients that drug prices would decrease; convince distributors and prescribers that access to more diverse, effective, medications would increase; and convince all these consumers of the environmental and national security implications CM can address directly.

6.2.3 Leveraging Lower End of Market/Niche Market

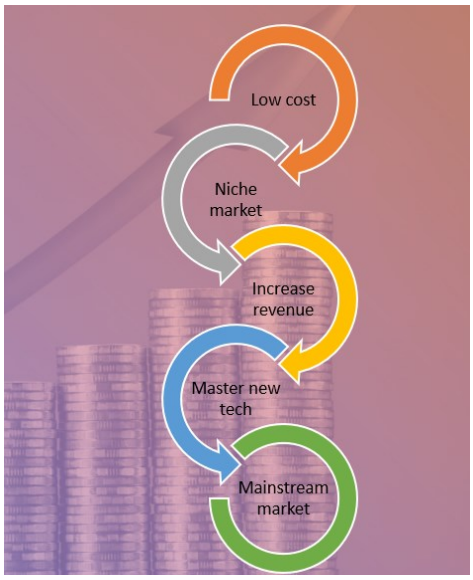

Figure 21 *Dominate a niche market to generate capital and master CM technology incorporation in preparation for eventual implementation up-market.*

It isn't enough to adopt one of the new architectural options and continue to pursue the same market share. The manufacturer will also have to make the architectural decision of where the new entity will enter the market. As part of this

'to-be' architecture, it makes sense for the firm to use the newly created organization to invest in the lower end of the market, or what could be described as a niche market (**Figure 21**). Disruptive innovations occur when a company finds a foothold in an underserved or lower margin market. Once a disruptive technology finds a home in this market, it can begin to move upmarket and begin to compete with and eventually dominate the incumbent. "A low-cost strategy only works if you have a high-cost competitor."[59] Once the low-cost product has eliminated the high-cost competitors from the initial foothold market, that firm needs to look upmarket or compete with the other players in the low-cost market.

This scenario can only benefit multiple pharmaceutical manufacturing enterprise stakeholders, who have found it increasingly difficult to afford medications. Through the described disruption mechanism, beginning at the low end of the pharmaceutical market and working up, the cost of medications will steadily decrease. For manufactured products such as steel, radios, cellphones, etc., as the low-cost market disrupter moves up market the higher cost market firms are freed to design and produce higher end products with increasingly complex and sophisticated features until they overproduce features there is no market for. Antithetical to these types of industries, as pharmaceutical manufacturers move up market, it is unlikely they will reach a point where the pharmaceutical products are over-produced. This appears to be an enabling scenario that would likely lead to accelerated medical breakthroughs. Adding ubiquitous CM capability to the pharmaceutical manufacturing enterprise lowers the barrier to entry for American drug

manufacturers. Thus, widens the aperture to pharmaceutical developers to pursue more potential hits in a wider variety of druggable targets.

To hasten CM adoption, a niche market can be established via the three architectural options listed individually or in combination, based on the best fit within the manufacturer's current culture. This niche market should focus on underserved or lower margin market portions. This lever will allow CM to continue to get a foot in the door using pilot projects such the pursuit of orphan drugs, the manufacture of veterinary products, over-the-counter medications, supplements, pre-regulatory starting materials, or even expanding to cosmetics or cleaning products. These niche markets serve two main purposes. First, as these niche markets become the leaders in CM incorporation, the technology will then be primed to move to the higher priced or more mainstream markets of patented drugs. Second, these lower end/marginalized markets can help generate revenue to supplement the manufacturers' investment in the new technology similar to the example of the Zongshen Industrial Group producing imitation/low-end products to generate revenue to finance their technological learning for higher-end products.[78] Additionally, because many of these product options don't carry the same degree of regulatory scrutiny, they are a less risky strategy to use while building technical competency.

6.2.4 Leveraging Manufacturers as Industrial Platforms

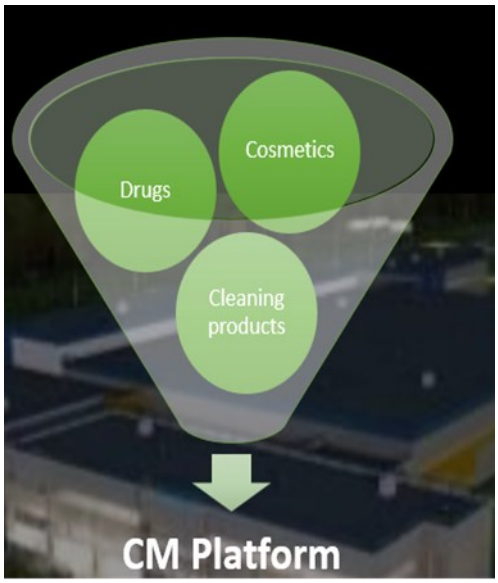

Figure 22 *Newly created CM facilities can be used as industrial platform services to help offset initial costs, maximize capacity utilization, and increase CM proficiency.*

Adding CM capabilities into batch manufacturing facilities sets these facilities up to become industry-wide service platforms (**Figure 22**), because CM provides the flexibility to pivot the manufacturing process not only between pharmaceutical products but also other products such as cosmetics or cleaning products. Platforming is the intentional sharing of parts and processes across products.[79] Using CM facilities as industrial platform services allows the manufacturers to provide similar products to multiple markets through the sharing of the manufacturing process. Consequently, the facility can achieve close to 100% manufacturing capacity allowing for little to no down-time in process capability. For example, if a CM process only needs 10 hours a week to fulfill a single drug product requirement, the facility could partner with other drug developers externally, other product lines internally, or other non-pharmaceutical products externally to use the remainder of the CM time (assuming it

can run 24 hours a day) to make products utilizing the remaining 158 hours a week. Additionally, because of the automation possibilities CM provides to a manufacturing facility, the operating capacity has a very real possibility of achieving the 24 hours a day operation capability.

This also leads to a network effect as more and more CM facilities are stood up; meaning pharmaceutical developers have more options for producing their products in parallel leading to faster time to market for these products. Also, the more facilities that add CM capabilities, the more products will be designed and optimized for CM producibility. Meaning this industry platform would have two sides. The first side would be the pharmaceutical and other product developers that produce their products on the network of these platforms. These developers would simply need to provide the production facility information on the manufacturing requirements of the product. The second side would be the pharmaceutical process designers who are intertwined in the development of the drug products. These designers will plan the drug and other product manufacturing processes specifically for CM.

6.2.5 Leveraging the Talent Pool

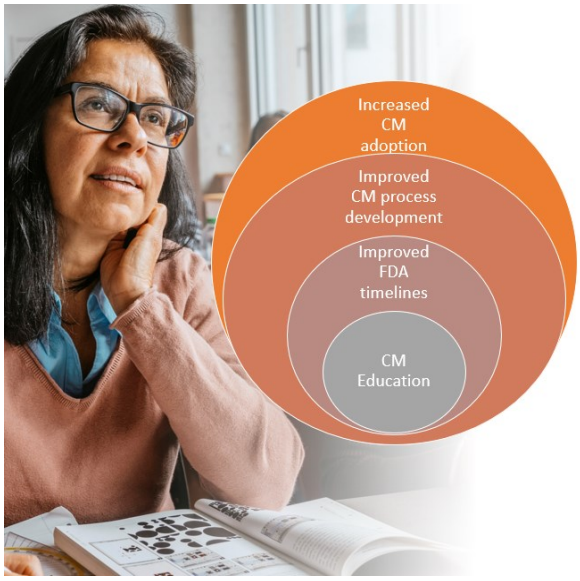

Figure 23 *Developing a workforce with a CM education would have ripple effects throughout the enterprise.*

Finally, a strategy based on developing new skillsets for the current and potential CM workforce is a lever that can be proactively used to facilitate CM incorporation (**Figure 23**). As with many other manufacturing technology skills,[80] there exists a large gap in knowledge regarding the design and operations of flow reactions. This lack of sufficient education and training in CM not only effects a manufacturer's ability to fully utilize the technology and reap the numerous benefits, but it also impedes regulators' ability to expeditiously approve incorporation of flow technology in NDAs or ANDAs. The regulatory bodies can't maintain a flow synthesis educated workforce, therefore drug applications involving the technology require extensive back and forth discussions between the applicant and the regulators. Understandably, this could result in hesitancy to invest in adoption of the technology, because a manufacturer would be focused on minimizing risk of delays in the approval process.

Flow synthesis is not a widely used tool employed in basic chemical education, but with the emergence of flow technology in multiple industries, universities have sporadically begun teaching the technique.[81] Designing a synthesis in flow is not trivial because avoiding parameters that could lead to problematic intermediate products involves thoughtful and strategic planning. While many reactions can be performed in flow, the state of flow synthesis technology is not quite up to the task of discounting batch reactions in pharmaceutical development due to the time required to set up customized flow configurations. An injection of a skillfully trained workforce could ameliorate that barrier and propel CM design and operation efforts to the commensurate level of batch manufacturing design.

This lever could be used by either CM platform/process developers, regulatory agencies, manufacturers, or any combination of these stakeholders. The easiest and least invasive strategy would be to begin funding CM focused graduate, and even undergraduate, fellowships to begin to build the talent pool. This strategy acts as both a jumpstart to CM adoption and a hedge against a potential disconnect between what workers are capable of and what the enterprise will require of them as CM becomes a dominant technology. Once CM begins to become adopted more widely, a training deficit would hinder the enterprise's ability to fully realize CM's potential. A second option would be the creation of a CM education system that trains workers in the technical skills and theoretical knowledge required to utilize CM technologies for the pharmaceutical manufacturing enterprise. To develop the required workforce needed to meet the industry's anticipated need, an education system focused on standardized skills, capable of permeating all levels of the enterprise is required. This education

system should be accessible to all levels of educational background and should also be aligned with industry's current and projected needs, so that workers can be trained in a variety of processes and applications.

6.3 View Element Comparison

In Chapters 4 and 5, the ecosystem and stakeholders along with the eight view elements were examined to describe the current pharmaceutical manufacturing enterprise architecture. To assist in the implementation of the new architecture aimed at widespread CM adoption, the key view elements that were highlighted as drivers for CM implementation will be examined at a deeper level using the view element anatomy.[1] The view element anatomy digs deeper into each highlighted view element to give a more nuanced understanding of how that element can be addressed for enterprise change, and the implementation strategies outlined in section 6.2 should be implemented to facilitate the change from the 'as-is' to the 'to-be' architecture. For CONTINUES, the view element anatomy will be used to compare the 'as-is' and the 'to-be' architecture as part of the implementation framework. The five parts of the anatomy are: Structure—configuration characteristics; Behavior—response to conditions are triggers; Artifacts—tangible documents; Measures—quantitative data; Periodicity—reoccurring cycles with pace and rate.[1]

Ecosystem

Table 2 *Ecosystem view element anatomy comparison*

Anatomy	As-Is	To-Be
Structure	Regulated by multiple agencies; financing through investors betting on blockbuster drugs; competes through new product development, IP, and generic formulas; moving toward more environmentally friendly practices; industry plays a key role in national security and the potential for reshoring manufacturing to the US	Streamlined processes to integrate CM seamlessly, aligning with regulatory requirements and industry standards. Materials and products are produced locally and in-house. Highly automated and interconnected equipment, and a flexible manufacturing approach. Personalized drug products are readily available and less expensive. Manufacturers financially benefit from environmentally friendly practices.
Behavior	Continual monitoring and enforcing compliance with regulations, and GMP; investing in drug development and manufacturing processes; conduct research and development, patent filings, and marketing; researching and developing new technologies; lobbying and advocacy for policies that support the industry	Government using demand side incentives to increase CM adoption. Regulatory policies overhauled to include CM consideration. The FDA and manufacturers now have improved understanding and alignment regarding CM processes. The FDA has also adopted more influential levers to increase and expedite CM adoption, such as incentivizing its use. Enterprise management actively championing taking advantage of the government levers to adopt CM.
Artifacts	Regulatory documents, such as NDAs and GMP certifications; financial reports and investment agreements; patents and marketing materials; technology specifications, environmental impact assessments and sustainability reports; governmental policy documents	Revised NDAs and ANDAs incorporating CM, documentation on safety and efficacy evaluations specific to CM processes. Updated standard operating procedures, manufacturing protocols, and quality control records. Patents include manufacturing parameters. Marketing materials aimed at CM benefits including improved environmental impacts. Policy documents aimed at incentivizing local manufacturing.
Measures	Compliance rates and FDA warning letters; ROI and profit margins, market share and revenue growth; process efficiency and product quality; waste generation and carbon footprint; policy adoption rates and public opinion polls	Percent reduction of COGS, time to market for new products, the percentage of manufacturing processes moved in-house, the increase in local production of off-patent products, and reductions in waste generation and drug prices
Periodicity	Regular inspections and updates to regulations; quarterly and annual financial reporting; product launch cycles and patent expirations; continuous improvement initiatives; election cycles and policy implementation timelines	Shorter lead times and increased efficiency. Increased time under patent. Innovation and adoption of new technologies sped up because more manufacturers are participating.

Stakeholders

Table 3 *Stakeholder view element anatomy comparison*

Anatomy	As-Is	To-Be
Structure	Stakeholders outlined previously in Chapter 4	Patients, physicians, developers, distributors, payers, and collocated residents have increased value to and from the enterprise. An additional stakeholder—flow platform manufacturer/process developer—has been added.
Behavior	Conduct R&D, obtain regulatory approvals, and market products; seek medical treatment, obtain prescriptions, and take medications as directed; review and approve drug products, inspect manufacturing facilities, and enforce regulations; negotiate reimbursement rates, pay for medications and medical services, and manage costs; invest in drug candidates, monitor performance, and seek a return on investment	Stakeholders requesting CM incorporation. Manufacturers collaborate closely with the flow synthesis platform developer/designer to ensure the integration and effective use of the standardized equipment. Providing CM education opportunities.
Artifacts	Drug products, patents, manufacturing facilities, marketing materials, and R&D reports, Prescriptions, medical records, and medication packaging, Complaints, environmental reports. Regulatory guidelines, inspection reports, and enforcement actions, Reimbursement policies, claims data, and payment records, financial reports, sales data	Equipment specifications, user manuals, maintenance procedures, and technical documentation. The enterprise would also have documentation related to the sales and servicing of the manufacturing equipment and the development of new processes using the standardized equipment. Environmental impact reports. Financial reports
Measures	R&D costs, time to market, sales revenue, market share, and profitability; health outcomes, medication adherence, and satisfaction with treatment; complaints filed, environmental impact assessments, and community engagement; compliance rates, inspection findings, and enforcement actions taken; costs per patient, reimbursement rates, and medication utilization; return on investment; distribution costs, inventory turnover, and sales revenue, Supplier lead times and costs; employee turnover, employment vacancies	Number of standardized equipment platforms sold, revenue generated from platform sales and process development services, user satisfaction ratings, and improvements in manufacturing efficiency and productivity. The enterprise would also measure reductions in pollution, drug prices, and shortages to assess the impact on collocated residents, payers, patients, distributors, pharmaceutical developers, and physicians.
Periodicity	Most are stakeholder dependent; R&D is ongoing, while regulatory approvals and marketing are periodic	Reduced frequency of drug shortages and shortened timelines for drug approvals.

Products

Table 4 *Product view element anatomy comparison*

Anatomy	As-Is	To-Be
Structure	Produces APIs and finished products. These products can be broadly classified into prescription drugs (both brand name and generic), over-the-counter medications, dietary supplements, and vaccines. These products can be further categorized based on their molecular structure, ranging from small molecules to biologics	Quick and easy changes to the production process, resulting in shorter lead times and increased efficiency
Behavior	Pharmaceutical products are designed and developed using a rigorous research and development process that involves extensive clinical trials to ensure safety and efficacy. The products act to prevent, treat, or alleviate various health conditions	Responding more quickly to market demands through R&D and clinical trials. Focus shifted to producing more generic, over the counter, and dietary supplement products locally, as these are lower value markets where CM has established a foothold. Manufacturers are also investigating where CM would make the most sense for biologics as the technology improves
Artifacts	Drug development plans, regulatory submissions, manufacturing process documents, quality control reports, and product labeling and packaging materials	CM incorporation protocols, standard operating procedures, batch records, and other documentation related to the CM process. These documents are essential for ensuring product quality, consistency, and compliance with regulatory requirements.
Measures	safety, efficacy, and quality monitoring, emphasizing adverse events and product recalls, clinical trial data, regulatory guideline, and standard compliance	Production output metrics, equipment utilization, downtime, and defect rates. These measures would be used to identify areas for improvement and optimize the CM process to achieve the desired outcomes.
Periodicity	new products are developed and introduced to the market in a non-regular timeline. The periodicity of clinical trials and regulatory submissions varies depending on the product and the stage of development. Ongoing monitoring of product safety and efficacy is also conducted on a periodic basis, with any necessary updates or changes made to the product labeling and packaging materials.	Reoccurring cycles of production adjust its pace and rate of production to meet changing market demands and other factors. Platform processes lead to maximum equipment utilization. Less downtime. Shorter period between equipment reconfigurations.

Knowledge

Table 5 Knowledge view element anatomy comparison

Anatomy	As-Is	To-Be
Structure	Based on IP from innovations in new products, centered around the synthesis of novel products that have been investigated for safety and efficacy in regulated clinical trials. The IP does not typically encompass the manufacturing process of the API or the finished product. Knowledge flows to the consumer in the form of advertising allowing the consumer to be more informed about possible treatment options.	IP can be maintained more carefully as more manufacturing is done in-house to include precursors. Increased CM adoption has increased the CM development capabilities.
Behavior	Strict compliance with safety, efficacy, and quality standards. Produce safe, effective, and profitable products based on clinical data and R&D often collaborating with academic institutions, other pharmaceutical companies, and government organizations to accelerate the discovery process. Protect intellectual property of new drugs. Publish scientific papers and regulatory documents.	Share common equipment across product lines. Maintain manufacturing capability inhouse. Collaborate with education to cultivate CM talent.
Artifacts	Patents, scientific publications, regulatory documents, manufacturing process documentation, and advertising materials. Patents Manufacturing process documentation ensures the consistency and quality of products, while advertising materials inform consumers about treatment options.	Patents, licensing agreements, and other legal documents related to IP protection. Manufacturing protocols, standard operating procedures, and other documentation related to the CM process.
Measures	The number of new drugs discovered and developed, the success of clinical trials, and the profitability of products.	Percent increase in IP generated. CM method competency. New technology incorporated. Cost savings.
Periodicity	New discoveries and advancements made every day. R&D is a long-term process that can take several years, and clinical trials are conducted over several phases, with each phase taking different amounts of time. Regulatory approvals can take several months to several years, depending on the complexity of the product. Advertising materials are periodically updated to reflect new scientific discoveries and changes in regulations.	Manufacturing processes are continuously improved and updated to ensure efficiency, safety, and quality without the need for FDA recertification.

Processes

Table 6 *Processes view element anatomy comparison*

Anatomy	As-Is	To-Be
Structure	Highly structured and regulated. Designed to ensure that products are safe and effective, and that the manufacturing process adheres to strict guidelines and regulations.	More flexible manufacturing processes while still maintaining strict standards. CM incorporated where it would be more efficient than bulk.
Behavior	High level of attention to detail and precision. They require collaboration and communication among various departments, including research and development, manufacturing, quality assurance, regulatory affairs, and supply chain management.	Deviations are reduced due to a higher degree of automation. Process development is more tightly bound to the actual manufacturing process.
Artifacts	Standard operating procedures (SOPs), batch records, test reports, product specifications, and regulatory filings. These artifacts serve as a record of the manufacturing process and are used to ensure consistency and traceability.	Updated SOPs. Reduced number of records needed to maintain consistency and traceability.
Measures	Quality of the final product, adherence to regulatory guidelines, and efficiency of the manufacturing process. Other measures include customer satisfaction, profitability, and safety.	Difference in time to approval for NDAs and ANDAs. Degree of improvement in efficiency, customer satisfaction, profitability, and safety profiles.
Periodicity	Research and development processes may occur over several years, while manufacturing processes may occur on a daily or weekly basis. Quality assurance processes may occur continuously throughout the manufacturing process, while regulatory filings may occur on an annual or as-needed basis.	Increased R&D pace, reduced equipment downtime. Required QA reduced due to increased automation. Number of regulatory filings increased, and number of refiling eliminated due to process changes.

Infrastructure

Table 7 Infrastructure view element anatomy comparison

Anatomy	As-Is	To-Be
Structure	Batch manufacturing platforms, ingredients purchased from vendors, workforce familiar with batch technology	Interconnected equipment that is monitored and controlled by sophisticated software and sensors. Highly automated.
Behavior	Use bulk reactors for large batches of products. Ingredients manufactured at other facilities and shipped. Outsourced supply chain.	Use a combination of bulk and CM processes, and design processes to be manufactured in CM where it makes sense. Ingredients are manufactured in-house via CM and/or are purchased from US vendors because more manufacturing within US borders.
Artifacts	Physical equipment, facilities, and processes, as well as software and IT systems used to support research, development, manufacturing, and distribution	CM equipment with new automation software and support. R&D focused on CM processes. Reduced facility footprint. More distributed capabilities.
Measures	Manufacturing capacity, equipment utilization, quality assurance metrics, and supply chain efficiency	Improved capacity, equipment utilization, quality assurance metrics, and reduced time to market. Number of drug shortages.
Periodicity	Equipment maintenance and calibration may occur regularly, while regulatory inspections and audits may occur annually or on an as-needed basis, for example, if a change to the manufacturing process is requested.	CM configuration changes as product requirements change. Reduced maintenance and downtime. Calibration is automated and done as needed. Adjustments to approved regulated processes are largely unnecessary.

Strategy

Table 8 Strategy view element anatomy comparison

Anatomy	As-Is	To-Be
Structure	Outlined using current market and projected needs; highly risky and uncertain, because most drug candidates fail to reach FDA approval. Detailed in portfolio of products, which can be categorized based on therapeutic area, stage of development, and market potential.	Established sequestered entities to focus on CM. Able to adjust to emerging needs. Leveraging automated and interconnected equipment to increase economy of scale. Optimized for improved quality assurance capabilities. Streamlined clinical trial to approval pipeline.
Behavior	Developing innovative products that meet safety and efficacy standards while maximizing profits for investors and maintaining IP protection. Invest heavily in R&D, take calculated risks, and rely on a thorough understanding of regulations and compliance measures to bring products to market.	New CM organization able to freely explore CM opportunities. Increase in the number of drugs making it to clinical trials and gaining FDA approval. Capitalizing on the decrease in manufacturing complexity and improved quality assurance capabilities to enhance safety and efficacy profiles. Additionally, the enterprise focuses on improving its environmental impact to increase customer satisfaction and build trust.
Artifacts	Business plans, research and development plans, marketing plans, and IP protection plans. Data on the specific drugs, clinical trial results, and FDA approval documentation.	New, sequestered business structure plan. Financial reports showing increased profits. Quality assurance documentation, environmental impact reports, and customer satisfaction surveys
Measures	Financial metrics such as revenue, profit margins, and ROI. Number of drugs in the pipeline, the success rate of clinical trials, the rate of FDA approvals, and IP protection success.	Benchmarked from previous financial and approval metrics. Post-approval surveillance for safety. Customer satisfaction surveys and feedback
Periodicity	R&D process for developing a drug can take 10-15 years, and the patent protection for a successful drug can last up to 20 years. Continual strategic planning and portfolio management.	New organization quarterly progress reports. Increased pace of clinical trials, FDA approval processes, and manufacturing operations accelerated due to the efficiency of CM

6.3.1 View Element Comparison Summary

The pharmaceutical manufacturing enterprise requires a transformative shift from its current 'as-is' architecture to a future 'to-be' architecture to realize ubiquitous CM adoption in the enterprise. In section 6.3, the view elements derived from the ARIES framework—**ecosystem, stakeholders, products, knowledge,**

processes, infrastructure, and **strategy—**were analyzed using their view element anatomy to dig deeper into the 'as-is' and 'to-be' architecture. **Tables 2-8** describe this analysis. This architectural change involves comprehensive transformations across multiple dimensions throughout the enterprise. These changes encompass closer regulatory alignment, stakeholder collaboration and incorporation, furtherance of process automation, stringent process knowledge management, infrastructure optimization, and strategic realignment of resources. The envisioned future state presents opportunities for increased efficiency, improved product quality, enhanced environmental sustainability, and ultimately, better healthcare outcomes for patients.

Ecosystem

In the 'to-be' architecture, the industry moves towards a more regulatory-integrated structure, driven by the adoption of CM practices. COGS and time to market are reduced and automation is increased. Multiple agencies collaborate to align regulatory requirements and industry standards, incentivizing manufacturers to embrace CM through government levers. Manufacturers benefit financially from environmentally friendly practices, while personalized drug products become more accessible and affordable.

Stakeholders

The behavior of stakeholders in the industry evolves, with a focus on collaborating closely with flow platform manufacturers and process developers to ensure effective and standardized integration of CM. Education and awareness initiatives are implemented to facilitate the adoption of CM throughout the

ecosystem. The artifacts that support stakeholders' activities are updated to include documentation specific to CM processes and the benefits it brings, including improved environmental impacts.

Products

The 'to-be' architecture focuses on the benefits of continuous manufacturing (CM) in terms of agility, efficiency, and market responsiveness. The enterprise aims to leverage CM to streamline production processes, optimize performance, ensure compliance, and adapt to changing market dynamics effectively.

Knowledge

Knowledge management undergoes significant changes as well, with increased emphasis on maintaining intellectual property as manufacturing processes are brought in-house. Knowledge sharing and collaboration among manufacturers and educational institutions are prioritized to cultivate CM talent and drive continuous improvement.

Processes

Manufacturing processes are restructured to be more flexible and automated, leveraging interconnected equipment and sophisticated software. CM is incorporated where it offers efficiency advantages over traditional batch manufacturing. The infrastructure evolves to include in-house production of ingredients, reducing reliance on external suppliers and optimizing supply chain efficiency.

Infrastructure

The ‘to-be’ infrastructure of the enterprise consists of interconnected and automated equipment, combination of bulk and CM processes, in-house manufacturing and purchasing from US vendors, new automation software and support, R&D focus on CM processes, reduced facility footprint and distributed capabilities, improved capacity, utilization, and quality assurance, reduction in drug shortages, reduced maintenance and downtime, and minimal adjustments to approved regulated processes.

Strategy

Strategic considerations encompass a focus on R&D and clinical trials, with increased success rates of drug candidates reaching FDA approval. The sequestered entities dedicated to CM allow for exploration of emerging opportunities, while quality assurance capabilities are optimized to enhance safety and efficacy profiles. Environmental impact and customer satisfaction are also prioritized to build trust and improve the industry's reputation.

Chapter 7 Conclusion

This chapter will briefly summarize the background and tools used to develop CONTINUES. The focus of this chapter is to highlight a few directions for further study that would bolster the implementation of CONTINUES.

7.1 Research Summary

This research is a system-focused method for facilitating broader CM adoption throughout the pharmaceutical manufacturing enterprise. Applying system architecting techniques, CONTINUES was developed using ARIES, disruptive

technology theories, and manufacturing innovation theories to assist the transition from predominantly batch architecture to an integrated CM architecture in the pharmaceutical industry.

7.2 Future Study

While developing this system, many potential avenues for further research became apparent. These research opportunities would be invaluable in ensuring the intended new enterprise architecture becomes a reality.

1. Design CM education system: The development of a training and education system, focused on developing broader CM proficiency will be crucial in ensuring that pharmaceutical companies can effectively adopt and utilize this new manufacturing approach. A research opportunity exists to design a CM education system aimed at education of current and future workforce by providing accredited and standardized educational offerings that would ensure proficiency and creativity in new and existing CM processes.

2. Automation and robotic technologies incorporation: Further investigation on how automation and robotic technologies are supporting CM and could further support CM implementation in the pharmaceutical manufacturing enterprise. A deeper dive into these areas could present more opportunities for streamlining processes and improving efficiency. Specifically, investigations into advancements in PAT and its potential contribution to CM advancements should be conducted. This was an area of interest for CONTINUES but the subject matter is extensive and would have required a significantly longer completion timeline. Analytical technologies can help address

concerns related to impurities, process controls, and real-time release testing, with the possibility of utilizing digital twins as substitutes for physical testing.[82]

3. CM system complexity characterization: When designing systems, complexity is introduced simply by asking the system to perform increasingly varied functions.[44] Because increased complexity typically brings with it increased cost, an interesting opportunity exists in conducting a thorough complexity characterization of CM implementation. This could provide valuable insights into the challenges and potential solutions associated with this enterprise architectural shift. The introduction of CM in the pharmaceutical manufacturing process does introduce increased complexity of the overall manufacturing facility system. However, the complexity is contained within the facility vs. spread among facilities as with the majority bulk manufacturing architecture. Therefore, the possibility exists that the complexity could be more easily managed. There are many factors that contribute to the increase or decrease in system complexity due to CM adoption. CM increases complexity within the development side of the equation because performance tolerance for CM of pharmaceuticals is very high. Complexity due to components is increased because there are more components with CM vs. batch. The interactions between components in CM are also relatively complex due to possible changes in pressure, heterogeneity, temperature etc. However, complexity due to topological formation is reduced as it should be essentially linear.

4. Improved configuration management: Research into how to better transition CM processes between products would assist in realizing CM's potential for maximizing capacity utilization. Reducing downtime for product transition would lead to greater

financial incentives for manufacturers. Configuration management will be crucial to continuous operations of a CM facility in order to maintain the flexibility of the manufacturing facility. Because the CM facility can be reconfigured to produce different products as needed, the change management piece of the operation will need to be monitored closely. However, because the changes may be confined to a specific set of products, these changes should be efficiently made as the facility becomes adept at reconfiguring between products.

5. Expanding CM use for biologically based products: Investigating the broader application of CM in the production of biological products, which are inherently more complex than small molecules, would greatly increase CM adoption in the enterprise. Biological products present unique challenges not seen in the manufacture of small molecule products. These products have become the standard of care for many diseases, and are produced using living organisms, or from components derived from living organisms. As a result, biologics are more difficult to purify into fully defined formulations and their production methods can dramatically affect their activity.[83] In addition to continuous manufacturing systems for protein drugs, other biologics such as peptides and oligonucleotides can be produced synthetically using continuous flow.[42] In-line quality control processes for analytical identification and purity verification for these products can present problems with CMC requirements. Utilizing cell-free systems and exploring innovative approaches will be essential in overcoming the manufacturing challenges associated with biological products.[84]

6. CM and improved/updated regulatory science tools: Processes are in place in an organization to enact that organization's strategy. When these processes are applied

to the tasks they were designed for, they work efficiently. But, when an enterprise strategy changes, the process will need to change as well, and all too often enterprises want to stick with the processes they already have in place. This leads to the required tasks being performed inefficiently at best. When venturing into new areas such as CM adoption, the enterprise could encounter challenges if existing drug product approval processes were not updated to account for the new techniques. Therefore, there is a need to develop new regulatory science tools that assist regulatory bodies and manufacturers in the approval of distributed pharmaceutical production and the incorporation of CM techniques. For example, a regulatory mechanism that allows for the review and approval of manufacturing technologies separately from specific drug products would support the increased CM implementation in the enterprise. This envisioned approval and incorporation model would be similar to that used for excipients in the enterprise.[21] This model could ensure that manufacturers feel confident in incorporating CM into their processes, thus streamlining production and enhancing efficiency.

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