# AN IMPROVEMENT FRAMEWORK FOR THE PHARMACEUTICAL VALUE CHAIN: USING LEAN METHODOLOGIES TO CREATE A PATIENT-CENTERED SUPPLY CHAIN

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Bachelor of Business Administration

**Supply Chain Management**

By

**Salman Farooqui**

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# A PRESCRIPTION FOR THE PHARMACEUTICAL VALUE CHAIN: USING LEAN METHODOLOGIES TO CREATE A PATIENT-CENTERED SUPPLY CHAIN

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## Abstract

The pharmaceutical supply chain and medication-use process function to deliver medications to the right patients at the right time. Together, these two segments form the pharmaceutical value chain. The processes of the pharmaceutical value chain have become more complex, with new technology, new types of therapeutics, changing supply chain designs, and stringent government regulations. However, these changes also offer many opportunities for pharmaceutical value chains to increase value for patients. Value is a function of quality, service, and cost; every organization in the pharmaceutical value chain impacts these three variables. The most important variable is quality, since a lack of quality could translate to a medication error that could cause the patient an adverse drug event. To reduce medication errors and resultant adverse drug events, pharmaceutical value chain organizations must consider process improvements with the goal of maximizing value for the patient. Lean methodologies and tools provide an improvement framework that can help achieve greater value. This includes concepts such as continuous, incremental improvement, multi-level employee involvement, experimental thinking, standardization of processes, and error-proofing.

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# 1 Introduction

In the field of healthcare, delivering *value* to patients is more than just providing a good product or service—it is a necessity to ensure the patient's health by maximizing benefits from care while minimizing the risks of any adverse events. Value can be seen as a function of quality, service, and cost. The United States spends nearly 18% of Gross Domestic Product on healthcare, which is more than any other developed nation, yet lags behind other countries in several health indicators (PGP Foundation, 2020). For example, the U.S. has a high rate of preventable medical errors that do more harm to the patient than good. A portion of these medical errors are *medication errors*, which are errors in the medication-use process that could potentially cause harm to the patient (Mayo Clinic Staff, 2020). In this research, we explore many of the ways value is impacted for patients throughout the pharmaceutical value chain. We then apply supply chain principles and Lean methodologies to the pharmaceutical value chain to help guide healthcare workers and pharmaceutical industry professionals in using the right improvement tools to achieve greater value for patients and reduce medication errors.

The pharmaceutical industry develops, manufactures, and sells medications to help improve patients' quality of life.

The processes of discovering, manufacturing, and distributing medications is a lengthy, complicated endeavor that requires many safety checkpoints and close coordination among the organizations involved in bringing the drug to the patient (Datex, 2020). While regulations and technology have increased the complexity of supply chains, there are now many opportunities for pharmaceutical value chain actors to cooperate and coordinate more effectively to provide the greatest value for patients.

Manufacturing and service firms have made supply chain optimization a priority since an efficient, agile supply chain can reduce costs while improving quality. The downstream pharmaceutical supply chain (PSC), as discussed in this thesis, refers to the networks between pharmaceutical manufacturers, distributors, healthcare providers, pharmacists, pharmacy benefit managers, and the end users; the PSC includes a multitude of processes, people, organizations, and flows of information and resources (Kenton, 2020). New technologies in product development and global manufacturing pose considerable challenges to governing bodies and PSC actors since they must navigate a complex supply chain with a unilateral goal of improving patient outcomes. Given these challenges, implementing supply chain principles and Lean methods can help manage the complexities, increase efficiency,

and improve quality. To maximize value for patients, PSC actors must consider the "Eight Rights": "…providing the right medication to the right patient at the right dose at the right time through the right route for the right reason with the right documentation, ultimately causing the right response" (Schuhmacher *et al.*, 2015; Kavanaugh, 2016). Though this concept is normally taught to nurses and caregivers (Vaughn, 2018), it can and should be translated throughout all components of the PSC. When viewing the PSC as a *value chain*, in which value is influenced by each PSC actor, we hope to determine the best practices to eliminate medication errors and improve patients' health.

In this research, we identify the meaning of value and safety for patients (e.g. reduction of medication error rates) as well as the role that PSC actors play in delivering this value. A model is presented to explain these roles and their interconnections, such as the relationships between the manufacturer, prescriber, dispenser, and administrator of the drug. Lean solutions are discussed to provide downstream PSC actors with an improvement framework for their segments of the supply chain.

The research method used is a critical analysis of information on downstream pharmaceutical supply chain issues and patient value, including literature reviews, a review of

current U.S. regulations of the pharmaceutical industry, and interviews with industry experts. We use the analysis to develop a theoretical framework for how value can be maximized through a patient-centered model of the PSC, rather than the traditional profit-focused model (Settani, et al. 2017). Modeling all material and information flows in the downstream PSC will help actors align their goals to create a smoother value stream. The model includes all downstream PSC actors: pharmaceutical manufacturers, distributors/wholesalers, prescribers (physicians and nurses), dispensers (pharmacies), pharmacy benefit managers (PBMs), drug administrators (patients/care givers), and the end users (patients) (Datex Corp., 2018; Williams, 2007). The patient-focused model will emphasize the alignment of all PSC actors with the common goal of ensuring the best patient outcomes.

## 2 Background on Pharmaceutical Value

In the discussion of building a truly patient-centered supply chain, value chain actors must consider what factors must be prioritized to drive the greatest value to the patient. While different value actors may have different goals and ideas of what value is, they can build a more patient-centered value chain by aligning interests and focusing resources on value-adding activities using Lean methodologies. Ideal value from a supply chain perspective involves supplying high-quality products that function as intended, are free of defects, are delivered on-time, and are cost-effective for healthcare payers. From a clinical perspective, providing value is to follow the "Eight Rights" in the MUP: provide the right medication to the right patient at the right dose at the right time through the right route for the right reason with the right documentation, ultimately causing the right response (Schuhmacher, et al., 2015; Kavanaugh, 2018). While these two definitions differ slightly, together they form a complete value statement to describe what patients need. Healthcare is a rapidly evolving field, and achieving the highest value requires a multi-faceted approach to help improve patient outcomes.

Value is a function of quality, service, and cost. Value can be increased if the quality of treatment is improved, if the service level is increased, and/or if cost (to the patient) is decreased. According to University of Utah Health's report on different perspectives of healthcare value, the equation below represents the overall value derived from care.

$$\text{Value} = \frac{\text{Quality} + \text{Service}}{\text{Cost}}$$

*Figure 1: The Healthcare Value Equation. Adapted from University of Utah Health's Value Equation.*

Every value chain actor influences all three factors: quality, service, and cost. By operationalizing and measuring these factors, actors can have a better what their segments of the value chain do to increase (or decrease) value. Below, each factor is characterized from a patient-centered perspective.

- *Quality* means that healthcare is safe, effective, timely, efficient, equitable, and individualized for the patient's needs (Health.gov, 2020). When high-quality medications are used for the right purposes, they should

produce the appropriate response in the patient, which is to improve the patient's condition with minimal side effects. Quality is the most important factor affecting value, since a lack of quality could be detrimental to the patient's health. Manufacturers and distributors must be able to assure patients that the medications they are using are safe to use, while medication-use process actors must further be able to prescribe, dispense, and administer a medication that will be the most effective for the patient. If quality fails, a medication error could occur. Medication errors, which are discussed in further detail in Section 3.3, may increase the risk of adverse drug reactions (ADEs).

- *Service* refers to the availability of care/treatment to the patient. Were the patient's individual needs addressed? Was the patient able to access care quickly and effectively, allowing him or her to use the right medication at the right time? Manufacturers, distributors, and pharmacies may view *service* as their ability to get the right medication to the patient, and avoid stock-outs, at the time the patient needs to use the drug. Healthcare providers/prescribers may view *service* as their ability to correctly identify the most effective, least-risk drug that would improve the

patient's condition. If service levels fail in any segment, the patient could be at risk of not being able to access necessary medication.

- *Cost* can be broadly defined as what the patient loses in exchange for healthcare. This can take the form of money—for example, it could be the patient's insurance premium, a co-payment, or even a full-price payment for a drug that is not on the patient's insurer's formulary. *Cost* can also take the form of time; for example, the length of time used to diagnose the patient, or the length of time the patient waits to obtain and use the prescription drug. If the patient feels as if there are too many costs to receiving care, they may forgo life-saving medication.

In the value chain, any failure to provide good quality or service at a reasonable cost can result in the patient not receiving the greatest possible care; in fact, it could cause the patient more harm.

# 3 Research Methods

## 3.1 Literature Reviews

Sections 4 and 5 provide a review of the literature on downstream pharmaceutical supply chains and the medication use process, respectively. Existing literature fails to connect these two arenas in healthcare. *Settani et al.* (2017) found that, through an in-depth analysis of literature on PSCs, majority of the models are product-centric, focusing solely on linear manufacturing and distribution processes. Through reviews of the downstream PSC and the MUP, we can better identify how these two segments play roles in delivering value to the patient.

In Section 4, we reviewed the downstream pharmaceutical supply chain, including the relevant PSC actors, trends and changes impacting PSCs' value-delivery systems, and the regulations that PSCs operate within to ensure drug supply safety and efficacy. This information was pulled from 58 sources, which include peer-reviewed articles, webpages, and more.

In Section 5, we reviewed the medication-use process, the very downstream-end of the PSC. We also reviewed the concept of value in health care and how medication errors reduce this

value. Altogether, this information was pulled from 45 sources, which included peer-reviewed articles, webpages, and more.

### 3.2 Interviews

To understand more about how the PSC and MUP work, I conducted interviews with three field experts. I first interviewed Saad Jamal, who owns an independent pharmacy in a low-income area. He told me about ways in which he manages supply chain flows and how he is working to increase value, such as mail-order pharmaceutical deliveries. My second interview was with a pharmacist that has done rotations and worked with different teams, Noemie Senawong. These two field experts provided substantial information regarding ordering medications, managing drug inventories through web-based software, handling discrepancies with drug prescribers, working with a pharmacy team, and technology usage. Finally, I interviewed Luca Boi, a Value Engineer at the University of Utah Health. He is well-versed in Lean healthcare, and he has worked with groups to implement Lean tools to improve value for patients.

## 4 Review of the Pharmaceutical Supply Chain

The pharmaceutical supply chain consists of all monetary, information, and material flows between the people and organizations that function to bring drug products to the end user—the patient. Though different medications require different types of delivery formats, the general process remains the same for prescription medications and those

administered in hospitals. In the diagram below, it is assumed that information flows are moving in all directions.

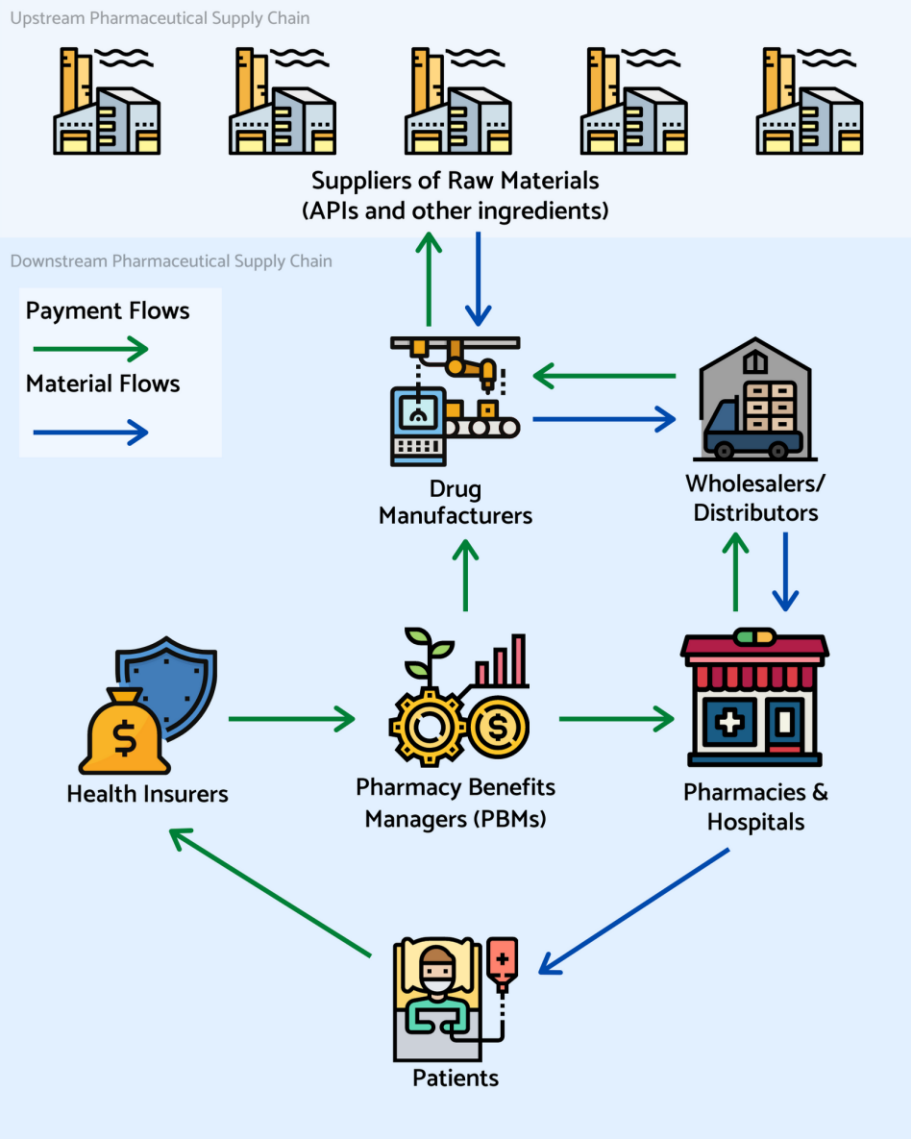


*Figure 2: The Downstream Pharmaceutical Supply Chain*

The PSC includes the materials suppliers, manufacturers, distributors, pharmacies, pharmacy benefit managers (PBMs), and patients. In this paper, the *upstream PSC* refers to all processes and flows that occur prior to the manufacturing of

medications, while the *downstream PSC* refers to all processes and flows to distribute medications to end users (starting from the manufacturing site).

By reviewing the roles of each PSC organization ("PSC actor"), we can identify how each downstream organization contributes to the final delivery of value to the patient. This includes drug labelling and RFID tagging, multiple quality and safety checks, and best practices to identify and manage errors. At each change of hands, drug products are prone to theft, tampering, and adulteration (White, 2016), which could ultimately lead to medication errors, stockouts, and other value-reducing issues.

## 4.1 Pharmaceutical Supply Chain Actors

The upstream PSC originates from the suppliers that supply raw materials to manufacturers. This includes suppliers of inactive ingredients and active pharmaceutical ingredients (APIs). While the formulation and design of the drug do impact its final value offering, this is beyond the scope of this paper.

### *4.1.1 Drug Manufacturers*

The downstream PSC begins with the drug manufacturer. There are brand-name pharmaceutical firms (often referred to as "Big Pharma"), such as Pfizer and Merck, that produce new

drugs after years of research and development, and there are generic pharmaceutical firms, which manufacture generic versions of brand-name drugs after the brand's patent expires. Manufacturers analyze market demand information to forecast demand and plan production levels, obtaining this information through prescribing physicians and other healthcare providers (Health Strategies Consultancy, 2005). The pharmaceutical manufacturer can also stimulate demand through advertising to healthcare providers and patients. For example, pharmaceutical firms may fund research studies that provide evidence of their drug's efficacy and safety compared to other options (Health Strategies Consultancy, 2005); this helps increase physicians' and patients' confidence in the drug. Often referred to as "Phase IV clinical trials", continuous research studies even after commercialization of a drug helps manufacturers assess safety, effectiveness, drug interactions, and any long-term side effects of a drug that were not found in previous clinical trials (Mandal, 2014).

Further, the manufacturer holds the greatest impact on prescription drug pricing. By analyzing competition, forecasting demand, and estimating costs, manufacturers determine a wholesale acquisition cost (WAC) for each drug product. Wholesalers and distributors must pay the WAC for

drug supply unless they are granted discounts or rebates (Datex Corp, 2019).

The manufacturer also plays a major role in securing the PSC's safety by creating informational labeling that falls within the U.S. Food and Drug Administration's (FDA) terms and conditions for approval of the drug (Health Strategies Consultancy, 2005). Mislabeling early on in the PSC can lead to detrimental effects downstream, including damage to the patient's health and costly drug recalls. Labeling helps follow regulatory guidelines by providing important information about the dosage, usage, side effects, ingredients, etc. of the drug product; it helps physicians and patients determine the value and risks of the drug to the patient's health. Labelling also helps keep track of medications throughout the supply chain, ensuring that any errors with a specific batch or lot can be traced. Recently, pharmaceutical companies have looked to automation, RFID tagging, and outsourcing of drug manufacturing to improve quality and decrease costs throughout the supply chain; this will be further discussed in Section 2.2. Although pharmaceutical manufacturers can ship products directly to pharmacies and hospitals, they typically sell to wholesalers and distributors.

### *4.1.2 Pharmaceutical Wholesalers and Distributors*

Pharmaceutical wholesalers and distributors have played an important role as logistical experts in delivering medications to a multitude of different recipients—clinics, pharmacies, hospitals, and care homes. There are three firms that hold over 90% of the pharmaceutical distribution market share: McKesson, Amerisource, and Cardinal Health (Fein, 2019). Distributors ensure convenient access of medications through nationwide dispensing sites, and they ensure all products are stored and transported appropriately to stay within FDA guidelines and to protect patients' health. According to a 2019 Deloitte report, pharmaceutical distributors connect 1,300 manufacturers to over 180,000 points of dispensation. This allows other PSC partners to focus more on core, value-adding activities, while distributors increase overall PSC efficiency through buying power and economies of scale in drug distribution. The healthcare savings gained through this efficient method of distribution is estimated to be between $33 billion and $53 billion annually (HDA, 2020); distributors influence value by not only providing widespread access to drug products, but also by translating cost savings to patients.

Investments in technology have also helped enhance safety and transparency across the supply chain, allowing providers

to better gauge drug supply and manufacturers to better gauge drug demand so that all PSC actors can best coordinate. Drug distributors have also evolved to provide more value-adding services aside from traditional distribution; for example, distributors help in delivering certain specialty medications, pharmaceutical repackaging, and drug buy-back programs (KFF, 2005).

Distributors function by filling totes with drug products to send to specific pharmacies. Then, after appropriate stocking of products, pharmacies and other dispensing units send back the totes (which can include any unneeded products) for reuse by the distributor (Deloitte, 2019). Although distributors can supply drugs directly to patients, the majority of their business is done through selling pharmaceuticals to points of dispensation.

#### *4.1.3 Drug Dispensers (from a Supply Chain Perspective)*

Points of dispensation, collectively referred to as *(drug) dispensers* in this paper, include independent pharmacies, chain store pharmacies (such as CVS and Walgreens), mail-order pharmacies, hospitals, long-term care homes, and any other institution where drugs are prepared for administering to patients. These actors are the link between the general PSC and the medication-use process, which will be discussed in Section 3. Drug dispensers place orders with

drug distributors and wholesalers, which then deliver directly to the dispenser or to larger dispensers' product warehouses. They often use electronic inventory management systems—when a prescription drug is out of stock, the system places an order automatically (Senawong, 2021; Jamal, 2021).

Serving as the interface between the PSC and the patient, dispensers have the greatest impact on the final value delivered to the patient since they must ensure that patients receive the correct, properly-stored drug with the correct dosing information (McGrail, 2020). Dispensers electronically manage and share drug claims information that can be used by other PSC actors to assess consumer activity (KFF, 2005). This helps the entire supply chain determine demand levels, prices, and healthcare needs.

#### *4.1.4 Pharmaceutical Benefit Managers (PBMs)*

Pharmaceutical Benefits Managers (PBMs) are PSC organizations that do not participate in any physical flows of the medications, but they do influence the price and accessibility of pharmaceutical products. PBMs are a middleman in the supply chain that manage many aspects of prescription drug benefits for health insurers, government programs, large employers, and other types of payers. They impact value for the patients by determining drug costs for payers, patients' access to certain medications through

formularies, and how much pharmacies are paid (Commonwealth Fund, 2019).

Firstly, PBMs develop and maintain the healthcare payer's drug formulary list, which includes all prescription medications that are preferred under a particular health plan. If the patient is prescribed a drug that is not the formulary list for his or her health plan, then the patient will have to pay the full out-of-pocket cost for the drug, or the prescriber must prescribe an alternative that is listed.

Second, PBMs negotiate rebates and discounts with drug manufacturers. As mentioned above, drug manufacturers determine a set *list price* for prescription medications. Because the manufacturer may want its drug on a certain health plan's formulary, it will grant rebates and discounts to the PBM in the form of a percentage off the list price. PBMs report typically passing on 90% of the rebate to the health insurers/payers, which pay administrative fees and expenses to the PBM for their services (Seeley and Kesselheim, 2019). The PBM contracts pharmacies, paying the pharmacies for drugs dispensed to beneficiaries (Commonwealth Fund, 2019). According to the Centers for Medicare and Medicaid Services, PBMs have helped decrease drug prices and reduce the growth of PSC spending. However, since PBMs are paid through retaining a percentage of the privately-negotiated rebates, they are

incentivized financially to place higher-margin drugs on the formulary rather than more cost-effective and clinically-effective drugs. Furthermore, a whitepaper on PBMs and healthcare reform discovered that higher drug rebates are associated with an increase in list price; on average, a $1 increase in drug rebates correlated with a $1.17 increase in list price by the drug brand manufacturer (Sood *et al*., 2020). Higher list prices cause price increases for the uninsured who must pay out-of-pocket costs for drugs, as well as those who must pay higher deductibles and coinsurance. Currently, policymakers are making efforts to increase transparency in PBMs' negotiations and contracts, as well as potentially changing the rebate system to increase value for the patient (Seeley and Kesselheim, 2019).

#### *4.1.5 Patients*

The final actor in the PSC is the patient. When the patient faces a medical issue, he or she may be prescribed and/or administered a drug to help manage the problem. Physicians must diagnose the patient and determine the appropriate drug that will provide the most therapeutic effect. In the United States, over 4 billion prescriptions are filled annually (Statista, 2020). Prescription medication use increases with age—a National Center for Health Services (NCHS) data brief showed that about 18% of children under age

12 used a prescription medication compared to 85% of adults over 60 (Crescent, *et al*, 2019). People with chronic conditions and older people facing more medical issues often require more prescription medications. With more medications needed, the patient is more prone to medication errors, as well as high drug costs that could result in the patient choosing to not take a particular drug. Additionally, if patients experience any medication issues, they should report it to the prescriber and dispenser to determine the source of the problem so it can be prevented in the future.

If patients receive the right prescriptions and use the drugs properly, they should experience health benefits. From a supply chain perspective, delivering value to patients involves having medications readily supplied when needed and at a reasonable price.

From a clinical perspective, delivering value to patients means delivering the right drug to the right patient at the right dose at the right time via the right route for the right reason with the right documentation to receive the right response (Kavanaugh, 2018). This is referred to as "The 8 Rights", and it will be discussed in more detail in Section 3. Supply chain and Lean methodologies, implemented throughout the downstream PSC, can help achieve both the supply chain and clinical perspectives of maximizing value.

Table 1 on the next page summarizes the roles that different PSC actors play and how they impact value for the patient.

*Table 1: How different PSC actors impact value*

| PSC Actor | How they impact value... |
|---|---|
| Manufacturer | ● Complete R&D necessary to develop drug<br>● Determine *list price* for drug based on competition, costs, etc.<br>● Assess drug demand and schedule production based on forecasted demand<br>● Label all batches/lots of drugs following FDA regulations<br>● Continue to assess drug safety after commercialization through "Phase IV trials"; issue a drug recall if necessary |
| Distributor/Wholesaler | ● Focus on distribution so that manufacturers and dispensers can work on more core, value-adding activities<br>● Achieve economies of scale in the distribution function of the PSC, helping to lower overall healthcare costs |
| Drug Dispenser | ● Order and stock drugs according to demand needs<br>● Appropriately store drugs so they do not lose safety or efficacy<br>● Dispense the correct amount of the correct drug<br>● Ensure labeling on the drug packaging is correct<br>● Reach out to the prescriber if there is an issue regarding the medication<br>● Inform patient on how to use the medication, its safety, and any potential drug interactions |
| PBM | ● Secure rebates for drug products from manufacturers, and share the rebate with health insurers/payers<br>● Develop and manage a formulary of drugs that will be paid for by the health insurer/payer, impacting patient accessibility to certain drugs |
| Patient | ● Must properly take the prescription drug following dosing instructions (if self-administered)<br>● Report any errors so relevant PSC actors are notified and can prevent the error from occurring again |

### 4.2 Current Developments in Pharmaceutical Supply Chains

In the past few decades, the pharmaceutical industry has faced radical changes that are forcing PSC actors to either adapt or suffer. PSCs have had to evolve to manage cutting-edge technological developments, supply chain structure reorganization, stringent regulatory measures, new categories of therapeutics, increased pressure to reduce drug prices, and trends that are changing the way medicine is prescribed, dispensed, and administered (Kartscher and Packman, 2011). With greater emphasis on patient outcomes and reducing healthcare costs, many developments in the pharmaceutical industry are streamlining PSC processes and increasing the value proposition provided to the patient. However, tied to these developments are new regulations and complexities that PSC actors must address in order to be successful in the marketplace. As PSC actors refocus their supply chain strategies to better manage the rapidly changing environment, a patient-centric approach should be taken. In this section, we discuss these developments and their impact on value for the patient. In Section 5, we discuss how lean solutions can help PSCs best manage the shift.

### *4.2.1 Technological Developments*

Similar to many other industries, the PSC has picked up plenty of digital tools and data management systems that have helped increase supply chain visibility and security. These tools include the use of integrated, cloud-based data storage software and monitoring devices that can track material flows. For example, Radio Frequency Identification (RFID) technology has been widely implemented across the PSC since it has strong track-and-trace abilities. The technology uses radio waves to scan a unique electronic tag attached to a certain batch of product; when the RFID tag is scanned, important information about the product is retrieved. Pharmaceutical manufacturers control the drug information associated with an RFID tag for a batch of drug products, so any other downstream PSC actor can use the technology to verify the legitimacy of the drugs (Coustasse, *et al.*, 2016). Every time drug products are handled, the handler can use the RFID technology to confirm the drug's origin, what is being done at the current facility, and where its destination is. Not only does this improve visibility into drug inventories and processes across the PSC, it also helps prevent the entrance of counterfeit drugs into the supply chain. According to the World Health Organization (WHO), approximately 10% of pharmaceutical trade has been

confirmed to be counterfeit. Counterfeit drugs, which can be tampered with, contaminated, and adulterated, endanger patient health, and reduce the overall value offering. RFID technology has proven to be useful in ensuring patient access to effective, safe drugs. For example, drugs that are recalled or expired can be more effectively tracked using RFID so that they can be handled properly. Furthermore, RFID technology grants PSC actors the ability to best assess where and how much inventory is at different parts in the PSC, thereby improving inventory management and ensuring a more agile supply chain. Tracking pharmaceutical products all the way to delivery to the patient gives PSC actors real-time data about patients, products, and processes, allowing PSC actors to best forecast operation needs as well as gain a greater perspective on patient health care and the effectiveness of prescription drugs. Data has become almost as important as the product itself. To form a more agile, patient-centric supply chain, data pertaining to drug usage and effectiveness can aid PSC actors in quickly responding to any issues that could risk the patient's health. Additionally, this data can help Big Pharma continuously perform research on their drug products, such as research on side effects and drug interactions.

The increase in data accessibility has led to a new development in healthcare—personalized medicine. The Personalized Medicine Coalition (PMC) defines *personalized medicine*, also called *precision medicine*, as a multi-faceted approach to patient care that not only improves the process of diagnosing and treating disease, but also offers the potential to detect disease at an earlier stage and treat it effectively based on the patient's individual characteristics. Data about the patient's living conditions, medical and family history, lifestyle, and especially his or her genome can help paint a more accurate picture of the patient's needs. A new area of research, *pharmacogenomics*, is studying genetic information to determine patient response to different kinds of medication (NIGMS, 2020). For example, certain cancer patients may overexpress a particular protein that leads to tumor development, while other patients with the same type of cancer may not be producing enough of a certain protein that ultimately causes similar tumor development. By preemptively stratifying these patient populations using genomic data, the right type of chemotherapeutic drug can be prescribed by the physician for either population. This is a better value offering than providing a drug that may not necessarily work due to the patient's individual characteristics. According to industry experts, drugs do not have the desired outcome in 30%

- 40% of patients. Blockbuster drugs are usually effective in 40% - 60% of patients, and chemotherapy often works well in only 30% of patients (Hu, *et al.*, 2018). With the aid of IT and data analytics, professionals can better serve patients. Obtaining and using patient information for the purposes of personalized medicine requires collaboration and integration throughout the PSC along with regulations that serve to protect patient health information; regulations are discussed further in Section 2.3. While precision medicine is still in an early, developmental stage, its realization is on the horizon. PSCs, which typically use batch production for drug products like capsules, tablets, and injectables (Wollenhaupt, 2019), must consider the forthcoming impact of personalized medicine on current business models; they must be able to adapt accordingly in order to remain competitive. By using technology to adopt continuous production and transportation methods, creating a "smart supply chain" using Lean and supply chain principles is very much possible. This would involve capturing real-time data on critical processes; developing complex, flexible multivariate models; and automatically compensating for any unexpected process disturbances that could affect drug quality (Kartscher and Packman, 2011). Therefore, PSC actors should, if not already, begin considering the infrastructural and logistical changes needed

to turn personalized medicine into a reality. Methods to make these changes, with patient value in mind, are discussed in Section 5.

Finally, another major development PSCs are facing is the progression of new types of pharmaceutical products. (Please note that this research does not delve into *how* medications are developed and formulated, but rather the PSC's impact on value when it comes to managing medications from manufacturing site to end user.) According to PwC's *Pharma 2020* report on expected changes in the pharmaceutical industry, several new categories of therapeutics have entered the marketplace within the past few decades (Kartscher and Packman, 2011). Several of these categories are described below.

- *Fixed-dose combinations*: a medication that includes two or more APIs contained in a single dosage form, which can provide more therapeutic value than either drug alone. By reducing the number of medications a patient needs to take, fixed-dose combination drugs help improve adherence to treatment regimens (Clinical Info HIV, 2020).
- *Therapeutic monoclonals*: antibodies produced from a single B-cell clone; these antibodies can be used to treat antigens from infectious diseases and even cancer cells.

- *Nano-medicine*: a rapidly developing science in which nanotechnology is implemented into pills and capsules that can be used for diagnostic imaging or target-oriented delivery of certain medications (Patra, *et al.*, 2018). For diagnostic imaging, providers can better determine root causes of patient problems. For site-specific, target-oriented delivery of APIs, medications can become more effective where they are needed while reducing side effects that impact other body systems.
- *Pharmacogenomics*: as described in the paragraph above, this developing field of medicine is based on genomic data. Pharmacogenomic drug products are targeted toward patient populations that have certain gene sequences, which results in better therapeutic value than other competitor drugs that target the same illness (NIGMS, 2020).
- *Gene-based therapies*: integrating a gene into a patient's genome to treat or prevent a disease. This involves replacing mutated genes with healthy genes, inactivating mutated genes, or even introducing a new gene into the body using inactivated viral vectors (MedlinePlus, 2020). While this type of treatment is still in a very early, experimental stage, it could help provide valuable

medical treatment to a large range of patients facing genetic-based illnesses.

Pharmaceutical research is rapidly changing the way medications are handled and administered. The downstream PSC is responsible for adapting to the marketplace for new types of pharmaceutical products, meaning that PSC actors must find ways to safely manufacture and distribute products without compromising the efficacy of the drug. Different therapeutics may require different methods of storage (i.e. climate and exposure to light), different lead times from manufacturing to the patient, and different forms of dispensing and administration. For example, the Pfizer-BioNTech COVID-19 vaccine, a novel type of RNA vector vaccine, requires storage at extremely cold temperatures of -80°C to -60°C. The logistical management of this vaccine involves specially-designed, thermal-monitored shipping containers filled with dry ice to protect the efficacy of the vaccine to its points of dispensation and administration (NCIRD, 2021).

As research progresses, new developments progress that impact the PSC's abilities to provide the greatest value to the patient. Changes and new additions will have to be made to current pharmaceutical business practices to more effectively respond in this new era of healthcare.

### *4.2.2 Trends in Pharmaceutical Supply Chain Design and Organization*

To a degree, pharmaceutical firms have already started undertaking measures to build stronger, secure, and more highly-utilized supply chains. This is the result of greater emphasis on patient outcomes, increased pressure to decrease healthcare costs, and increased adoption of new technologies. FDA regulations, which are discussed in Section 2.3, also play a significant role. Some of the structural changes PSCs are facing include pharmaceutical consolidation, outsourcing of core activities, improving delivery networks and methods, and new types of pharmacies.

Over the past few years, the number of pharmaceutical firms has been consolidated through plenty of mergers and acquisitions (M&As). In 2018, M&A deals reached $265 billion—a 25% increase from 2017 (Jewell, 2019). As the patent cliff inches closer for many blockbuster drugs, Big Pharma must focus on developing new products to continue making the large profits they have enjoyed in previous years. However, given that pharmaceutical development has over a 90% failure rate (Hingorani, *et al.*, 2019), there is a lot of risk involved. As such, Big Pharma often looks for M&A deals with smaller pharmaceutical firms that are nearing FDA approval for a new

drug product. This is because Big Pharma has the infrastructure to obtain the approval, scale up drug production, deliver to distributors, and negotiate with PBMs. Aside from M&As, pharmaceutical companies have also invested more into outsourcing of other core activities, such as R&D and solid dose manufacturing. Large pharmaceutical companies attribute improved quality and reduce time-to-market as major reasons for outsourcing with contract organizations (GEP, 2019). Outsourcing offers specialized services for important PSC value-adding processes, ultimately increasing the final delivery of value to the patient.

Additionally, in PwC's Pharma 2020 report, the researchers highlight four different options for possible operating strategies upon which PSC actors could benefit.

| Operations Strategy | | | |
|---|---|---|---|
| Specialist Therapies | | Mass-Market Medicines | |
| Virtual Manufacturer | Service Innovator | Low-Cost Provider | Profit Centre |
| Create a virtual network of integrated supply partners | Build a service-oriented supply chain to enhance brands and differentiate company from its competitors | Build a reliable, 'no-frills' supply chain to deliver products as economically as possible | Combine agile, economic manufacturing and distribution with the provision of satellite services to generate profits |

Source: PwC

*Figure 3: Pharmaceutical operation strategies in 2020, from PwC's Pharma 2020 report*

These four strategies are highlighted and briefly described below.

*Specialist therapies* require different production methods and logistical measures than regular, mass-market therapies. They haven't achieved the same economies of scale, so implementing lean into the supply chain for these therapies can help create higher-performing supply chains. The PwC report says these manufacturers have two options:

- *Virtual manufacturers*: use an operations strategy solely based on outsourcing the entire supply chain by building a network of fully integrated supply partners. In essence, the pharmaceutical company plays the role of the orchestrator, determining which partners need to act and when. While there are benefits to this, there are also concerns about quality. According to the report, 91% of firms using outsourcing have experienced a "significant incident" due to quality problems or delays compared to only 59% of those that manufacture in-house (PwC, 2011).
- *Service innovators*: build PSCs that can (a) manufacture and distribute specialty, complex treatments, while (b) also commissioning and managing a number of suppliers that can provide supporting health management services. This strategy involves paying special attention to

patients' healthcare needs by constantly reviewing and analyzing provider and patient feedback. While this is a more difficult route to pursue, it is truly patient-centered since the focus is to drive value to the patient in innovative ways.

*Mass-market medicines* are medications that have deeply penetrated the pharmaceutical marketplace and are widely available. This includes top-prescribed medications, such as levothyroxine (thyroid hormone for hypothyroidism) and metformin (for diabetes type 2). Many of these popular medications have long passed their patent expiration dates, so generic producers are also involved in mass production. Although these drugs have established supply chains, the PSC actors involved must focus on enhancing their strategies to keep up with the changing climate of the industry. There are two strategies that the PwC Pharma 2020 report describes for mass-market medications:

- *Low-cost provider*: use lean production techniques to cut costs wherever possible while trying to improve quality and service levels. As healthcare policymakers demand drug prices that align with the value of the drug, PSC actors must implement lean supply chain solutions. This involves sustaining a culture of continuous improvement

as well as defining workflows for each product to determine where improvements can be made and to ensure regulatory compliance.

- *Profit centre*: combine efficient manufacturing and distribution practices with the provision of satellite services for patients. This requires supporting multiple methods of manufacturing, investment in infrastructure and management resources to build a global network of service providers, and robust demand forecasting (PwC, 2020). To be successful, pharmaceutical firms pursuing this type of supply chain should look for new opportunities to add value through stronger use of data.

In re-assessing supply chain strategies, pharmaceutical firms should consider the needs of their individual product pipelines. The options described above fit within Marshall Fisher's diagram on choosing the right supply chain based on the product.

| | Functional Product | Innovative Product |
|---|---|---|
| Efficient Supply Chain | MATCH | MISMATCH |
| Responsive Supply Chain | MISMATCH | MATCH |

Pharmaceutical companies have also begun putting together "critical teams", which are cross-functional teams of professionals involved in different siloes of the

pharmaceutical industry. These critical teams are responsible for collecting and analyzing information regarding medical and regulatory affairs to provide insights and strategic plans for pharmaceutical companies (Datex, 2019). These teams help to advance the entire supply chain, rather than focusing on their own individual segments of the business.

Another major development in PSC structure is improved "final mile" distribution networks to more efficiently dispense medications to patients. *Mail-order pharmacies* are pharmacies that mail prescription orders with 90-day fills directly to the patient's doorstep; however, this delivery system works only for certain non-urgent and/or long-term "maintenance" medications (Jamal, 2021). Medications used for acute infections or specialty medications that require extra safety in storage and transport should be picked up from a local pharmacy that can provide the drug much faster (Smith, 2020). Mail-order pharmacies provide more value to patients in some cases by saving patients time and money. Through partnerships with certain health insurers (through PBMs), patients can get prescriptions delivered with a co-payment of only a few dollars, or even $0 and free shipping in some instances (Davis, 2018). Mail-order pharmacies also offer advising for medications if the patient reaches out with any

questions. In other cases, patients will benefit more by going to a local pharmacy, picking up a prescription right away, and interacting with the pharmacist face-to-face to learn about how and when to use the medication properly.

Good supply chain design is very important in ensuring that maximum value is provided to the patient. As new products enter the market and healthcare regulators demand more security and value from PSCs, making the right decisions for the right changes at the right time for the right product lines can be difficult. As PSC actors look to improve supply chain strategies, they should center their strategies around building value for the patient. In Section 5, we discuss how lean solutions can be applied to aid professionals in taking the right steps.

### *4.2.3 Increasing Complexities*

In this research, we take a more general view of the PSC when discussing the role that each actor plays. PSCs are highly complex, given the technological developments discussed above, global manufacturing, and increasing regulations. *Rossetti, et al.* (2010) conceptualize the PSC as a complex adaptive system, in which participants are coupled in a value chain of production where any participant's actions can potentially affect any other participant. The PSC's evolution

arises from each PSC actor's actions and interactions, as well as the healthcare regulatory environment. In this section, we briefly discuss the added complexities of this evolution as PSC actors adapt to new circumstances.

One of the main factors contributing to more complex PSCs is globalization. Pharmaceutical firms may outsource manufacturing to factories in other countries, which can be well-managed with information technology (IT) to assess production capability and quality levels in some cases. However, it is difficult to hold foreign manufacturers accountable to FDA standards. According to *White* (2016), the number of drug products manufactured in foreign factories has more than doubled since 2002. The FDA struggles with the logistical challenges of conducting regular inspections of these foreign establishments, and a screening system for imports could be very costly without providing enough benefit. To ensure a safe and secure drug supply, it is up to pharmaceutical companies to guarantee that outsourced production partners follow good manufacturing practices and perform regular quality testing.

While developments in technology have helped improve data management and value delivery, these developments also pose challenges for PSCs. Determining the best way to use

technology and urging supply chain partners to use it in a standardized manner are not simple tasks. For example, the progression of personalized medicine means PSC actors will have to work together to implement creative solutions to deliver specific drug products to specific patients. New therapies with shorter life cycles are forcing PSCs to move away from the conventional practice of relying on blockbuster products for profits (Datex, 2019). To manage these changes, PSC actors will have to make supply chain integration and agility key matters in strategizing, since value can be increased through better communication and coordination.

Another factor is the growing scrutiny to perform more efficiently—to improve value for patients while making sure to comply with FDA regulations. Regulatory measures are put in place ultimately to protect the end user; we discuss these in the next section.

### 4.3 Review of Pharmaceutical Supply Chain Regulations

Pharmaceutical regulations are defined as "the combination of legal, administrative, and technical measures that governments take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of

product information" (Al-Worafi, 2020). Since patients cannot be expected to assess the quality and efficacy of their medications themselves, it is up to PSC actors and legislative bodies to ensure that high standards are upheld to protect public health. The U.S. Food and Drug Administration (FDA) can be considered an external PSC actor, since it influences many of the actions that PSC actors must adhere to. The FDA ensures product integrity through drug product and facility registration; inspections; chain-of-custody documentation; and technology solutions to protect against counterfeit, diverted, adulterated, expired, and misbranded/mislabeled drugs (Dabrowska and Thaul, 2018). The original Food and Drugs Act was passed on June 30, 1906, prohibiting selling of misbranded and adulterated food and drugs. In 1938, the Federal Food, Drug, and Cosmetic (FDC) Act expanded the responsibilities and abilities of the FDA, requiring pharmaceutical companies to prove drug efficacy through clinical trial data, undergo inspections, and properly label drugs with instructions for safe use. These changes were prompted after a toxic chemical, diethylene glycol, led to adverse drug events that killed 107 people, including children (Laws Enforced by FDA, 2018). The FDC act has since been amended many times to further secure America's drug supply and distribution.

### *4.3.1 FDA Regulations*

In this section, we list many of the relevant legislative actions that have helped shape the PSC today. By taking the right actions to comply with FDA regulations, PSC actors can best deliver value to patients. Table 2 lists and describes regulations, appointments, and actions used by the FDA. This information was acquired from various FDA pages, especially the FDA's page *Milestones in U.S. Food and Drug Law*.

*Table 2: A list of FDA regulations and actions over the past century, from various FDA pages*

| Act | Purpose |
|---|---|
| Food and Drugs Act (1906) | Prohibits interstate commerce of misbranded and adulterated food, drinks, and drugs. Established the FDA. |
| Federal Food, Drug, and Cosmetic Act (1938) | Requires new drugs to be proven as safe before marketing. Authorizes factory inspections. Adds remedy of court injunctions to previous penalties of seizures and prosecutions. |
| Alberty Food Products Co. v. U.S. (1950) | Rules that directions for usage on a drug label must include purpose for why the drug is used. |
| FDA Consumer Consultants appointed (1952) | Consultants are appointed in each field to maintain communications with consumers to better understand their needs and problems. |
| Kefauver-Harris Drug Amendments (1962) | Ensures drug efficacy and safety. Requires drug manufacturers to prove to the FDA the effectiveness of drug products before publicly marketing them. |
| Federal Anti-Tampering Act (1983) | Makes it a crime to tamper with packaged consumer products. |
| Orphan Drug Act (1983) | Enables FDA to promote research and marketing of drugs meant to help treat rare diseases. |
| Drug Price Competition and Patent Term Restoration Act (1984) | Expedites the availability of less-costly generic drugs by allowing the FDA to approve applications for generic versions of brand-name drugs without having to repeat the research to show that the drug is safe and effective. |
| Reporting system *MedWatch* instituted (1993) | Consolidates several adverse reaction reporting systems. Designed for voluntary reporting of problems associated with medical products to be filed with FDA by health workers. |
| Data Quality Act (2000) | Requires federal agencies to issue guidelines to maximize quality, objectivity, utility, and integrity of information that they generate. |
| Current Good Manufacturing Practice (CGMP) Initiative (2002) | Focuses on the greatest risks to public health in manufacturing operations, to ensure that process and product quality standards to not impede innovation, and to standardize the approach to these issues across the FDA. |
| "Innovation or Stagnation? - Challenge and Opportunity on the Critical Path to New Medical Products" Published by the FDA (2004) | Report that examines the critical path needed to bring therapeutic products to reality, how FDA can collaborate with PSC actors in the process (including production and end use), and how to make medical breakthroughs available for those in immediate need. |
| FDA Amendments Act (2007) | Expands and reaffirms many of the responsibilities and abilities granted to the FDA. Increases FDA's power to require post-approval studies as well as the implementation of risk evaluation and mitigation strategies (REMS). |
| Food and Drug Administration Safety and Innovation Act (2012) | Promotes innovation to bring safe and effective products to market faster. Increases stakeholder involvement in FDA processes, and enhances safety of the PSC. |
| Drug Quality and Security Act / Drug Supply Chain Security Act (2013) | Outlines steps for an electronic and interoperable system to identify and trace certain prescription drugs throughout the U.S. |

According to *Dabrowska and Thaul* (2018), there are a few key activities in which the FDA is interested in regulating: ensuring product integrity, labeling, reporting and surveillance, post-approval drug studies, managing risk, and dissemination of information. The way the FDA regulates these functions is highlighted below.

- *Product Integrity* - The FFDCA requires annual registration of all domestic or foreign drug manufacturing facilities, warehouses, and transportation methods by giving each a unique identifier. It also requires that these organizations submit a list of ingredients and product labels, adhere to cGMP, and allow for risk-based assessments and inspections. Beyond manufacturing facilities, the FDA uses track-and-trace requirements (established under Title II of the Drug Quality and Security Act) to further monitor product integrity as products make their way through the PSC. Each package of drug products must have a unique identifier, and when a package is transferred or altered in some way, that information should be recorded and made readily available. Whenever a PSC actor suspects that a product may have been tampered with or adulterated, the FDA should be notified immediately so that proper

handling of the error can ensue. (This is where RFID technology, discussed in Section 2.2.1 is important.)

- *Labeling* - Prescription drugs are packaged with a paper insert that includes information that is useful in helping healthcare professionals determine the most effective drugs for their patients. Required information includes the product name and date of approval, any recent major changes, indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, common adverse drug events (ADEs), drug interactions, and other relevant information (Kremzner and Osborne). The formatting and information requirements enforce accurate and understandable information regarding the safe and effective use of the drug.
- *Surveillance and Reporting* - The FDA continues to monitor the safety of drugs in the market by gathering information about ADEs. Drug manufacturers are required to report any ADEs, and health professionals and patients may report ADEs through FDA's *MedWatch* system. According to the FDA's webpage on MedWatch, the system receives approximately 25,000 voluntary reports annually alongside reports from manufacturers. Reports are analyzed to determine what course of action should be taken to

prevent future ADEs—for example, conducting more studies to determine the cause of the ADE or updating the labeling of the drug. In 2016, the FDA also launched its *Sentinel* initiative, the largest multisite distributed database in the world. The Sentinel system uses computer algorithms to analyze electronic healthcare data obtained from electronic medical record (EMR) systems from data-sharing healthcare partners. According to *SentinelInitiative.org*, the algorithms use statistical methods to study patterns and relationships in EMRs; this helps identify where certain treatments have caused ADEs and whether the FDA should take action.

- *Drug Studies* - Pharmaceutical firms perform a series of clinical trials to prove the drug's effectiveness to gain market approval from the FDA. However, the FDA may recommend or require that the firms complete additional drug studies after the drug enters the market to further prove clinical benefit. For example, the FDA may grant accelerated approval of some drugs, such as in cases where a breakthrough therapy for an emerging disease or pandemic is found. If the post-market studies fail to prove the efficacy of the drug or many ADEs are reported, then the FDA can withdraw approval. Additionally, under the Pediatric Research Equity Act, manufacturers must

submit a pediatric assessment for any application for a new API, new indication, new dosage form, or new route of administration (Dabrowska and Thaul, 2018). Pediatric studies may be deferred so that drug sponsors can submit these data after approval.

- *Risk Management* - The FDA may determine that certain risk-management actions need to be taken for certain drugs that pose special circumstances. *Risk* is the combination of the probability of harm and the severity of the harm; it is often difficult to align all stakeholders on the same idea of risk management since they may perceive different levels of risk for their respective processes (FDA Quality Risk Management, 2006). In quality risk management, as recommended by the FDA, PSC actors should focus on upholding certain quality standards throughout the product's life cycle so that its quality in practice is consistent with its quality in clinical trials. Risks should be evaluated based on scientific knowledge and accurate data. Any failure in quality that poses danger to patients should be readily identified and managed. Figure 3 below shows the typical quality risk management process proposed in the FDA's 2006 report on quality risk management.

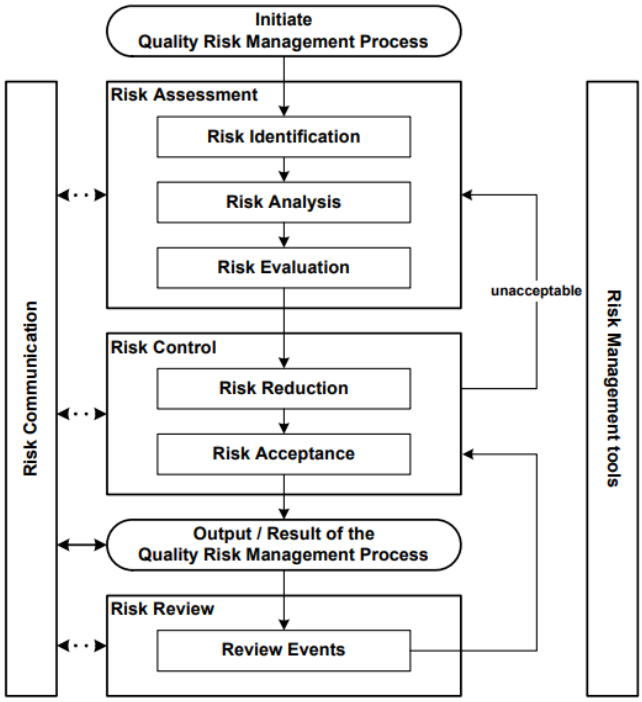


*Figure 4: Risk Management Process. From the FDA's Q9 Quality Risk Management Report.*

Assessing and controlling risks prevents potential ADEs from occurring once the drug makes it to the patient. The FDA Amendments Act also allows the FDA to enforce REMS, which are risk mitigation strategies applied for certain drugs, especially those that are considered high-risk. These strategies include providing patients and healthcare providers with specialized information and enforcing certain requirements for how the drug is dispensed in the medication-use process. For example, certain drugs may only be dispensed in a particular

healthcare setting, or patients must have special documentation to obtain a certain drug. This has helped promote safer prescribing for some products, while others have been less beneficial; i.e. REMS programs covering long-acting opioids often focus more on how to use the product rather than how to decrease prescribing (Avorn *et al.*, 2018). Despite these cases, sustaining a strong risk management system helps add value in the PSC by improving decision making and optimizing drug quality. In Section 5, we discuss the relevant key performance measures that different PSC actors can use and share to assure quality at each step to manage risk.

- *Information Dissemination* - The FDA uses several communication channels to inform healthcare professionals and the general public about the safety and effectiveness of drugs. For example, the agency may establish advisory committees to communicate risks, report information to Congress, and hold public meetings with stakeholders.

All regulatory measures implemented by the FDA are to increase the benefits and decrease the risks of therapeutics in the marketplace. In this manner, the FDA's actions as an external PSC actor help raise the bar for value standards in the pharmaceutical industry.

### *4.3.2 Drug Recalls*

When a pharmaceutical firm determines that a drug poses great risk to patients based on events such as reports of ADEs or quality concerns caught after drugs pass through the PSC, they may initiate a *drug recall*. The FDA may also recommend or request that firms initiate a drug recall based on risk assessments. Recalls are defined as "a method of removing or correcting products that are in violation of laws administered by the U.S. Food and Drug Administration", and they serve as the most effective way to protect the public from any potentially harmful products (Miller, 2020). A Kaiser Health News investigation found that, from January 2013 to October 2018, about 8,000 medications were recalled across the United States (Huggins, 2019). Active recalls can be found on the FDA's *Recalls* page: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts.

Many of these recalls are attributed to facilities that "slip through the cracks" of FDA inspections. As noted earlier, the FDA can perform inspections on both domestic and foreign facilities where drugs are managed. A Kaiser Health News analysis found that, in the past decade, more than 2,500 facilities have gone more than 5 years without drug-quality inspections (Lupkin, 2019). Furthermore, these inspections

provide only a "snapshot" in time—they do not capture the full breadth, nor depth, of manufacturing operations. Additionally, with an increase in outsourcing of manufacturing functions, many drug products are being produced abroad. According to Senate Finance Committee Chairman Chuck Grassley, 80% of APIs are produced abroad, with the majority being produced in China and India (Grassley, 2019). Because these facilities are not inspected consistently, given the logistical challenges of performing these inspections (White, 2016), defective drug products can enter the U.S. and cause ADEs, risking patients' health. This is where it becomes important for pharmaceutical companies to implement robust track-and-trace systems as well as routine quality checks in all drug-handling facilities.

# 5 Review of the Medication Use Process and Medication Errors

When reviewing the downstream pharmaceutical supply chain, it becomes clear that the general model of the PSC fails to account for the flows between drug prescribers, dispensers, and administrators. These downstream actors impact clinical value for the patient in the *medication-use process* (MUP), which is centered on improving the patient's condition. Figure 4 is a diagram of the informational and material flows in the MUP.

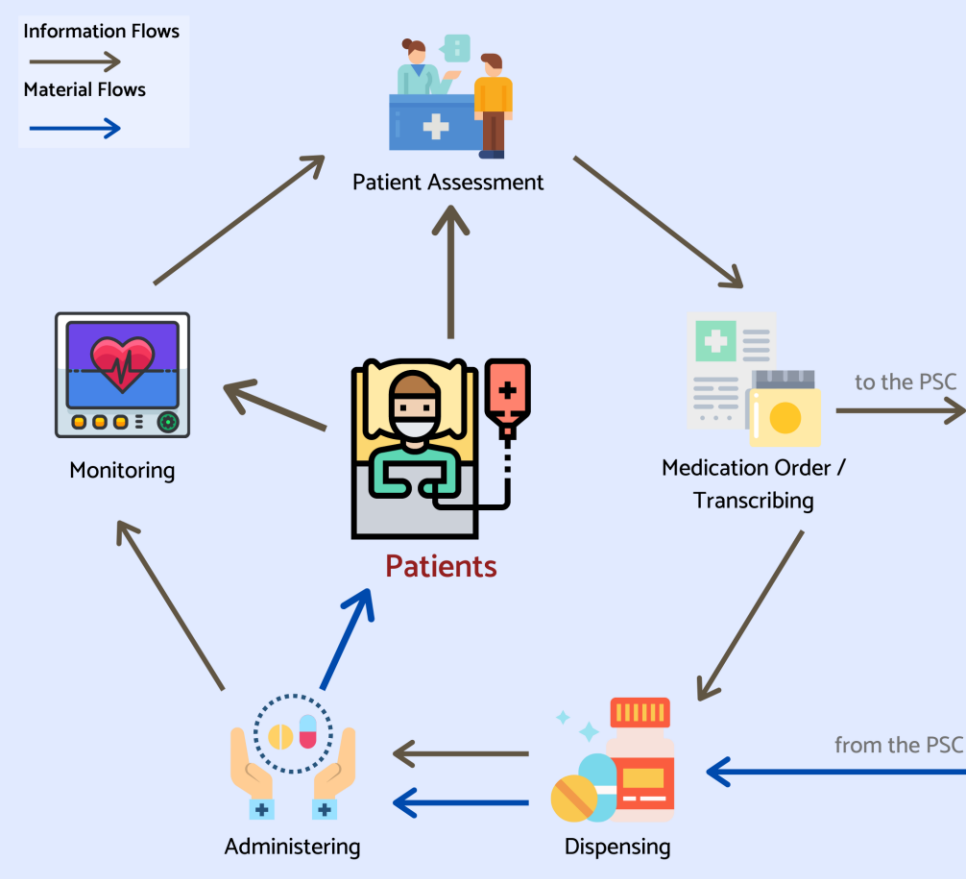


*Figure 5: The Medication-Use Process*

The MUP includes the healthcare provider/prescriber, the drug dispenser, the administrator of the drug (if not the patient), and ultimately the patient. In this paper, the MUP should be thought of as the final downstream entity in the PSC. As the interface between patient healthcare and the PSC, the MUP has access to important information regarding the drug's usage, demand, safety, and effectiveness in different kinds of patients—information that is important to upstream PSC actors. Since MUP actors interact more closely with the patient, they have a very strong influence on the value that is provided.

## 5.1 Actors in the Medication-Use Process

The MUP includes all actors that help identify and provide the right drug to the patient. In this section, we discuss the functions and impact on value that each MUP actor has.

### *5.1.1 Drug Prescribers (Healthcare Providers)*

The MUP begins when the patient visits a healthcare provider to be assessed. Providers are well-trained healthcare professionals that help patients determine what medical problems they are experiencing through diagnostic measures, then provide them with a treatment plan that can

include activity changes, procedures, and of course, medications. In this thesis, prescribers/health providers include physicians, dentists, podiatrists, and anyone else who can legally prescribe medications to a patient.

The provider has knowledge about different types of pharmaceutical products and how they work to manage certain medical conditions, but they must be very cautious in communicating the associated risks of any medications. For example, if the patient is currently taking a medication for diabetes such as Metformin, then the provider should be knowledgeable of this information and should monitor the patient for any signs of lactic acidosis, a common side effect of Metformin that can cause the patient nausea, weakness, fatigue, and shortness of breath. Another example is that patients with diminished liver and kidney function may have higher risks for certain medications, since regular doses could overwhelm these organs and do more harm than good. Therefore, providers play a significant role in understanding the patient's individual and developing an appropriate treatment plan. Additionally, the provider should consider what drugs are covered by the patient's insurer's formulary so that if a patient is unable to cover the cost of a drug, an alternative which is on the formulary may be prescribed.

Once the provider determines the best drug treatment for a particular patient, based on the patient's medical history and diagnostics, then they can send an order to the drug dispenser for the appropriate drug with the correct dosing information. This order can be either a transcribed, signed note with the pertinent prescription information (i.e. medication, dose, instructions, etc.), or it can be sent electronically through e-prescribing software. According to Porterfield, et al. (2014), research suggests that e-prescribing reduces medication errors, increases efficiency, and helps save $140 billion to $240 billion on healthcare costs. In 2019, 80% of all prescriptions were sent through electronic prescription software (Statista, 2020); this percentage is increasing since e-prescribing provides many more benefits and lacks the error-proneness of written prescriptions that may have ineligible writing, distortions, or confusing directions.

In addition to electronic prescribing software, electronic health record (EHR) systems have also significantly reduced medical risks. Note that e-prescribing is a function in many EHR systems. EHR systems are rich in patient data, allowing healthcare providers to view and update patients' medical history, active medication lists, lab results, and

more. Used effectively, EHR systems help providers make more informed decisions regarding patients' diagnoses and treatment plans; for example, if the provider prescribes a medication that interacts with another medication the patient is actively using, the system will alert the provider. According to The Office of the National Coordinator for Health IT, EHR adoption among office-based physicians approached 90% in 2017, more than doubling over a 10-year time span. Aside from government incentives, the benefits of improving efficiency and patient outcomes are driving this growth.

### *5.1.2 Drug Dispensers (from a Clinical Perspective)*

Drug dispensers hold the greatest impact on the final value delivery to the patient. They play a multifaceted role—they must work with PSC actors to be able to supply the right medications at the right time, and they must also work with healthcare providers and patients to provide clinical value. In Section 2.1.3, we discussed the supply chain role that dispensers play—i.e. placing orders with drug distributors, maintaining stock levels, facilitating payments to group health plans, and, if the medication is not already packaged in its final form, then filling prescriptions by dispensing the right amount of the right drug into a prescription

container. In this section, we will discuss the clinical role that dispensers play.

In the MUP, the drug dispenser receives a prescription order from the prescriber with the patient's information and dosing instructions. Once the patient arrives to pick up his or her prepared prescription, the dispenser will verify the patient's name and date of birth. Dispensers are not just responsible for the simple transaction of drug products, but also managing patients' medications to improve educated usage and treatment adherence. For example, when the dispenser is giving the drug product to the patient, he or she should explain the correct usage of the drug (e.g., what time to take it, whether to take it before or after a meal, any drug interactions). The dispenser should also be able to answer any questions the patient may have about a medication. If there are any discrepancies in a prescription order, the dispenser must reach out to the prescribing physician to determine the correct order.

To further provide value and reduce medication errors, pharmacists can perform medication reviews and reconciliations. A medication review is defined as "a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about

treatment, optimizing the impact of medicines, minimizing the number of medication-related problems, and reducing waste," and medication reconciliation is defined as "the process of obtaining and maintaining a complete and accurate list of the current medication use of a patient across healthcare settings" (Geurts *et al*., 2012). By reviewing the patient's records and addressing the patient's concerns, pharmacists can determine the best way for medications to be administered. The Joint Commission (TJC) proposed five major steps to accomplishing this:

1. Obtain and/or update the list of medications the patient is currently taking.
2. Define which types of medication information (i.e. name, dose, frequency) are to be collected.
3. Compare the list of medications the patient is currently taking to the list of medications that were actually prescribed for the patient. This helps find and resolve discrepancies.
4. Provide the patient with an informative list of the medications he or she should be taking.
5. Explain to the patient why it is important to manage his or her current medications appropriately. (TJC, 2020)

This process helps improve value by reducing the risk of ADEs. It is especially important for patients who use polypharmacy, or patients who take multiple medications concurrently. For example, if three actively-used drugs interact and provide less therapeutic value, then the pharmacist can help create a customized schedule that will help the patient better manage the timings of his or her doses so that they are more effective (CVS, 2017). Since pharmacists interact directly with patients, this is a form of personalized care that can make a huge difference in the value of medication use.

Additionally, drug dispensers can take on clinical roles that provide more healthcare outlets for patients. For example, some pharmacies may train their workers to administer immunizations for the seasonal flu, meningitis, and chicken pox (CVS, 2017). Patients can sign up for vaccinations and receive them quickly at one of many, easily-accessible locations. This is an important role that will help fight the COVID-19 pandemic both logistically and clinically. Furthermore, some states have started to grant prescribing authorities for certain drug categories to trained pharmacists (Ismail, 2020). While prescribing authority varies from state to state, this is a recent development that allows patients to access necessary medications more efficiently. Many states

grant prescriptive authority to pharmacists under a Collaborative Practice Agreement (CPA). The Centers for Disease Control (CDC) defines a CPA as a "formal agreement in which a licensed provider makes a diagnosis, supervises patient care, and refers patients to a pharmacist under a protocol that allows the pharmacist to perform specific patient care functions" (CDC, 2013). This helps pharmacists perform a variety of value-adding healthcare services through increased collaboration and coordination with healthcare providers.

### *5.1.3 Drug Administrators*

Most often, patients administer their prescription medications to themselves by following the provided dosing instructions. (Intentional misuse of a medication is not considered here.) In some cases, the patient may misunderstand the instructions or simply forget to take a medication. Older patients, who tend to have more medical problems, are especially prone to these errors when taking multiple medications. Accidental misuse of medications is not the fault of the patient, but the result of failures in the pharmaceutical value chain. When the proper usage of a medication is fully communicated to the patient, stronger adherence to drug regimens can be achieved and administration

errors can be reduced. This includes aspects of medication use such as why the medication must be taken, how to time doses with meals, aids to manage polypharmacy, and potential side effects and how to manage them.

Aside from the patients, drug administrators are those who administer the medication to the patient directly. This may be a nurse preparing an intravenous (IV) drug injection or a pharmacist giving a patient an immunization shot. Drug administrators that are not patients must be extra careful to follow the "Eight Rights" of drug use for safe drug administration. For example, a drug administrator may accidentally give a patient twice the dose of a drug without knowing another healthcare worker administered the dose previously. These are medication errors that stem from drug administration, although medication errors can occur anywhere along the entire supply chain. In Section 3.3, we review the topic of medication errors.

### *5.1.4 Drug Reaction Monitors*

After the drug is administered, the patient and/or a healthcare worker should monitor the effects of the medication(s). Was there an improvement in the patient's condition? Did the patient experience any side effects or drug interactions? Did the patient experience a medication

error, and did an ADE result? For most self-administered medications, patients may be able to monitor their own condition over time and report any problems to their physician and/or pharmacist. Patients and physicians are able to directly report medication errors through the FDA's *MedWatch* system (FDA, 2019). By reporting problems with medication, prevention efforts can be established to protect other patients; these efforts can include a label or packaging revision, a drug recall, or further research studies to better characterize the drug product. Information regarding medication errors can and should travel back to the point of error in the PSC so that a course of action can be taken to prevent the error from recurring. For example, if an error occurred because clinic staff misread a drug dosage, then the clinic must determine why it happened and how to ensure that drug dosages are read correctly in the future. This is discussed further in Section 5.

In special cases, monitoring the effects alone is not adequate. For drugs that have narrow therapeutic ranges, express high pharmacokinetic variability, and/or pose higher risk for unwanted side effects, *Therapeutic Drug Monitoring* (TDM) should be utilized (Kang and Lee, 2009). TDM is "the measurement of specific drugs and/or their breakdown products

(metabolites) at timed intervals to maintain a relatively constant concentration of the medication in the blood" (LabTestsOnline, 2020). For example, the cardiac drug digoxin, which is used to treat heart failure and arrhythmias, is often monitored through TDM since it has a very narrow therapeutic range. Too little of the drug could cause a recurrence of symptoms, while too much of it could be toxic (LabTestsOnline, 2020).

Because different patients' bodies respond differently to the same medication, TDM can be used to maintain an appropriate drug concentration range customized for specific patients. This enables physicians to better understand the needs of their individual patients so that the ideal of personalized medicine can be more closely achieved. Personalized medicine is discussed in more detail in Section 2.2.1. TDM helps improve value for the patient by (1) attempting to maximize the patient's body's therapeutic response, and (2) decreasing the likelihood of an ADE (Kang and Lee, 2009). Additionally, TDM can be used to check if patients are noncompliant with their prescribed medication regimens (Kang and Lee, 2009); in this case, the physician can explain to the patient why and how they must adhere to the treatment plan.

Table 3 summarizes how the different MUP actors impact value for the patient.

*Table 3: How different MUP actors impact value for the patient*

| MUP Actors | How they impact value... |
|---|---|
| Prescriber (Healthcare Provider) | • Interact with patients to diagnose medical conditions and prescribe the appropriate treatments<br>• Assess how effective a medication would be for a particular patient based on the patient's physical characteristics, medical history, active medications, and more<br>• Use EHR systems to check the patient's medical history as well as place e-prescription orders (which are less error-prone than written prescription orders)<br>• Perform medication reviews and reconciliations |
| Drug Dispenser - from a Clinical Perspective | • Verify that the right patient receives the right medication by double-checking relevant information<br>• Explain the correct usage of new medications and answer any of the patient's questions<br>• Resolve discrepancies in prescription orders by contacting the prescriber prior to giving the patient the medication<br>• Perform medication reviews and reconciliations<br>• Administer immunizations<br>• Obtain a CPA to strengthen collaboration and coordination with other healthcare workers<br>• Prescribe certain medications (limited to certain states) |
| Drug Administrator (Usually the Patient) | • Follow the appropriate dosing instructions<br>• For polypharmacy, use aids like a calendar or a pill organizer to manage doses<br>• If not the patient, then ensure that the drug is administered safely according to the "8 Rights" of medication use |
| Drug Reaction Monitor (Usually the Patient) | • Evaluate the effects of a drug - side effects, drug interactions, ADEs<br>• Report problems with medication use so that preventative efforts can be enacted at the appropriate point in the PSC<br>• If not the patient, then use TDM for medications that require very specific dosing |

## 5.2 Medication Errors and Adverse Drug Events

The U.S. National Coordinating Council for Medication Error Reporting and Prevention defines medication errors (MEs)

as "any preventable event that may cause or lead to inappropriate medication use while the medication is in control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, distribution, administration, education, monitoring, and use." Medication errors can occur anywhere throughout the PSC and MUP (FDA Working to Reduce MEs, 2019). As discussed previously, MEs increase the risk of ADEs that can harm patients, thereby reducing value for the patient. ME and associated ADE rates vary across different clinical settings and are difficult to quantify due to varying definitions and classification systems (Payne *et al.*, 2016). MEs and ADEs burden patients, PSC and MUP actors, and the overall economy; MEs are estimated to "impact more than 7 million patients and cost almost $21 billion annually across all care settings" (Silva and Krishnamurthy, 2016). According to the CDC, ADEs cause 1.3 million emergency department visits annually, and 350,000 of these patients even require further hospitalization. Figure 6, which shows the general relation of MEs and ADEs, is adapted from *Morimoto, et al.,* (2004).

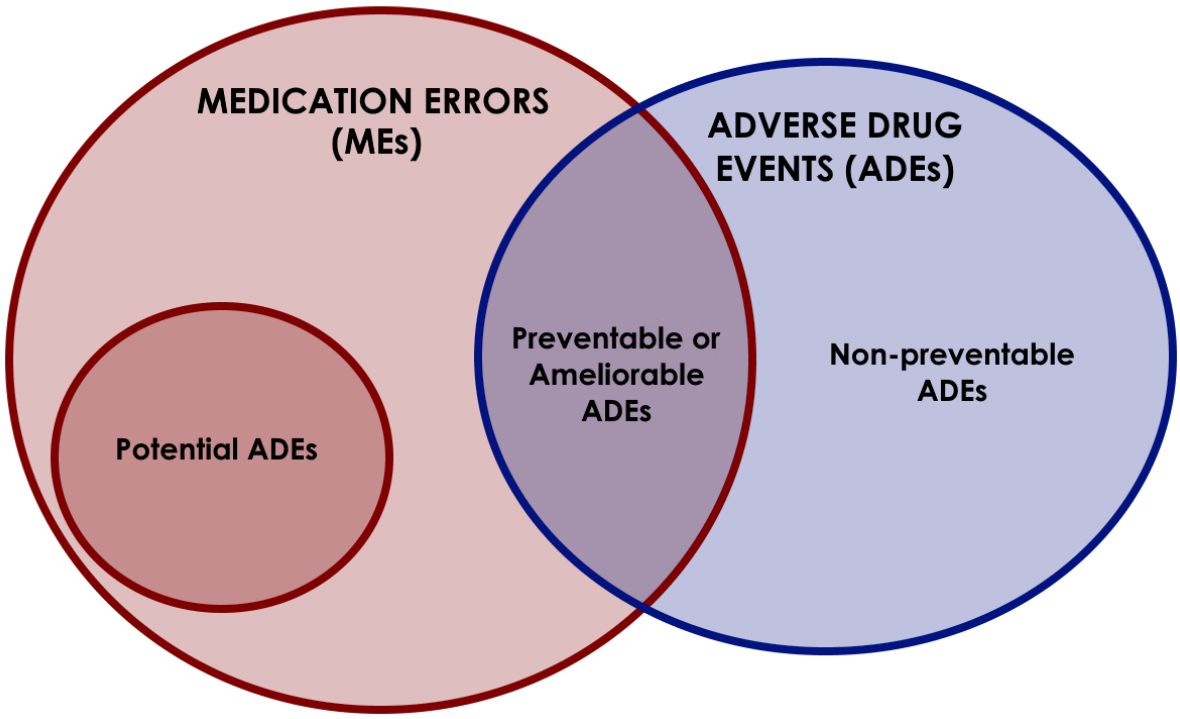


*Figure 6: Relationship between Medication Errors and Adverse Drug Events. Adapted from Morimoto, Gandhi, Seger, Hsieh, and Bates (2004).*

A few key points:

- MEs are much more common than ADEs.
- Most MEs do not cause substantial harm to the patient.
- Potential ADEs derive from MEs that could cause harm to the patient, but the error is managed before making it to the patient or the patient does not end up experiencing any harmful effects.
- Most ADEs are non-preventable - as in, these adverse events could not be prevented by any PSC or MUP actor. Non-preventable ADEs are also referred to as adverse drug

reactions (ADRs). An example of an ADR is a patient having an unexpected allergic reaction to a medication.

- Preventable ADEs are those that result from avoidable errors committed by any PSC or MUP actor. Ameliorable ADEs are those in which the severity or duration could have been significantly reduced if a different course of action had been taken (Morimoto, *et al.*, 2004).

The ideal of maximizing value means that preventable and ameliorable ADEs must be reduced to zero, which places special emphasis on the need to minimize MEs, or at least mitigate them before they reach the patient. This is a multifaceted effort that requires communication and coordination between different actors. Reducing ADEs is expected to provide many benefits, including "safer and higher quality health care services, reduced health care costs, more informed and engaged consumers, and improved health outcomes" (health.gov, 2020). Using Lean methodologies as an improvement framework may help in not only detecting and removing errors, but preventing them altogether so that ADEs do not occur.

### *5.2.1 How Medication Errors Occur*

Medication errors are the result of failures in processes. Errors can be managed not by punishing those who commit errors, but by identifying the systemic failures that

led to an error and determining how changes in processes can deter the error from occurring again (Tariq *et al.*, 2021). This is central to Lean thinking, and it will be discussed in more detail in Section 5.2. The Swiss Cheese Model of system accidents, developed by psychologist James Reason in 2000, presents a diagrammatic explanation of process failures that result in adverse events (Silva and Krishnamurthy, 2016).

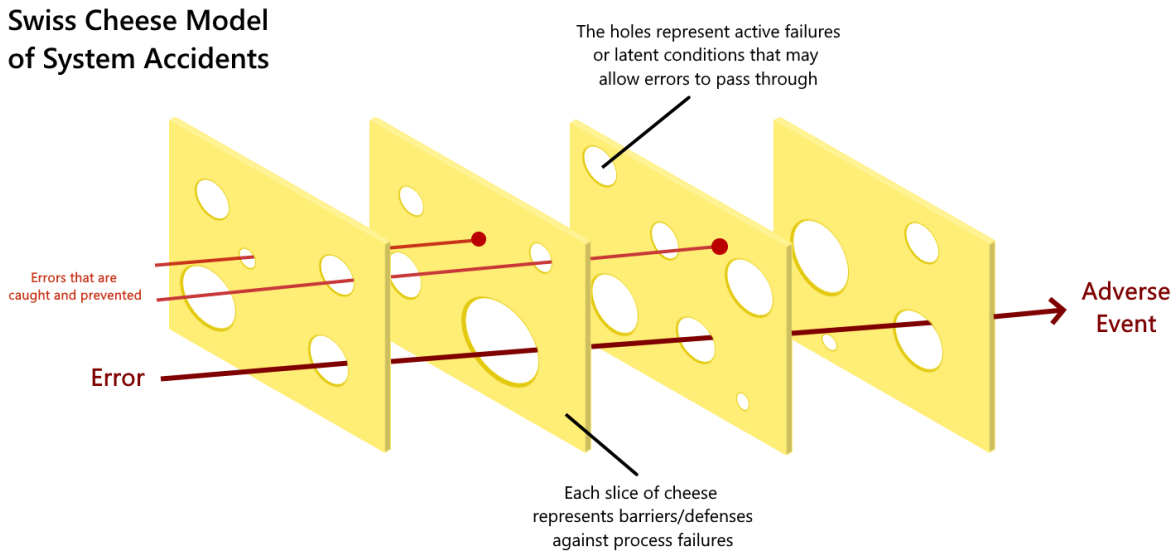


*Figure 7: Swiss Cheese Model of System Accidents. Adapted from James Reason (2000)*

It is important to note that active failures and latent conditions (the holes) are changing and moving, depending on causal factors present in different scenarios. When an error passes through fail points in the barriers, an adverse event could occur. For example, a patient may tell his or her nurse

that he or she had an adverse reaction with a certain anesthetic prior to an operation in the past. If the nurse forgets to tell the anesthesiologist or to type the information in the EHR, then the anesthesiologist may think that there were no previous complications; this could result in a preventable ADE. The failure of the nurse to notify the anesthesiologist or surgeon and the failure of the anesthesiologist or surgeon to double-check with the patient exemplify the "holes" in system processes.

There are many factors that can create or propagate medication errors to the patient. In the WHO's Technical Series on Safer Primary Care, researchers found several factors contributing to MUP medication errors. These factors, acquired from the WHO's *Medication Errors* report, are listed below.

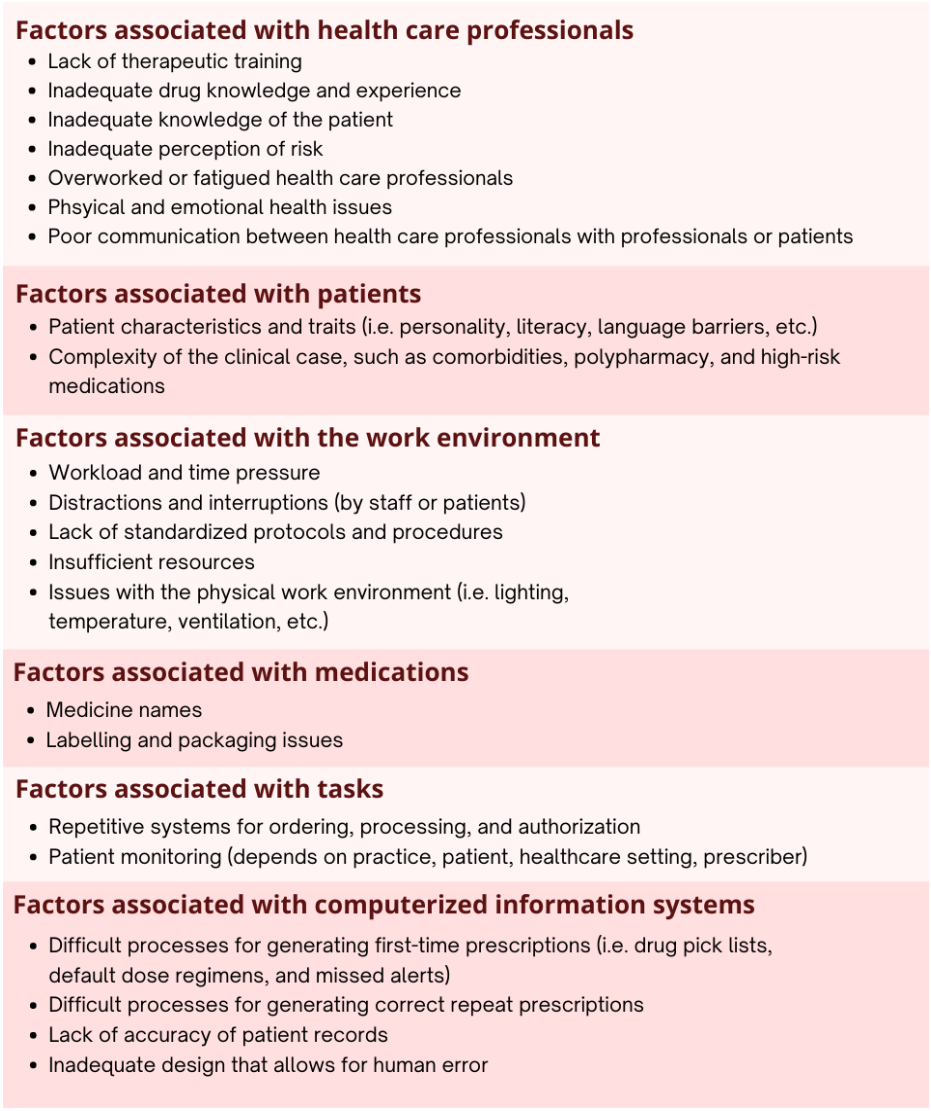


*Figure 8: Factors Contributing to Medication Errors. Adapted from the WHO's Report on Medication Errors.*

When medication errors are identified, they should be traced back to causal factors such as those listed in *Figure 8* above. By determining how such factors played a role in an ME, PSC and MUP actors can draw a course of action to prevent the error from recurrence. Even if an error does not result in an ADE, it exposes a weakness in the system that should be

examined before a clinically significant event does occur (Aronson, 2009).

### *5.2.2 Approaches to Classifying Medication Errors*

There are several ways to classify MEs. A physiological classification system was developed by *Ferner and Aronson* (2006), categorizing errors into either mistakes or skill-based errors. Mistakes are further subdivided into knowledge-based errors and rule-based errors, while skill-based errors are subdivided into action-based errors (slips) or memory-based errors (lapses). While the definitions of each type of error is outside the scope of this paper, it is important to mention that Lean methodologies may help address these different types of errors. For example, health care workers should be educated on higher-risk medications so that knowledge-based errors are avoided. To avoid memory-based errors, posters could be placed around a workspace to help remind certain health care workers of proper procedures.

MEs may also be classified based on what caused the error to occur. *Allan and Barker* (1990) identified several types of errors that could occur in the MUP:

- Wrong medication
- Omission errors

- Wrong dose errors
- Unordered medication errors
- Wrong dosage form errors
- Wrong time errors
- Wrong route errors
- Deteriorated drug errors
- Wrong rate of administration errors
- Wrong administration technique errors
- Wrong dose preparation errors
- Extra dose errors

The most common types of medication errors include the wrong medication, wrong route or dose, or the wrong frequency of doses; these errors contribute to nearly 50% of all known, preventable medication errors (Tariq *et al.*, 2021).

Another way to classify MEs is by where in the MUP the error occurred - in prescribing, ordering, dispensing, administering, or even monitoring (Al-Worafi, 2020). Errors can also occur far upstream in the territories of other PSC actors, which could lead to widespread patient ADEs if the errors are not corrected before the drug reaches patients. MEs occur most commonly at the prescribing and ordering stage in the MUP (Tariq *et al.*, 2021). Classifying MEs in this way helps to trace the error back to a particular event. For

example, if the correct drug was prescribed but the wrong drug was dispensed, then the error should be examined at the dispensation site. Improvements can be targeted toward the staff and processes involved at the point of error.

By appropriately addressing the cause of an ME, changes can be made in systemic processes so that the risk of MEs, and thus ADEs, can be reduced. Reducing errors also decreases unnecessary health care costs, which ultimately increases value for patients by guaranteeing access to safe and effective drug supply.

# 6 Supply Chain and Lean Solutions to Maximize Value

Improving pharmaceutical value for patients requires a multifaceted effort directed from all actors along the PSC and MUP. Each actor plays a role in getting the right doses of the right medications to the right patients at the right time. In this section, we discuss an improvement framework for all PSC and MUP actors that can help reduce ME and ADE rates and increase pharmaceutical value. This improvement framework includes different lean tools to increase quality and service while decreasing associated costs.

First, we propose a model that incorporates the MUP into the PSC. This will be referred to as the pharmaceutical value chain (PVC), and its information, material, and monetary flows are diagrammed under Section 5.1 in Figure 8. The concept of the PVC will help align all PSC and MUP actors in their goals of achieving greater pharmaceutical value. Communication and coordination of these flows will help establish a well-aligned value chain.

Second, we propose a variety of Lean tools in Section 5.2. We explain how these tools can be applied to help improve communication between PVC actors as well as improve value at each segment in the PVC.

## 6.1 Combination Model - The Pharmaceutical Value Chain

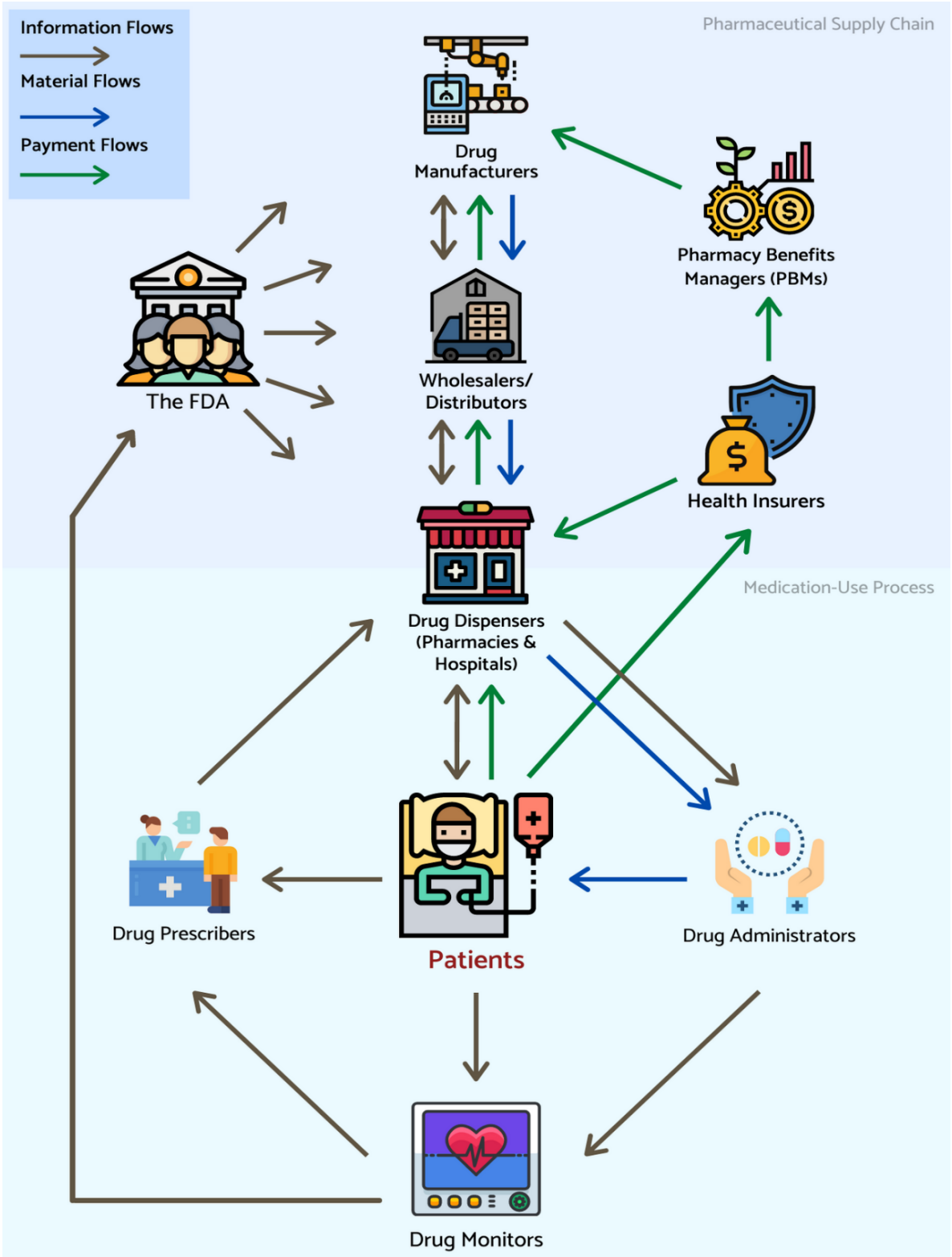


*Figure 9: The Pharmaceutical Value Chain (PVC).*

By evaluating the connections between all PVC actors in Figure 9, we focus our discussion on how information, material, and monetary flows impact the health care value equation. Remember that increasing quality and service levels increases value, while increasing cost decreases value. When the entire value chain aligns its strategy, then the goal of improving value will be better achieved.

Material flows are generally straightforward in the PVC. The manufacturer produces, labels, and packages medications in accordance with a planned production schedule, and then these medications are sold to wholesalers/distributors. Pharmaceutical manufacturing involves several value-adding processes that use machines to achieve necessary physical and chemical attributes. These processes include dry granulation, in which low-density powder is compacted to a granule; power blending, in which various ingredients are blended to create a homogeneous mixture to be used for the solid dosage form; wet granulation, in which materials are densified to improve uniformity or wettability or to improve dispensing qualities; drying, in which the moisture content of powders can be controlled; milling, in which coarse particles are broken down into fine particles; and tablet coating, in which a film coating is applied to solid oral dosage-form medications

(BulkInside, 2020). The manufacturer also has a responsibility to RFID-tag drug products so that they can be traced back to the manufacturing site. The wholesaler places an order with the manufacturer to receive and warehouse the products, where they can be stored and distributed as needed. While wholesalers play a major role in distributing medications from 1,300 manufacturing sites to over 180,000 points of dispensation (Deloitte, 2019), they have started to provide additional services such as specialty pharmaceutical distribution and drug buy-back programs (Healthcare Global, 2021). When a drug dispenser needs to re-stock a certain medication, they place an order with the wholesaler through a web-based software. For example, CVS Pharmacy uses a software called RxConnect, which allows pharmacy workers to place new orders, check inventory levels, see information on patients' drug histories, and more (Senawong, 2021). The leadtime to receive drug products from the wholesaler is usually short – only about 1 to 2 days (Jamal, 2021). When stock levels are low or none, the system may automatically place an order with the wholesaler (Senawong, 2021). This helps ensure high service levels at the drug dispensation site. The patient visits with a health care provider (prescriber), who may send in a prescription through an electronic system, often within an EHR. The patient receives their drug from the dispenser

(walk-in or mail-order) after the prescription is received and processed. When the patient is not the drug administrator, another health care worker administers the drug to the patient.

Monetary flows are not as straightforward. As discussed in Section 2, patients pay premiums to health insurers, and the health insurers pay PBMs to negotiate drug prices with the manufacturer. The drugs that are covered by a health insurer are included in a drug formulary, which is managed by the PBM. Sometimes, the patient may have to cover some of the drug price through a copay. If the drug is not on the patient's insurer's formulary, then the patient bears the full price of the drug. It is also important to note that medication errors add unnecessary cost to our healthcare system, which sometimes may come out of the patient's pocket. Additionally, wholesalers must pay a wholesale acquisition cost (WAC) to the manufacturer to receive the products. The WAC is set by the manufacturer, but the process to determine this price is beyond the scope of this paper.

Information flows are moving in all directions throughout the PVC. In the PSC, drug manufacturers rely on information from downstream partners to determine and forecast production needs. This information comes from wholesalers, who obtain

demand data from drug dispensers. In the MUP, information flows occur mainly between the prescriber, patient, and drug dispenser. The patient describes their medical needs, and the doctor provides information regarding the best way to manage those needs. The communication between the prescriber and the dispenser is very important, since discrepancies in prescription information are literally MEs that can potentially cause ADEs. The dispenser may also give the patient information on how to best use a medication – for example, spacing out doses of two different medications to avoid drug interactions. After a patient takes their medication(s), they should be monitored for any side-effects, either by themselves or by a health care provider. For certain higher-risk medications, such as the cardiac drug digoxin, TDM can be used for quantifiable data. Information from drug monitoring – particularly when a medication is ineffective or causes an ADE – is important for drug manufacturers as well as the MUP actors that were involved in getting the medication to the patient. When an ADE occurs, it should be reported through the *MedWatch* system. This gives the FDA information that can be used to set new standards and communicate with the appropriate party so that future cases can be avoided. The FDA emanates information in all directions, making recommendations or instituting requirements

for operations in the PVC (but particularly the PSC). Essentially, the PSC and MUP are connected through information flows at two main points: (1) the point where drug dispensers receive prescription information, which gives upstream partners demand data for different drug products (Jamal, 2021), and (2) the point where FDA uses information from drug monitoring/surveillance to make decisions for the PVC.

### *6.1.1 How Value is Created in the Pharmaceutical Value Chain*

As discussed in Sections 2 and 3, each PVC actor influences value in some way, and this partly depends on interactions with other PVC actors. For example, if the drug manufacturer does not align its production plans with demand data from downstream actors, then they could risk a shortage that leaves individuals without their medications or a surplus that increases inventory costs. Thankfully, new technology such as RFID tagging gives manufacturers access to end-to-end supply chain visibility, and supply chain management software can help manufacturers set productions levels and safety stock levels (Morvan, 2019). However, sometimes technology can cause issues as well. According to *Senawong* (2021), pharmacy-ordering software can occasionally not send an automatic order to a drug wholesaler if the system requires an update or is running slow – this could result in a shortage of the drug at

the dispensation site, causing a decrease in service level. Additionally, value can be lost if the drug prescriber fails to respond to a patient's or drug dispenser's concerns regarding a certain medication. According to *Jamal* (2021), some higher-risk prescriptions may require that the dispenser verifies the prescription order with the prescriber; in some cases, the prescriber may not respond, causing a delay and failure of service to the patient.

While we identify such failures in value, it is important to consider *how* value is created in the value chain. Value is derived from each PVC actor completing their respective duties, with good quality management, while working with other PVC actors to ensure that drug products are distributed, in the correct amounts and with the right information, to those who need it. At each PVC process, quality, service, and cost are impacted in different ways. There are several processes that directly add value, such as the actual manufacturing of drug products, patient consultation with a physician, prescription filling by a pharmacist, and more; however, there are also several non-value adding processes that impact value delivery to the end user. This will be discussed in further detail in the next section.

The value generated by each actor can be measured through tracking key performance indicators (KPIs). According to KPI.org, KPIs are "the critical indicators of progress toward an intended result." PVC actors will have different KPIs that are relevant to their operations, but by constantly striving to meet certain target measures, each actor can guarantee other actors that medications will be available and effective. Good KPIs are well-defined, quantifiable, communicated throughout the organization, and crucial to achieving goals (Jackson, 2019). In Table 4, we propose patient-centered KPIs that could be used by different PVC actors.

*Table 4: Relevant KPI examples for different PVC actors*

| PVC Actor | Examples of Key Performance Indicators |
|---|---|
| Drug Manufacturer | • Various Quality Measures (depends on drug being produced)<br>• Number of Defects (drug products that fall outside quality requirements)<br>• Service Level/Delivery Reliability<br>• Leadtime to Drug Wholesalers<br>• Asset Utilization Rates |
| Drug Wholesaler/Distributor | • Number of Drug Products Discarded (due to expiration, improper storage, etc.)<br>• Service Level/Delivery Reliability<br>• Leadtime to Dispensation Sites<br>• Asset Utilization Rates |
| Drug Dispenser (Pharmacies, Hospitals, etc.) | • Number of Prescriptions Filled per Day<br>• Average Time to Fill Prescriptions<br>• Number of Drug Products Discarded (due to expiration, improper storage, etc.)<br>• Active Prescriptions per Patient<br>• Number of Times Patients Turned Away Without Prescription (due to shortages, un-prepared prescriptions, etc.)<br>• Number of Prescription Discrepancies<br>• Medication Error Rate |
| Prescriber (Healthcare Provider) | • Average Hospital Stay Time<br>• Patient Drug Cost Per Visit<br>• Treatment Costs<br>• Active Prescriptions per Patient<br>• Patient Satisfaction<br>• Medication Error Rate<br>• Number of Prescription Discrepancies<br>• Patient Readmission Rate due to ADEs<br>• Patient Readmission Rate due to Ineffective Treatment |
| Drug Administrator (Non-Patient) | • Medication Error Rate (or Number of Violations of the “Eight Rights”) |
| Drug Reaction Monitor (Non-Patient) | • Number of ADEs<br>• Side Effects Experienced by Patients<br>• Number of Patients Effectively Treated with Medication |

By meeting goals for each KPI, value is created. For example, a wholesaler improving from a 99% service level to a 99.9% service level is value generation, since the wholesaler can promise more reliability to dispensation sites. Reducing MEs

and patient readmission rates due to ADEs is, of course, value generation.

## 6.2 Lean Applications as an Improvement Framework

According to the Lean Enterprise Institute (LEI), the central idea of Lean is "to maximize customer value while minimizing waste" – or, doing more with less. It is often used as an improvement framework by organizations to optimize value streams. Lean concepts were pioneered in Japan by auto manufacturer Toyota (LEI, *n.d.*), so many of the Lean tools we discuss in this thesis are based on Japanese words, including *Kaizen*, *Muda*, *Kanban*, and more. The *Shingo Prize* framework for operational excellence, developed in 1988 by Utah State

University, highlights several requirements for successful lean implementation (Bicheno and Holweg, 2016).

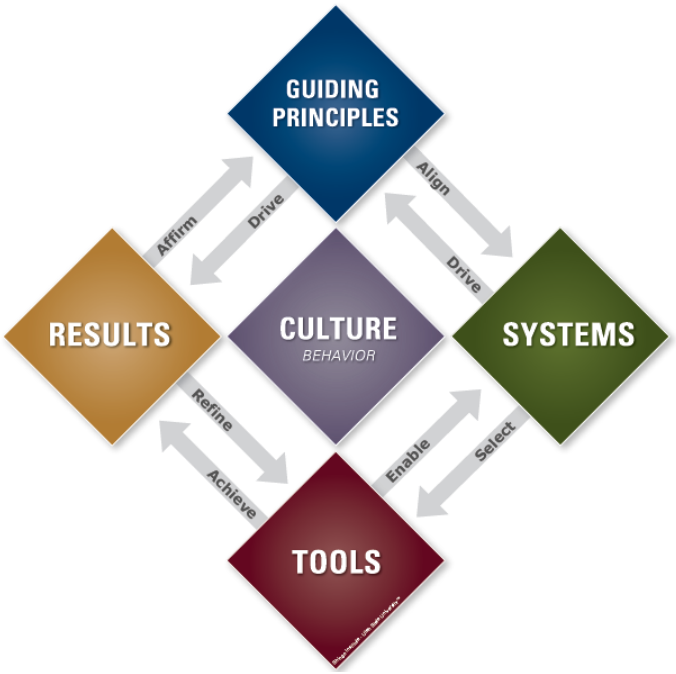


*Figure 10: The Shingo Prize Model. From the Shingo Institute at the Jon M. Huntsman School of Business at Utah State University*

According to Shingo.org, the guiding principles of the Shingo Prize model include respect for every individual; lead with humility; seek perfection; embrace scientific thinking; focus on process; assure quality at the source; improve flow and pull; think systemically; create constancy of purpose; and create value for the customer. In the PVC improvement framework discussed throughout this section, these guiding principles should be kept in mind.

A common misconception is that lean is only useful for manufacturing operations; in fact, many Lean methodologies can

be utilized in service operations as well. There are five principles in Lean, which outline the general path to implementing Lean. Here, we discuss these principles in the context of the PVC.

1. *Define value from the standpoint of the patient.* Identifying the patient's exact needs helps PVC actors determine the best way to meet those needs (Do, 2017). Based on our reviews of the PSC and MUP, pharmaceutical value to patients involves (1) supplying high-quality drug products that are effective, free of defects, efficiently delivered on-time, convenient, and are cost-effective for healthcare payers; and (2) following the tenants of the Eight Rights while administering medications. Patients will receive ideal value when they can always be guaranteed that they will receive their medications at the right time and that their medications will effectively manage their symptoms, with minimal side effects if possible. While the ideal may never be reached, it provides a goal to PVC actors that should constantly be strived for.
2. *Map the value stream.* For successful Lean implementation, it is vital to identify which steps and processes in the PVC generate value and which ones do

not. PVC processes can be categorized as "value-added", "non-value added but necessary", and "non-value added and unnecessary" (Do, 2017). Value added (VA) activities are those that directly change the product or service in a way that benefits the end user; these activities are necessary and should be the central focus of value creation. For example, in the PSC, direct manufacturing, packaging, and distribution of drug products are VA activities. In the MUP, patient consultation with the prescriber and medical reconciliation with the dispenser are VA services. Non-value added (NVA) activities that are necessary do not change the product or service, but they must be completed to achieve certain objectives. NVA activities that are unnecessary are considered *waste*. (In this thesis, "NVA activities" will refer solely to those that are unnecessary for simplification purposes.) This waste amounts to large monetary and time costs, negatively impacting PVC actors and patients. These wastes are often baked into VA processes. For example, if a worker must travel far in a distribution warehouse to bring a drug product to the loading dock, then the time spent going to find, pick, and bring back the box is NVA. Patients waiting to be seen by a doctor is another NVA activity that does nothing to improve the patient's

condition. Targeting and reducing such wastes is vital for lean implementation, and it is discussed in more detail in Sections 5.2.4.

3. *Create flow.* Once wastes are identified and removed, more time can be spent optimizing VA activities. Ensuring these activities run smoothly helps reduce delays and interruptions, allowing value to flow to the patient more efficiently. Creating flow can involve multiple strategies, including breaking processes down into simple steps, standardizing processes, re-organizing the physical placement of tools and workers, training workers, establishing cross-functional teams, and more.
4. *Establish pull.* A pull-based supply chain takes a *just-in-time* approach, acting more responsively to meet the needs of end users. It is more demand-driven and responsive than a push-based supply chain, which depends on upstream actors "pushing" product to downstream actors (Koo, 2020). In the PVC, a push-pull hybrid system may be used in which a *decoupling point* switches the supply chain from push to pull (Koo, 2020). There will be different decoupling points in the PVC for different drug products, depending on the type of drug and route of administration. For medications with more predictable, less variable demand, a push-based system will play a

larger role. Medications that are more specialized may require an earlier decoupling point, with a pull-based system playing a larger role. As the field of personalized medicine advances, PVC actors must be able to establish pull to best manage resources and efficiently deliver to patients. Kanban helps accomplish this, and it is discussed in more detail in Section 5.2.5.

5. *Pursue perfection.* Perfection means ideal value for the patient – zero defects or errors, minimum waste, available in the right amount exactly when needed, and therapeutically effective to treat the patient's condition (Bicheno and Holweg, 2016). Applying the first four principles helps prevent waste, but continuous improvement is the cornerstone of a sustainable lean culture. Every worker in every PVC organization should be motivated to seek improvements in the processes that they work in. Through constant learning and applying, perfection can be more closely achieved (Do, 2017). Creating a culture of continuous improvement is discussed in more detail in Section 5.2.1.

### *6.2.1 Kaizen: Continuously Improving*

Continuous improvement, referred to as *Kaizen* (which means "change for good"), is an organizational strategy in which all workers, regardless of position, are motivated to pursue incremental improvements in processes by removing waste and creating flow. Kaizen helps to establish a culture that respects employees, offering ways for them to make direct impacts beyond regular work processes (Srinivasan and Shah, 2018). Employee involvement is crucial since each employee operates in his or her own *Gemba* ("the actual place") – they know the steps that create value in the processes that they act in. One can only truly understand how to improve value from the perspective of the Gemba, so managers and supervisors should go on *Gemba walks* in which they see processes from the perspective of working employees. Additionally, fostering a Kaizen culture means taking less discipline-based approaches to errors and mistakes. *Poorolajal et al.* (2015) explains that a well-organized reporting system is necessary for an effective error reduction program. In their study, *Poorolajal et al.* (2015) found that about half of their subjects committed but did not report medical errors. If workers fear punishment, mistakes and errors will go unreported and lead to larger problems. The greatest service to patients is to

investigate the source of errors and determine solutions to prevent them in the future.

When an opportunity for improvement is identified, workers and managers could plan and enact a *Kaizen event*. Kaizen events are a "means to get cross-functional and multi-level teams involved in a Lean transformation" (Bicheno and Bolweg, 2016). They are brainstorming sessions in which teams map out the value stream for a process, discuss innovative solutions, and then experiment to determine the best way to update the process. Kaizen events typically last approximately one week (Sherman, 2018; Bicheno and Bolweg, 2016), but shorter kaizen events may be enacted depending on the context. The general process is described below.

1. Prior to the Kaizen event, the team should determine which process or value stream they would like to improve. This is so that relevant data can be collected regarding the value stream.
2. At the beginning of the Kaizen event, the team should go through introductions, discussions over objectives and goals, and basic Lean training (Bicheno and Holweg, 2016).
3. Next, the team should closely observe the process, which will involve Gemba walks. They should map the value

stream, determining which steps are VA or NVA (Villanova U, 2020; Bicheno and Holweg, 2016). This helps identify waste and other problems. For services, such as those in the MUP, input from the end user will be useful.

4. After observations and data collection, the team must brainstorm solutions. The team should work as a group, formulating priorities and discussing an implementation plan (Bicheno and Holweg, 2016).
5. Once the team commonly decides on a set of potential solutions, they should try implementing them experimentally. Results (or KPIs that are relevant for the specific process) should be measured. This will reveal what works and what doesn't.
6. The team should perform one final check to ensure the updated process is, in fact, an improvement from the previous state. Then, the process should be documented, and in some cases standardized, to set the Kaizen efforts in stone. The team should also generate an A3 report (which is discussed in more detail in Section 5.2.4) to outline the characteristics of the improvement. The team must further discuss how to sustain the new and improved process (Villanova U, 2020).
7. The team should present their findings and then celebrate their hard work!

Please note that the scientific method is embedded into the Kaizen event. Experimentally testing different solutions with a tool called PDCA is central to continuous improvement, and we discuss it in more detail in Section 5.2.4.

In the context of the PVC, Kaizen events will be useful for addressing vulnerabilities that could cause medication errors. MEs should be considered defects, or failures in quality, in the services provided in the PVC. If an ME does occur, then the point of error should be determined so that the processes surrounding the error can be evaluated through a Kaizen event. For example, if an ME is classified as a dispensing error, the pharmacy may inspect the processes that caused the ME. If a process is found to include plenty of NVA activities or error-prone steps that could have contributed to the ME, a Kaizen event may be warranted. Indeed, Kaizen events can be performed regardless of whether an ME occurred or not; anytime an opportunity to reduce waste and improve flow is appreciated, workers should be motivated to find solutions. The concept can be applied across the entire PVC. Manufacturers can use Kaizen philosophy to prevent quality issues before they occur, eliminate wastes that add cost, and smooth the flow of products so that production is more demand-driven rather than forecast-driven (Kaizen Institute Blog,

2015). Drug wholesalers can use it to improve flow in other services that they provide, such as distributing specialized medications or drug buy-back programs. By instituting a continuous improvement culture, each PVC actor will be able to improve value for patients and adapt to changing market conditions (Bicheno and Holweg, 2016). As mentioned before, actors can track results by regularly measuring KPIs.

### *6.2.2 Root Cause Analysis: Identifying Problems*

In Lean culture, problems are seen as opportunities for improvement. When an error is identified, the direct cause may not necessarily be the problem. For example, if a pharmacist makes a mistake filling a prescription on a busy day, it may be the result of fatigue or confusion that results from time spent doing NVA activities that stem from inefficient processes. Finding the root cause of defects or errors can direct attention to where improvement is needed the most. Two tools that help analyze root causes are *fish bone diagrams* and *interrelationship digraphs*.

Fish bone diagrams, also known as *Ishikawa diagrams* or *cause-and-effect diagrams*, help determine larger problems that contribute to errors. Rather than merely addressing the symptoms of a larger problem, workers can find solutions for the main problem(s) at hand. An example fish bone diagram is

shown in Figure 11, with possible causes that can contribute to medication errors at a pharmacy according to *Senawong* (2021) and the WHO's *Medication Errors* report. Please note the six categories covered in the diagram – Man (personnel), Machine, Methods, Mother Nature (the environment), Materials, and Measurements. These are referred to as the *6 M's*, and they help users consider a wide range of processes that can lead to the main problem being investigated (iSixSigma, *n.d.*). The problem statement (written on the right side) branches off into these six process categories, and each of these branches has smaller branches with contributing causes. The goal is for a team of workers to brainstorm the contributing causes

together, soliciting consensus from all participants (Brassard & Ritter, 2018).

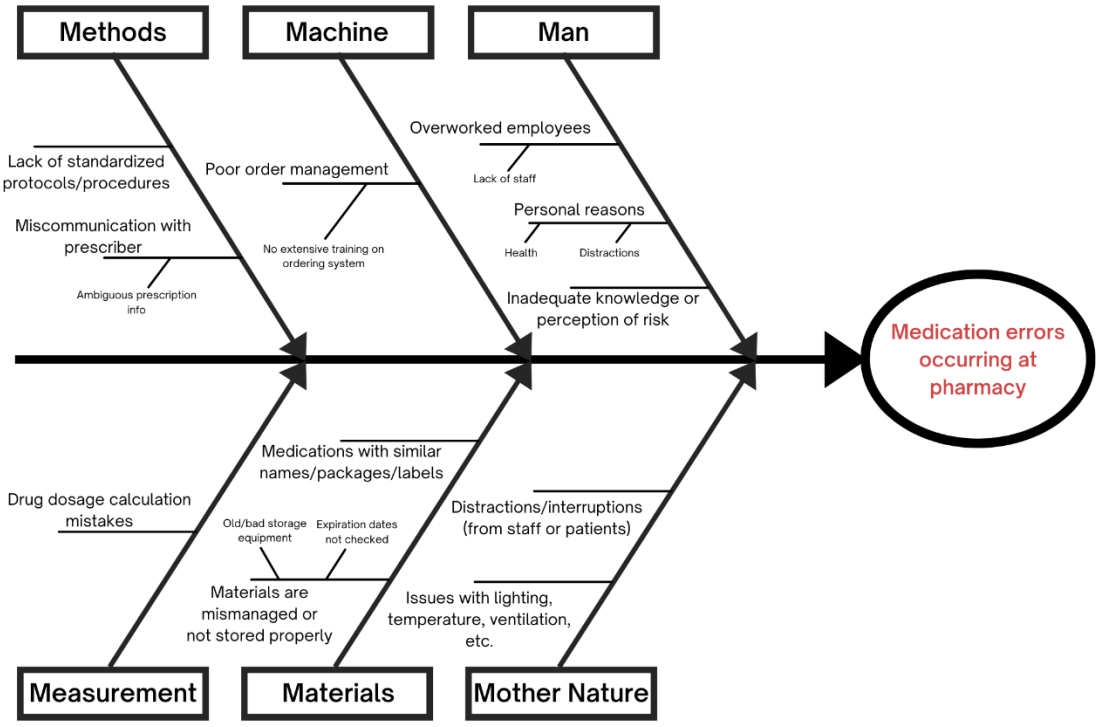


*Figure 11: Fishbone diagram with causes that could potentially lead to medication errors at a pharmacy.*

Interrelationship digraphs work similarly to fishbone diagrams, involving team brainstorming to identify the root causes of a complex issue. However, creating an interrelationship digraph takes a more systematic approach to evaluate causes; therefore, these diagrams are often constructed following the use of a fishbone diagram (MN Dept. of Health). The general process to creating an interrelationship digraph is described below.

1. Write a problem statement on a card to define the main issue that the digraph will explore. Place this card at the top of the workspace.
2. Brainstorm with the team to determine causes that could contribute to the problem. Write these contributing factors/ideas on different cards, and then place them in a circle with room to draw arrows.
3. Starting with the first contributing factor at the top of the circle and moving clockwise, determine if it is related to any other factors. If the team agrees that it strongly influences another factor, then draw a unidirectional arrow from the first factor to the influenced factor. Note that there may be multiple influenced factors or there may be none. Go around the circle of cards and repeat this process for each factor/idea.
4. Count the arrows going in and out for each factor and write these numbers below each box. The factors with the most outgoing arrows are *main causes/drivers*, while the factors with the most incoming arrows are *main effects*.
5. Lastly, the team should analyze the interrelationship digraph and determine what critical issues require solutions. Since the team worked together on constructing the diagram, there should be consensus

around what problems must be focused on (MN Dept. of Health; Brassard and Ritter, 2018).

Figure 12 shows an example of an interrelationship digraph for possible factors that could contribute to a drug manufacturer accidentally allowing a large amount of contaminated product to reach patients. Please note that this example only shows five contributing factors/ideas for simplification purposes; in reality, there could be over twenty factors that must be considered for a problem of this magnitude. The factor with the most outgoing arrows shown here is that production is outsourced to a very distant country; this causes unsatisfactory communication between management and the production facility, lack of inspections at the facility, and lengthy lead times that require faster production output.

Therefore, management should focus on their outsourcing strategy to avoid future errors.

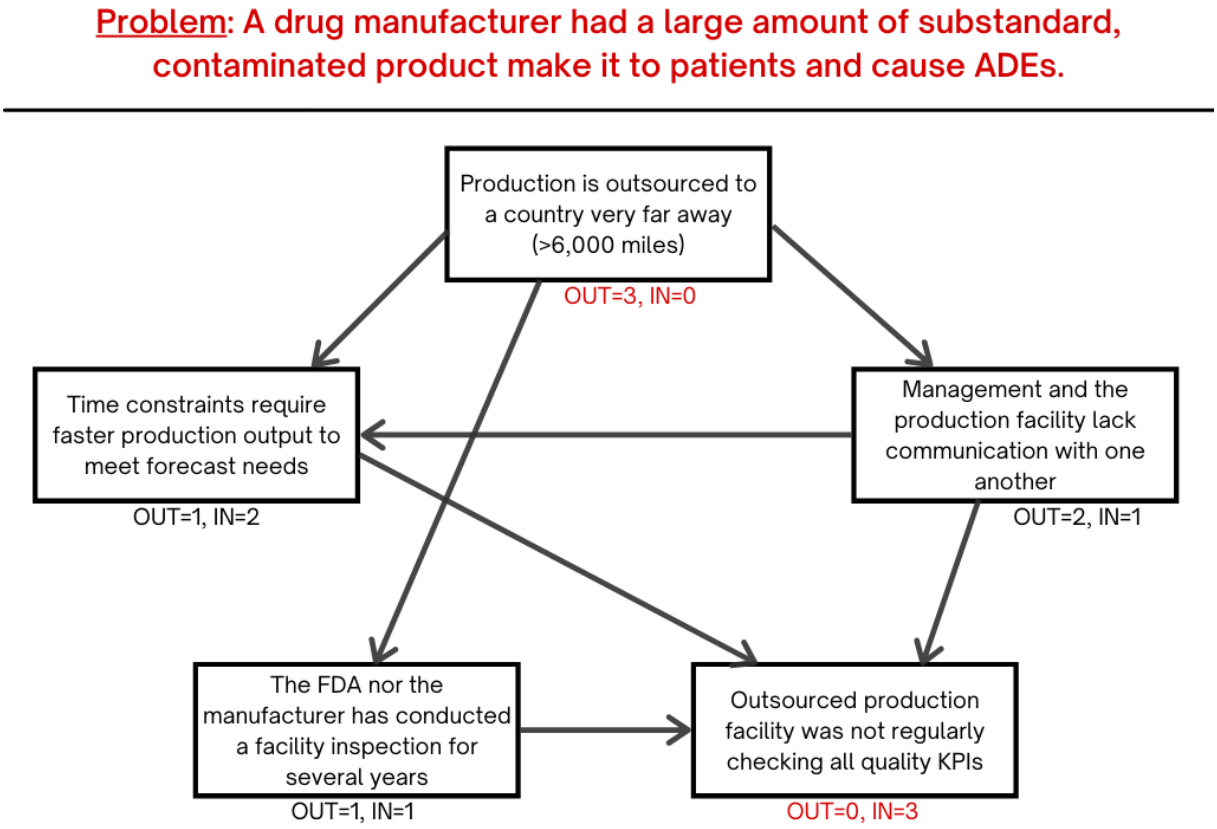


*Figure 12: Interrelationship digraph showing potential factors contributing to a drug manufacturer delivering contaminated products to patients.*

*Pareto charts* are another tool that can be used to help identify and prioritize problems. Although they do not uncover the root cause of a specific problem, Pareto charts can highlight the main problems an organization is facing. Pareto charts are bar charts used to indicate the frequency of different types of defects/errors (Lamarre, 2019). On a spreadsheet, the types of defects/errors can be listed in one column, their number of incidences in the second column (in

descending order), and the cumulative percentage of each type. After placing the frequency values in descending order, the cumulative percentage of each type of defect/error can be displayed on a line graph to highlight which problems cause the largest impact in an organization. For example, Figure 13, pulled from the *New South Wales Government Clinical Excellence Commission*'s page on Pareto Charts, shows an example Pareto chart for the frequency of different types of MEs.

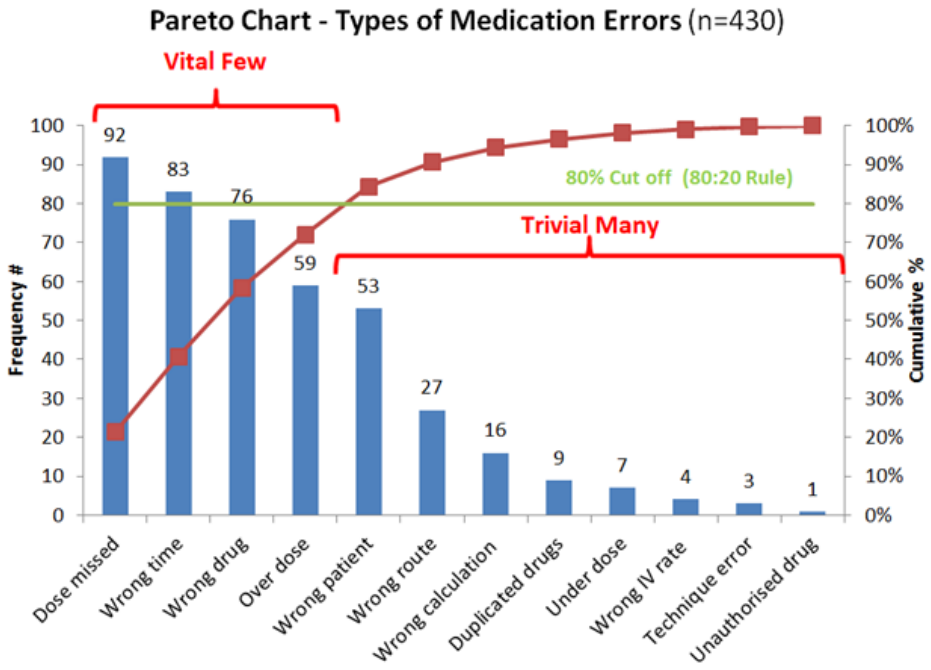


*Figure 13: Pareto chart example from the NSW Government Clinical Excellence Commission. The Pareto chart shows frequencies for different types of medication errors based on an audit.*

The *Pareto principle* is that about 80% of the effects come from about 20% of the causes. The example in Figure 13 shows that missed dose, wrong time, wrong drug, and overdose errors

contributed nearly 80% to the total amount of MEs based on the clinic audits. PVC actors can use Pareto charts to analyze what defects or errors are causing the most impact. This can help PVC actors determine which issues should be prioritized.

### *6.2.3 The PDCA Cycle: Finding Solutions*

*PDCA* stands for *Plan*, *Do*, *Check*, *Act*, and it essentially follows the principles of the scientific method to improve processes. In Lean methodology, the PDCA model is not just a one-time procedure – it is a cycle that should be completed multiple times since processes can always be improved. It is very productive for Kaizen events in which teams must plan, test, and implement solutions.

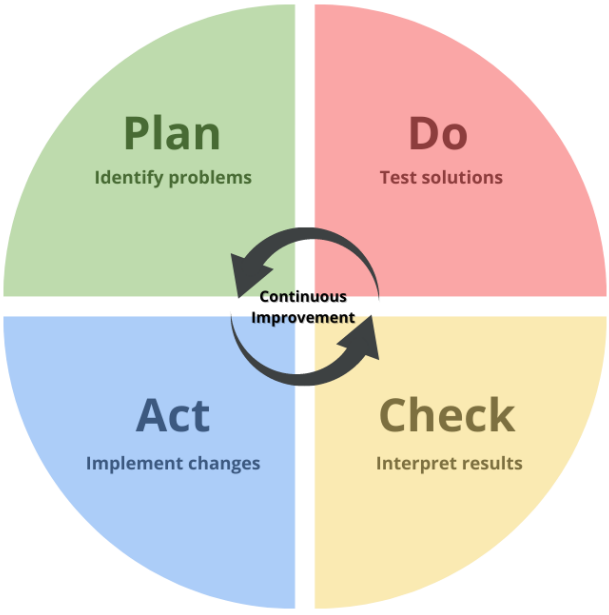


*Figure 14: The PDCA Cycle*

Each step of the cycle is described below.

1. *Plan*. The team should first identify and study the problem or opportunity for improvement. For cases in which a ME has occurred, the relevant PVC actor should evaluate the processes that led to the ME and determine a solution so that the ME does not occur again.
2. *Do*. Once a solution is identified, it should be tested on a small scale. This is to ensure no disruptions to other processes and no added waste. Solutions can include altering the physical placement of tools or personnel, using checklists and visual aids, or adding error-proofing devices called *poka-yokes* (which are discussed in more detail in Section 5.2.6).
3. *Check.* The team should analyze the results of the change(s) that they made in the previous step. Were target measures achieved? Was waste reduced? Did the changes have any side-effects on other processes? If the changes did lead to improvement, then the team can advance to the next step; if the changes did not lead to improvement or caused other problems, then the team should return to the first step and try different solutions.

4. *Act*. The improvements should be implemented, through training and/or standardization of the improved process. Improvements can be documented and standardized using A3 reports, which are described in the next section. (Mind Tools Content Team, 2016; Kanbanize, *n.d.*).

The PDCA cycle is a powerful tool that can be applied anywhere across the PVC. The scientific method is already deeply ingrained into the development of medications, but also applying it to the processes of the PVC can help significantly improve value from an operational and medical standpoint.

### *6.2.4 A3 Reports: Sustaining Progress*

*A3* refers to a standard sheet of paper upon which an improvement strategy is documented and standardized. This forces problem-solvers to be concise rather than writing a lengthy report—often, diagrams, charts, and sketches are included to best clarify a problem or solution (Bicheno and Holweg, 2016; ASQ A3 Report, *n.d.*). The A3 report consist of seven different sections, with the left side of the sheet highlighting characteristics of the problem and the right side explaining the solution. Along the top of the paper, the theme or title of the report should be written along with the date and department involved. At the bottom of the paper, the

employees involved should sign-off to agree to the improvement plan.

On the left, there are four blocks:

1. *Background information.* This section includes a statement of the problem as well as pertinent information to help understand the scope and context of the problem.
2. *Current conditions.* This section shows what is currently happening during the process that is the focus of the report. This can include a map of the value stream, a spaghetti diagram, statistics that quantify the problem, and other diagrams or sketches that represent the process.
3. *Target conditions.* This section hypothesizes the expected outcomes or goals of an improvement strategy.
4. *Cause analysis.* This section should involve cause-and-effect analysis through the "five whys", which is a technique used to find the root cause of a problem by continuously asking "why" a problem and its immediate causes occurred. This section can include fishbone diagrams, interrelationship digraphs, Pareto charts, or other cause analysis tools to describe the root cause(s) of the problem.

On the right, there are three blocks:

5. *Countermeasures.* This section proposes countermeasures to solve problems associated with each root cause.
6. *Implementation Plan.* This section includes the activities and personnel needed to enact the countermeasures. A Gantt chart, for example, could be used to assign responsibilities, show timelines, and explain expected outcomes. The plan should highlight what action is needed, who is responsible, when it should be completed, and where the action should take place.
7. *Monitor/Follow-up.* This section requires employees to (1) have a plan for monitoring results of the improvement, and (2) add to this section of the A3 report as results are collected. Results should be written in a different colored ink than the rest of the report. (Bicheno and Holweg, 2016; ASQ A3 Report, *n.d.*; Lee and Kuo, 2009).

A3 reporting is a powerful tool that standardizes the process of standardizing improvements. It helps employees learn how to implement scientific thinking into their work, as well as provide an easy way to explain their ideas to others (Shook, 2009). Figure 14 shows a simplistic example of an A3 report for staff at a clinic that have committed MEs by forgetting to give patients doses and, in some cases, accidentally giving patients twice their dose.

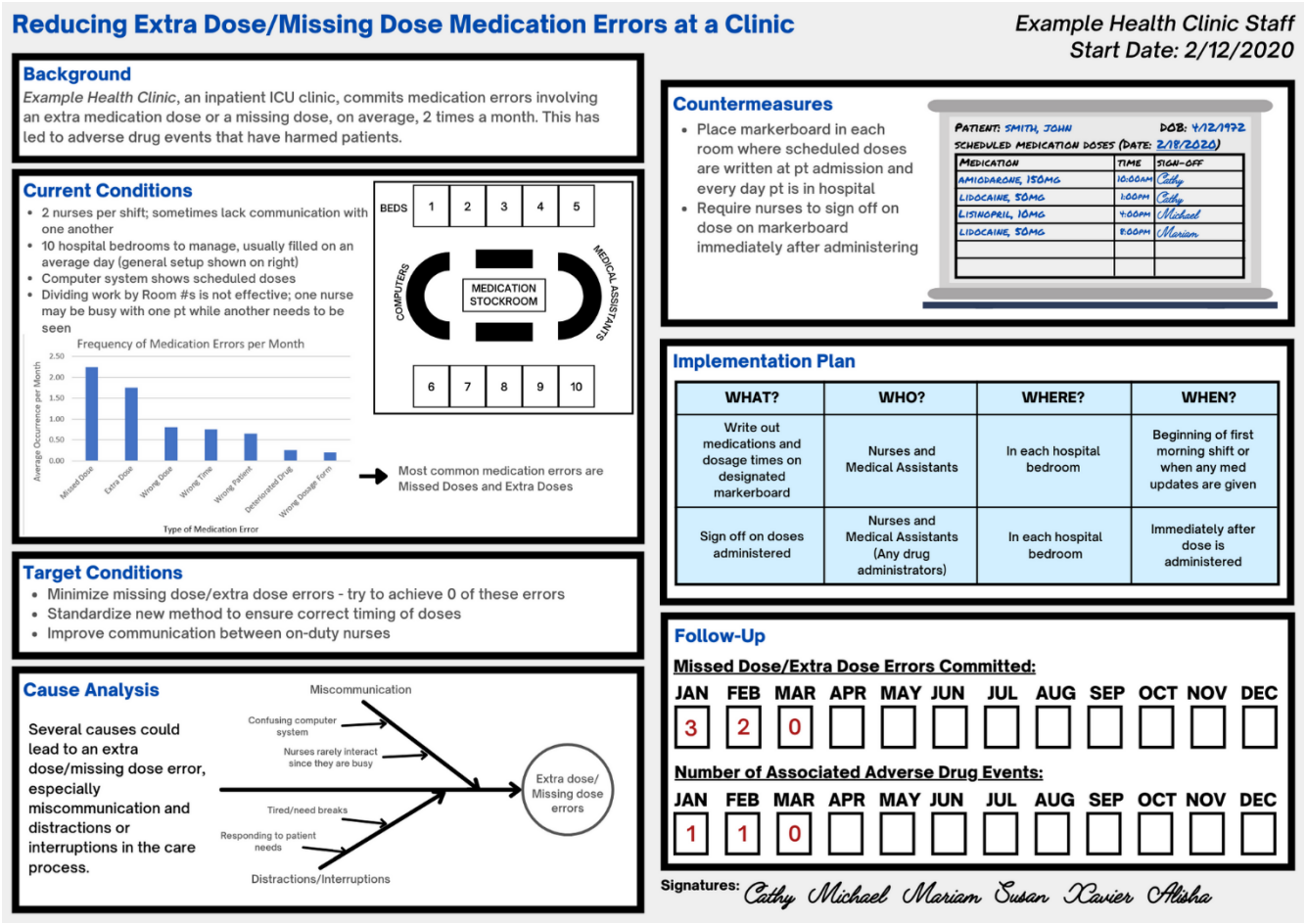


*Figure 15: A3 report for an inpatient clinic trying to reduce missing dose/extra dose medication errors*

### *6.2.5 Waste Reduction: Creating Flow*

Eliminating waste is one of the most essential goals of Lean methodology since it has resounding effects throughout an organization's operations. Waste is called *Muda* in Japanese, and it should be seen as the converse of value (Bicheno and Holweg, 2016). The goal of Lean is to increase the ratio of time spent doing VA activities to time spent doing NVA activities. By improving value and reducing waste, the ratio improves.

There are eight wastes that consume unnecessary time, space, resources, and effort. These wastes are placed in the context of the PVC below.

- *Overproduction.* When too much product is made, a large amount of inventory space will be used up and discourage a smooth flow of products to end users. Drug manufacturers should aim to create flow so that they do not have to worry about shortages or surpluses that can negatively affect the value chain. Other downstream PVC actors should also carefully forecast service needs to not only help drug manufacturers set production levels, but also ensure smooth operations without doing too much or too little.
- *Waiting*. Time spent waiting is time wasted. It is an NVA activity that adds up to substantial amounts of waste in many organizations. While machines may add value to the product during manufacturing activities like blending, granulation, and drying, waiting on these machines to complete their functions does not add value; this time can instead be spent doing other VA processes to achieve better flow. Waiting also takes a large toll on value in the MUP, where patients often wait long

periods of time to meet with a doctor or receive prescriptions (Millard, 2020).

- *Unnecessary motions.* Depending on the location of supplies, equipment, and personnel, motion can take up time that could be spent performing VA activities. Note that unnecessary motion creates micro wastes that accumulate over several processes throughout the PVC. Rearranging the workspace can help not only reduce this waste, but also improve the ergonomics and quality of work that workers can perform (Bicheno and Holweg, 2016). To target unnecessary motion, organizations can use a tool called a *spaghetti diagram* to track motions (as well as transportation and waiting times) throughout a process. To start a spaghetti diagram, the improvement team must create a floorplan of the workspace with labeled machines, materials, workstations, and other relevant factors in the process. While the worker completes the process, the team draws a single line (without removing the pen) to track all the movements involved. Based on this motion map, the team can determine where motion was taking up NVA time; this can help find better ways to rearrange process factors.
- *Transporting.* Transportation is necessary in many cases, but it is an NVA activity that should be minimized.

According to *Bicheno and Holweg* (2016), the "number of transport and material handling operations is directly proportional to the likelihood of damage and deterioration." This is true of the PVC, which has complex processes that "present multiple opportunities for product to be contaminated, diverted, or otherwise adulterated" (White, 2016). Additionally, *Bicheno and Holweg* (2016) explain that transportation is closely linked to communication; when PVC actors are separated by larger distances, there is a negative impact on communication and therefore quality. Since transportation is necessary, PVC actors must consider the logistical tradeoffs of different transportation methods. For example, in Section 2 we identified the tradeoff of losing personal interactions with pharmacists by having prescriptions mailed to patients.

- *Overprocessing/Inappropriate processing.* This waste occurs when PVC actors attempt to add more value when it is not necessary or required for the patient. This violates the Lean goal of doing more with less; in fact, it is doing less with more. For example, drug manufacturers may invest in single, large machines that appear to be a better investment, when multiple smaller machines can help avoid bottlenecks and improve flow

(Bicheno and Holweg, 2016). In the MUP, overprocessing can include running multiple, unnecessary diagnostic tests, overprescribing medications, unnecessary paperwork, or performing a medication reconciliation for a low-risk patient who is taking only two or three different low-risk medications (Millard, 2020).

- *Unnecessary inventory.* Inventory is often necessary to attain a high service level. Drug distributors must hold inventory so that they can readily provide products to dispensation sites, which improves value by ensuring the right drugs are accessible to patients at the right time. However, excessive inventory can affect quality and productivity—products can expire, get damaged, or become obsolete (Boi, 2019). Through proper communication, PVC actors can ensure that inventory is maintained at only necessary levels.
- *Defects.* In this thesis, we identified and discussed medication errors as defects that arise from quality failures in PVC processes. Drug manufacturers must follow strict quality standards to ensure that medications will be safe and effective for patients. Even if defects are detected and managed before arriving to the end user, it wastes money and time that could be spent on VA activities. Manufacturers must comply with

current Good Manufacturing Practices (cGMPs), which include "minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product" (FDA cGMP Regulations, 2020). These regulatory measures address issues that could impact quality; if inspections find that cGMPs are violated, then the FDA may issue warnings, product seizures, recalls, or fines (Engelberg Center, 2014). To avoid this waste, PVC actors should adopt *Quality by Design* (QbD), a concept based on building quality into the design of a product or service, rather than only reacting to changes in KPIs (Yu *et al*., 2014). While manufacturing defects can have more widespread negative impacts, defects/MEs can occur in any of the services provided by other PVC actors. For example, distributors may accidentally send out counterfeited product (White, 2016), healthcare providers may misdiagnose patients, or dose administrators may omit or forget a dose. By implementing QbD for all drug products and services, MEs and ADEs can be avoided to increase value for patients.

- *Untapped human potential.* This waste, added later to the original seven wastes, prevents employees from learning, improving processes, and coming up with innovative ideas.

> Essentially, this waste is derived from the separation of management activities from production and servicing activities (Skhmot, 2017). By giving employees room to learn, improve, and innovate, a Lean culture can be established in which all workers are motivated to pursue perfection.

By recognizing and targeting these wastes for reduction, the value stream can flow better.

### *6.2.5 Kanban Systems: Establishing Pull*

*Kanban* is a pull-based, just-in-time strategy that uses visual signals "to instruct an upstream process to manufacture a certain amount of product" (Alicke *et al.*, 2010). In a push-based approach, planners rely more on forecast data; in a pull-based approach, planners rely more on true demand, making product as-needed. With a Kanban system, a signal is sent to an upstream process to alert workers that the process needs to be completed, thereby "pulling" the product or service to the next step. A hybrid system can be used in which earlier purchasing and production processes can be "pushed" to ensure availability, and then after a decoupling point, products are "pulled" based on actual demand. The push-to-pull strategy depends on the medication; for specialized medications with

less stable demand, a largely pull-based approach will be favorable. In some cases, pull is already an aspect of the PVC—distributors receive signals from pharmacies when a medication is out of stock, healthcare providers may be signaled that a new patient has arrived, and drug dispensers fill prescriptions in response to orders through e-prescribing software (Senawong, 2021).

Kanban systems help improve flow by utilizing visual cards to show workers what processes must be completed, which ones are in process, and which processes are completed (Papalexi *et al*., 2016). Many organizations use Kanban software to plan processes. According to *Sabry* (2010), there are six rules to establish an effective Kanban system:

1. End user (downstream) processes obtain items in the exact amounts specified by the Kanban.
2. Supplier (upstream) processes produce items in the exact amounts and sequences specified by the Kanban.
3. No items are made or moved without a Kanban.
4. The Kanban should accompany each item, every time it is moved.
5. Defects or incorrect products are never to be sent to downstream processes.

6. Kanbans should be minimized to lower inventories; this can reveal problems, which may be addressed using the PDCA cycle.

### *6.2.6 Poka-Yokes: Error-Proofing*

*Poka-yoke*, Japanese for "mistake-proofing", involves the use of a device or method to make it impossible for errors to occur, or it makes the error glaringly obvious that it can be detected and managed (ASQ Mistake Proofing, *n.d.*). Once the source of an ME is identified in a process, a poka-yoke device or method could be used to prevent the error in the future. Brainstorming, testing, and implementing poka-yokes may be central to some PDCA improvement cycles. According to *Grout* (2014), good Poka-yokes are effective at reducing harm to patients, inexpensive, and easily implemented. Poka-yokes can be classified as those that prevent the error from being made altogether and those that immediately detect the error so that it can be corrected. Everyday examples of Poka-yokes include lane-keeping assist in cars, washing machines not turning on if the door is not closed, and overflow outlets in sinks (LeanFactories, *n.d.*).

Poka-yokes may be very effective at reducing or managing MEs before they reach patients. In the table below, we highlight several Poka-yoke uses in the PVC. Note that these

are broad ideas for Poka-yokes, but the actual development and use of a Poka-yoke depends on the context of error-prone processes in the Gemba.

*Table 5: Examples of how different PVC actors can use Poka-yokes to error-proof processes*

| PVC Actor | Examples of Poka-Yoke Uses |
|---|---|
| Drug Manufacturer | • Use lights, buzzers, or other signals to indicate when a batch of product fails a particular quality test (i.e. wrong particle size distribution, medication firm, amount of moisture, etc.)<br>• Do not name new medications with a similar-sounding name as other medications<br>• Package and label medications so that dispensation and use is easily understood |
| Drug Wholesaler/Distributor | • Automatically scan the RFID tag on every incoming product to verify source<br>• RFID information should include expiry date; if drug is expired, it should be automatically marked for disposal with a signal |
| Drug Dispenser (Pharmacies, Hospitals, etc.) | • Automatically place an order with distributors for drugs that are out of stock or low on stock<br>• If a prescriber sends any relevant information regarding dosage timings, it should be automatically labeled on the pharmacy's product packaging label<br>• If a medication is high-risk, it could be filled into a different-colored bottle to alert patients<br>• Polypharmacy patients could be given a calendar that shows all dosage dates and times to improve treatment plan adherence |
| Prescriber (Healthcare Provider) | • When prescribing through e-prescribing software, the system should make sure the physician verifies what condition each prescription is needed for<br>• For patients with polypharmacy, the EHR system should verify that new prescriptions do not interact with other active prescriptions |
| Drug Administrator (Non-Patient) | • Use a markerboard with scheduled doses written down; every time a dose is given, the administrator should mark on the board next to the scheduled time<br>• Patients should have a patient identification wristband with name, gender, and date of birth so that they can be verified before receiving a dose |

# 7 Conclusion

The PVC consists of all relevant organizations that function to deliver value to patients. Ideal value from a supply chain perspective involves supplying high-quality products that function as intended, are free of defects, are delivered on-time, and are cost-effective for healthcare payers. From a clinical perspective, providing value is to follow the "Eight Rights" in the MUP: provide the right medication to the right patient at the right dose at the right time through the right route for the right reason with the right documentation, ultimately causing the right response (Schuhmacher, et al., 2015; Kavanaugh, 2018). Value is decreased when the quality of PSC products or MUP services fail, when service levels fail to provide the right medication at the right time, and when costs to the patient are increased. Although technological developments and FDA regulations have helped improve pharmaceutical value significantly over the past few decades, patients are still at risk of MEs that can negatively impact their health. Focusing on value improvement for patients is important in building a stronger, more patient-centric supply chain that guarantees patients timely access to safe and effective medications.

Improving value for patients is a multifaceted effort that involves both process engineering and systems thinking among all PVC actors. PVC actors must be aligned on the same concept of ideal value for the patient, working to communicate and coordinate in an effective way that leaves no room for error. Additionally, by improving their own processes using Lean methodologies, PVC actors can best perform their VA functions to guarantee PVC partners and patients that they have upheld their responsibilities in providing value.

As PSCs become more complex and pressure rises for the U.S. healthcare system to produce better patient outcomes, Lean methodologies offer a variety of tools and concepts that can help all PVC actors adapt to changing circumstances. In this thesis, Lean methodologies are discussed as a conceptual framework for improvement that can help increase value and reduce MEs and ADEs. Several case studies have shown that Lean has helped improve KPIs, cycle time, and efficiency while reducing waste and defects/errors (Boi, 2021; Schulze *et al.*, 2009; Chowdary and George, 2011; Nenni *et al.*, 2014). In this thesis, we do not explore any individual case studies due to time constraints; however, real-world Lean practice is expected to result in substantial improvements for PVC actors as they work to increase value for patients. Based on the

provided framework, future research should focus on actual implementation of Lean in the Gemba—case studies should be conducted in which different PVC actors utilize Lean tools to achieve target goals, such as a zero percent ME rate.

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