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Quality Management Initiatives in the Pharmaceutical Industry: *An Economic Perspective*

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality

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Introduction

With the potential to increase efficiency and decrease costs, robust quality management has long been credited as a key factor for business success.¹⁻⁴ Quality management emerged as a core component of modern manufacturing following foundational work in the 1950s that led to achievements in the electronic and automotive industries.⁵ Modern research has continued to confirm that strategic investments in quality management initiatives can yield returns.⁶⁻⁸ Building on knowledge from these accomplishments, quality management experts have developed and promoted a variety of multi-industry standards and awards that promote mature quality management practices (e.g., the International Organization for Standardization's ISO 9000 standards, the European Foundation for Quality Management Global Award, the Baldrige Award). Mature quality management practices advance the paired goals of increasing profits and delivering better products. This includes cultivating a quality culture mindset in the organization and empowering employees to reduce waste and inefficiency.

The movement toward mature quality management practices is gaining traction in pharmaceutical manufacturing. International groups (e.g., the International Society for Pharmaceutical Engineering, the Parenteral Drug Association), universities (e.g., University of St. Gallen), and consultants (e.g., McKinsey & Company) have launched programs to measure and promote mature quality management practices. In parallel, government agencies (e.g., the Food and Drug Administration) are encouraging pharmaceutical manufacturers to implement mature quality management practices. This growing momentum is driven by both business- and patient-centric goals. Not only do pharmaceutical manufacturers have the opportunity to realize a return on investment, but they also have the opportunity to provide a reliable supply of medications to patients and consumers.

This paper describes how strategic investments in quality management initiatives in the pharmaceutical sector have the potential to yield returns for companies and for public health:

- **Part I describes the potential economic return on investment.** This section outlines how these investments can increase efficiency in addition to reducing the costs of poor quality (e.g., product defects, waste, recalls, lost revenue). To do so, this section illustrates standard economic principles in the context of pharmaceutical manufacturing.
- **Part II describes the potential public health return on investment.** Mature quality management practices can help companies remain agile and reliable while navigating evolving challenges and an increasingly complex global landscape. By investing in quality management initiatives, companies can foster innovation and help mitigate the costs of drug shortages. Part II outlines the shortage-related costs that mature quality management practices can help mitigate.

The Economic Return on Investment for Quality Management Initiatives

Since the 1950s, much has been written about the benefits of mature quality management practices.¹⁻⁴ In addition to seminal works from quality management experts such as Deming and Crosby, modern research has continued to support that investments in quality management initiatives can yield financial returns.⁶⁻⁸ Aragon et al. discuss quality management case studies specifically for pharmaceutical product manufacturers.⁹ They show how companies who invest in quality management initiatives realize lower costs associated with product recalls, warranties, waste, and rework. These findings are presented in a multistage model, where companies can attain varying levels of returns based on the maturity of their quality management practices. In one example, the authors discuss the outcomes for a biopharmaceutical manufacturing site that has intermediate quality management practices. This site reduced product defects by more than 50% and waste by 75%; additionally, they were able to redirect 25% of their staff to other activities. These case studies are not one-off situations produced by special circumstances. Rather, the benefits of mature quality management practices can be connected to standard economic principles and illustrated through examples from the pharmaceutical industry.

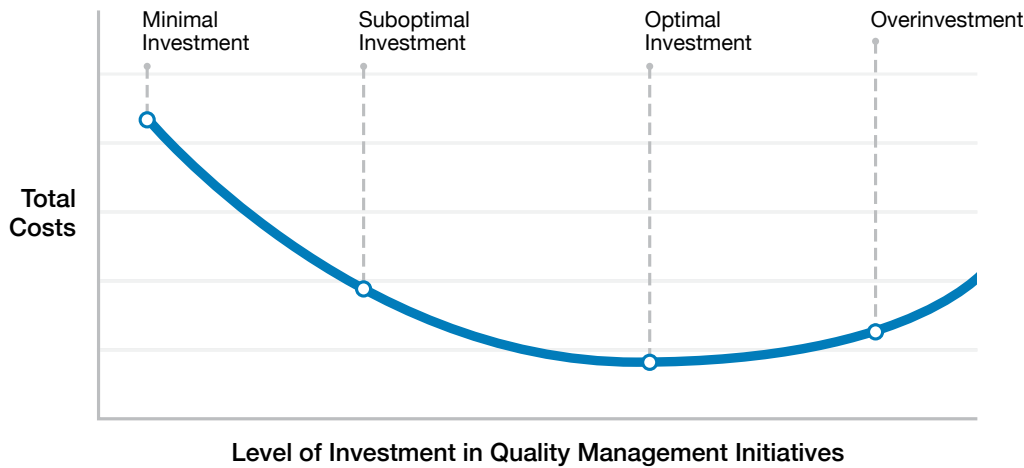
Microeconomic cost structures and the basic principles of quality management can be used to demonstrate how incremental investments in quality management initiatives can yield returns.¹⁰ The resulting conceptual model can be applied across multiple industries; however, this section links the model with strategies and citations that are specific to pharmaceutical manufacturing. To provide a focused discussion about investments in quality management initiatives, the model describes the economics of individual companies, not the economics of the pharmaceutical market as a whole. Although the model does not account for the external complexities of the pharmaceutical market,¹¹ the model does demonstrate that investments in quality management initiatives can be tailored to each manufacturer's specific context and needs. Together, the model and the examples from pharmaceutical manufacturing demonstrate that these investments are not an all-or-nothing proposition. Incremental investments in quality management initiatives can yield returns.

This section describes four scenarios for investing in quality management initiatives: minimal investment, suboptimal investment, optimal investment, and overinvestment (Figure 1). Similar to other models of the cost of quality, Figure 1 uses a cost curve to model the relationship between total costs and the level of investment in quality management initiatives.^{6,12} As investments increase (up to

Mature quality management practices prioritize patients, drive continual improvement, and enhance supply chain reliability through the strategic integration of business decisions and manufacturing operations with quality practices and technological advancements.

an optimal level), total costs decrease. These decreases are mediated by savings from increased efficiency and decreased waste. Beyond the optimal level, total costs begin to increase. Figure 2 shows how these changes in investments and costs relate to optimal output, revenue, and profit.

Figure 1. The Relationship Between Investments in Quality Management Initiatives and Total Costs. The graph shows the total cost curve for investments in quality management initiatives. Four investment scenarios are indicated along the curve. The outset below shows the supporting equation and key terms.



Supporting Equation for the Total Cost Curve

Total Cost (TC) Curve Terms

Total Costs = Fixed Costs + Variable Costs +
Level of Investment in Quality Management Initiatives –
Savings for Fixed Costs – Savings for Variable Costs

Fixed and Variable Costs (F and V)

Fixed costs are one-time costs in the short run. This can include costs such as buildings and equipment. The term F represents fixed costs.

Variable costs are costs that change relative to the level of production. This can include costs such as supplies and employee wages. The term V represents variable costs.

Level of Investment in Quality Management Initiatives (sQ)

Q is an investment in quality management initiatives, and s is the per unit cost of the investment. The term sQ represents the level of investment in quality management initiatives.

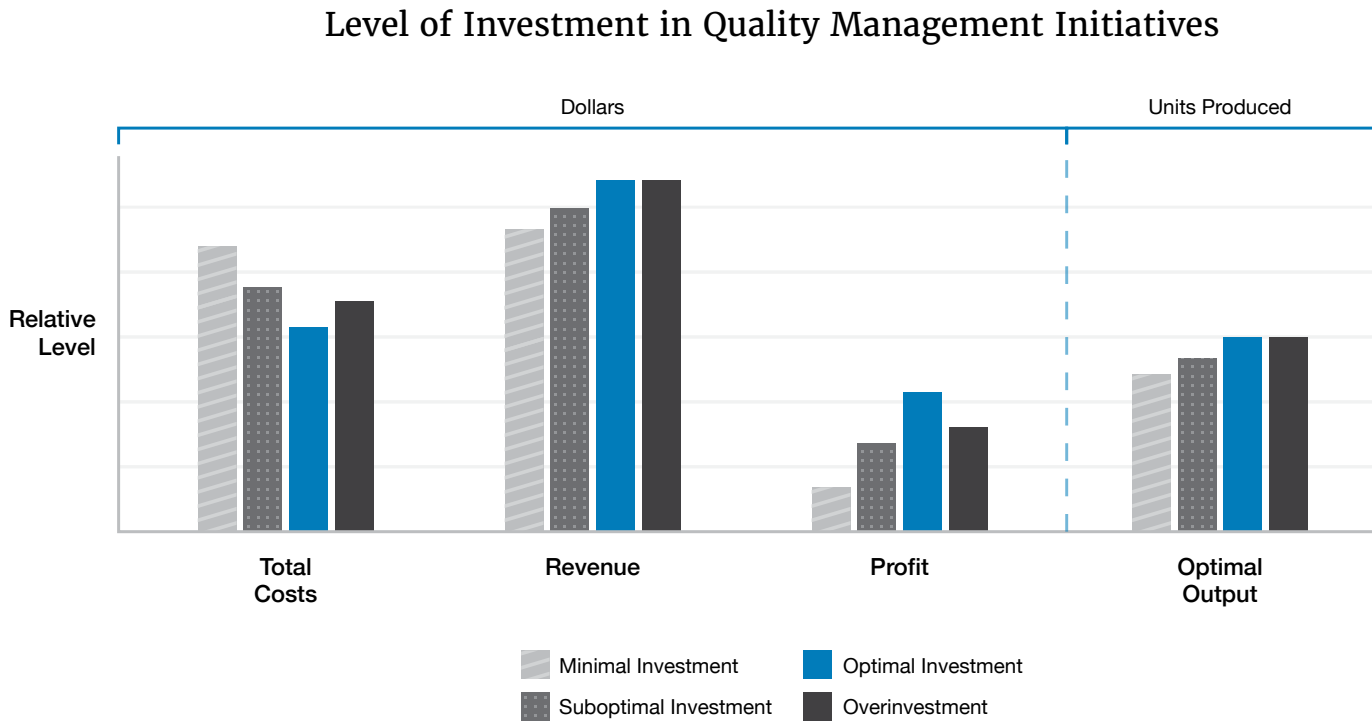
Savings for Fixed and Variable Costs ($f(Q)F$ and $g(Q)V$)

Different levels of investment in quality management initiatives yield different levels of savings. So, savings for fixed and variable costs will vary based on the level of investment in quality management initiatives. The terms $f(Q)F$ and $g(Q)V$ represent the savings for fixed and variable costs.

Total Cost Curve Equation

$$TC = F + V + sQ - f(Q)F - g(Q)V$$

Figure 2. The Relationship Between the Level of Investment in Quality Management Initiatives, Total Costs, Revenue, Profit, and Optimal Output. The graph shows the total cost, revenue, profit, and optimal output across four levels of investment in quality management. The outset below shows the supporting equations and key terms.



Supporting Equations for the Relationship Between Investments in Quality Management Initiatives, Total Costs, Revenue, Profit, and Optimal Output

Level of Investment in Quality Management Initiatives (sQ)

From Figure 1's equations, sQ (the investment multiplied by the per unit cost) represents the level of investment in quality management initiatives.

Total Costs (TC)

From Figure 1's equations, the total costs are the sum of the fixed, variable, and investment costs minus the savings for fixed and variable costs that are generated by the investment.

$$TC = F + V + sQ - f(Q)F - g(Q)V$$

Optimal Output (q^*)

In a perfectly competitive market, the optimal quantity (q^*) to produce occurs when the cost of producing another unit (marginal cost) equals the market price (p). This is the quantity where profit is maximized.

Revenue (pq^*)

Revenue at optimal output can be calculated as the optimal quantity (q^*) multiplied by the price (p).

Profit (Π)

Profit at optimal output can be calculated as revenue (pq^*) minus total costs (TC).

$$\Pi = pq^* - TC$$

SCENARIO 1

Minimal Investment in Quality Management Initiatives

Companies that invest minimally in quality management initiatives might have several costs associated with inconsistent product quality and inefficient workflows. This can include costs created by high error rates, high rework rates, delayed lead times, and delayed cycle times.^{9, 13-15} Additionally, these companies may need to replace goods, manage high employee turnover, and investigate a high number of complaints.¹⁶⁻¹⁸ Together this creates a situation of high total costs coupled with low output, revenue, and profits (Figure 2). Poor quality management practices may contribute to compliance actions or recalls that further increase total costs. As a consequence, these companies spend time and money fixing these issues.¹⁹ In addition to the regulatory penalties associated with these situations, poor quality management practices have caused billions of dollars in lost revenue for the pharmaceutical industry over the past two decades.^{19, 20} Furthermore, these situations can damage stock market performance and corporate reputation.^{21, 22}

SCENARIO 2

Suboptimal Investment in Quality Management Initiatives

With incremental investments in quality management initiatives, companies can shift from unnecessary costs toward efficient operations. For companies in the early stages of this journey, investments could include management strategies such as fostering a culture of quality. Quality culture improvements, which can include practices such as advanced preventive maintenance, enhanced employee training, and mature management of supplier quality, have been linked to higher performance.^{9, 13, 18, 19, 23-26} As performance increases, defects, waste, and rework decrease.^{9, 19, 27} In one example, a company implemented a quality culture initiative that promoted continuous improvement, problem-solving capabilities, and quality best practices.²⁴ This initiative resulted in decreased deviations and improved on-time in-full delivery rates. With these types of improvements, companies could ultimately see lower total costs in addition to higher revenue, profits, and output (Figure 2). Even with a suboptimal investment in quality management initiatives, companies can gain returns on investment through decreased costs and increased performance.

SCENARIO 3

Optimal Investment in Quality Management Initiatives

As companies move toward the optimal level of investment in quality management initiatives, total costs continue to decrease, while profits continue to increase. This level could include changes such as Lean Six Sigma process optimization^{14, 15, 28, 29}

and the incorporation of advanced manufacturing technologies.^{9, 29-32} For example, a company that was already performing well further improved its manufacturing labs' productivity by 40 to 50 percent through schedule optimization via an advanced-analytics digital-twin solution (31). Performance gains at the optimal level of investment could lead to extensive decreases in the cost of poor quality, including decreased deviations and yield loss.^{9, 28, 29, 31, 32} At this level, companies can fully realize the benefits of mature quality management practices with minimized total costs and maximized revenue, profit, and optimal output relative to investment in quality management initiatives (Figure 2). Furthermore, companies can reinvest the profits into areas such as research and development, infrastructure, and advanced technologies, creating a competitive advantage through a reliable supply and a strong reputation.^{15, 27, 33, 34}

SCENARIO 4

Overinvestment in Quality Management Initiatives

It is possible to move beyond the point of optimal investment in quality management initiatives. In this hypothetical scenario, investments no longer generate sufficient increases in efficiency and savings. Optimal output and revenue begin to stagnate, total costs increase, and profits decrease. Although overinvestment is unlikely to occur, this scenario could span a few hypothetical categories. For example, overinvestment could involve making unnecessarily complex changes that are costly to implement and involve levels of precision that do not result in meaningful improvements. Overinvestment could also include excessive redundancies for equipment, staff, or materials.

Summary of the Economic Return on Investment for Quality Management Initiatives

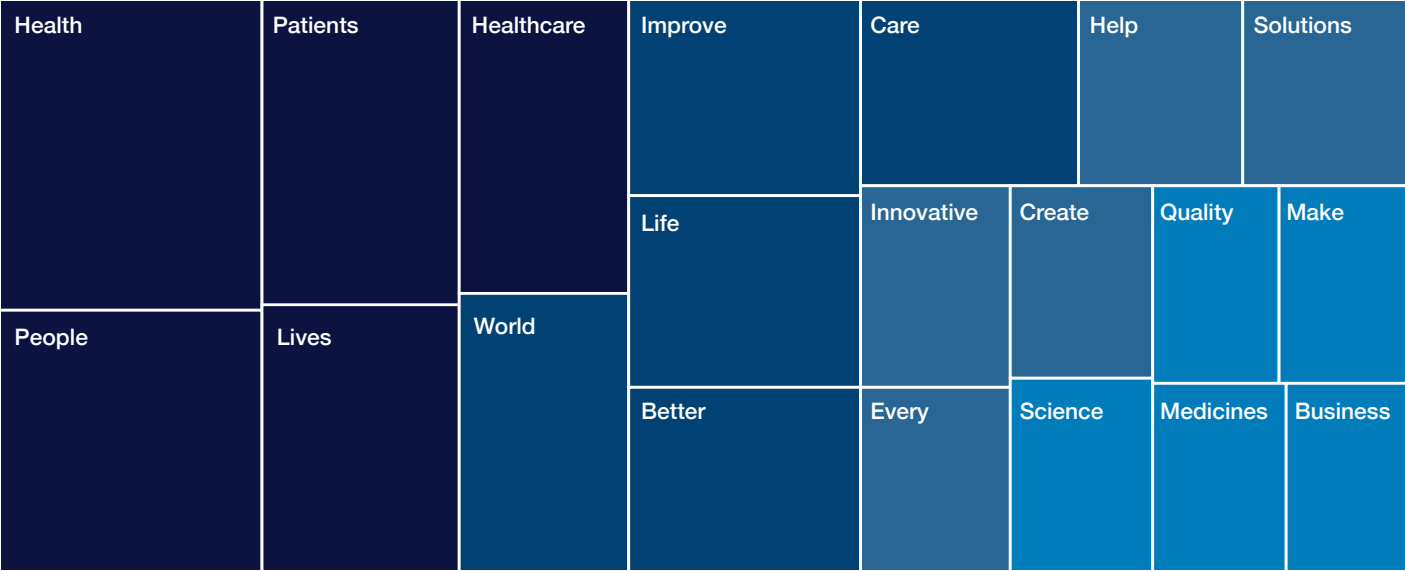
These scenarios illustrate that companies can use stepwise, scalable approaches to improve their quality management practices and realize returns on their investments. Investments in quality management initiatives can improve productivity and efficiency and lower costs from rework, defects, and recalls. Furthermore, these investments are not an all-or-nothing proposition. Whether a company is beginning its quality management journey or working its way toward the optimal point, each investment provides the opportunity for additional returns. As companies progress along the curve in Figure 1, they can strategically augment their quality management practices in stages that align with their business model and competitive situation. Although the benefits of mature quality management practices involve an investment, there are strategies at every resource-level that can provide returns.

The Public Health Return on Investment for Quality Management Initiatives

In addition to creating economic returns, investments in quality management initiatives can help companies align with their patient-centric goals. As shown in Figure 3, the vision and mission statements of the top 50 health and pharmaceutical companies emphasize public health. Mature quality management practices can increase companies’ stability and reliability, which can ultimately contribute to a reliable supply of medications that improve patients’ lives and strengthen the health care system.³⁵ For example, during the COVID-19 pandemic, a pharmaceutical manufacturer used a Lean Six Sigma approach to identify and mitigate a tablet feed issue.²⁸ The manufacturer improved multiple operational metrics and generated almost half a million dollars in savings (with additional projected savings for implementing this change at sister sites). Beyond the operational improvements and savings, this initiative ultimately helped the manufacturer efficiently deliver medications to patients during a time of increased demand.

Figure 3. Treemap Chart of the Most Frequently Used Words in the Vision and Mission Statements of the Top 50 Health and Pharmaceutical Companies. This treemap chart shows the relative frequencies of the top 20 words using relative sizing and a color gradient. The larger, darker rectangles indicate a higher frequency, and the lighter, smaller rectangles indicate a lower frequency. With 32 mentions, health is the most frequently used word. In contrast, the word business only has 9 mentions. The information for this treemap chart is from companies’ websites and independent sites that aggregate data about these companies. The top 50 companies were determined by revenue.³⁶

Most Frequently Used Words in the Vision and Mission Statements of the Top 50 Health and Pharmaceutical Companies

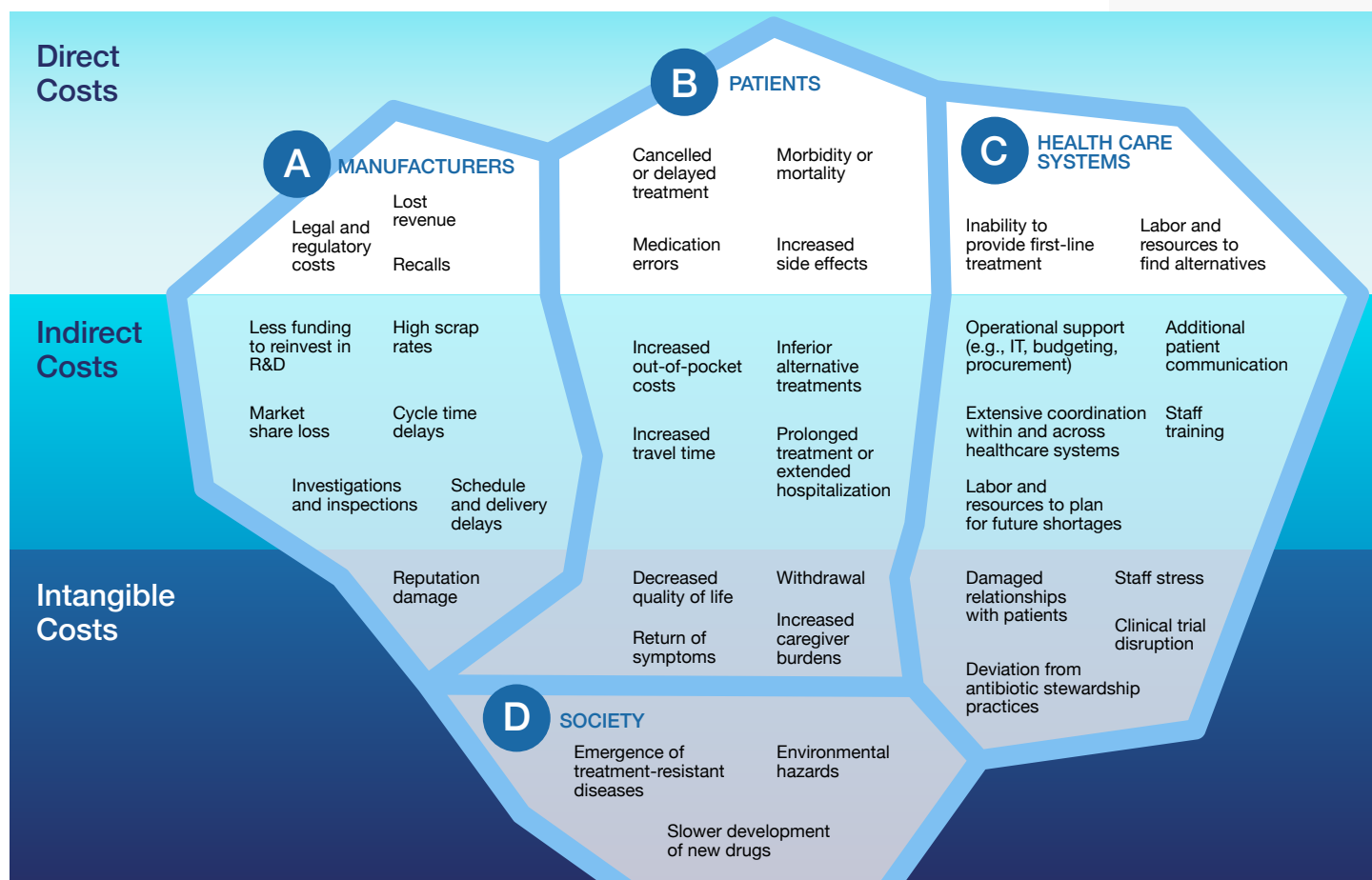


To understand how investments in quality management initiatives can yield returns for public health, it is important to understand the public health costs that result from poor quality management practices. Poor quality management practices can potentially lead to drug shortages and other supply chain disruptions.³⁷ Although the effects of drug shortages are heterogeneous and have not been systematically quantified, several key costs can still be identified.³⁸⁻⁴⁰ To describe these far-reaching costs, the following sections will use the pharmacoeconomic terms of direct, indirect, and intangible costs.⁴¹ Traditionally, direct costs represent treatment (e.g., appointments, medicine, diagnostics), indirect costs represent the systems that support treatment, and intangible costs represent treatment-related effects and unintended consequences that are not easily quantified (e.g., altered quality of life). These terms can be expanded to apply to drug shortages and poor quality management practices:

- **Direct costs** include the costs for manufacturers, patients, and health care systems as they manage the initial effects of drug shortages.
- **Indirect costs** include the secondary costs associated with manufacturing, obtaining, and delivering treatment. This can include costs at multiple time points:
 - Before treatment (e.g., for manufacturers, this could include the scrap rate from an inefficient manufacturing process)
 - During treatment (e.g., for patients, this could include the cost of traveling to an alternative treatment center)
 - After treatment (e.g., for health care systems, this could include labor and resources to plan for future shortages)
- **Intangible costs** include costs that are difficult to quantify. These can apply to each population, and they can extend to broad consequences for society as a whole.

Figure 4 depicts these costs through the iceberg paradigm. Each cost is a horizontal band, with direct costs above the surface and indirect and intangible costs below the surface. The panels depict the costs of poor quality for manufacturers (Figure 4A), patients (Figure 4B), health care systems (Figure 4C), and society (Figure 4D).

Figure 4. The Iceberg of Direct, Indirect, and Intangible Costs of Quality Management Issues in Pharmaceutical Manufacturing. Manufacturers, patients, and health care systems each have a vertical region with direct costs above the surface and indirect and intangible costs below the surface (4A-C). Intangible societal costs are at the bottom of the iceberg (4D).



Costs for Manufacturers

Part I discusses the costs of poor quality management practices for manufacturers, so this section will not delve into these costs. Instead, this section will provide examples of categorizing these costs using pharmacoeconomic terms. Figure 4A categorizes these costs relative to drug shortages, with immediate costs related to recalls, lost revenue, and legal and regulatory costs.^{19, 20} The indirect costs largely relate to issues throughout the manufacturing process, including high scrap and rework rates and delayed cycle and lead times.^{9, 13-15} The indirect costs can also relate to the aftermath of the shortage when companies may face market share loss.²¹ This can further extend to the intangible cost of reputational damage.²²

Costs for Patients

When poor quality management practices contribute to supply disruptions and potential shortages, patients face profound costs (Figure 4B).

“Unfortunately, we now must fight another battle—the Growth Hormone Shortage. My daughter’s life depends on this drug! PWS [Prader–Willi Syndrome] children that have gone without Growth Hormone (GH) during this shortage are and will continue to suffer detrimental outcomes on their long-term brain and body development.

I have spent countless hours of my time and mental sanity trying to make sure we could get at least some of her needed GH, an additional stress no medical parent needs. We also will no longer be able to participate in a preventative trial due to the delay being so long (a trial to prevent hyperphagia from ever happening, and an extremely promising one). The loss of this life-saving opportunity was directly because of the ongoing shortage and cannot be described in words...

Even when supply is available her treatment is still impacted. Before the shortage, we took a blood test quarterly to assess our daughter’s GH deficit and ensure she was getting the right amount. This test allowed our medical team to adjust dosage to ensure she was getting the right amount as her body grows. Due to the shortage, we are unable to get the tests because of the sheer amount of paperwork and phone calls our provider must navigate to get her patient’s GH. She simply could not accommodate writing up the additional blood labs to send out.

I am sick thinking about what this may mean for her future. Our smart, funny, happy little girl is being denied the life-changing opportunity to develop like any typical child.”

Aileen – Mother of a 3-year-old patient⁴²

Direct Costs: As drug shortages continue to affect several high-stakes fields, including emergency medicine,⁴³ oncology,^{44–47} infectious diseases,⁴⁸ and anesthesiology,⁴⁹ patients face costs that can be immediate and severe. Rather than receiving potentially life-saving treatments, patients could face cancellations or delays, medication errors, increased side effects, and, in the worst cases, morbidity or mortality.

Indirect Costs: In addition to treatment-related medical issues, patients may struggle to obtain treatment. They may need to transfer to other institutions, travel farther to obtain treatment, or pay more for treatment.^{45, 50–52} Additionally, alternative treatment plans may include the use of less effective drugs⁴⁶ or drugs that can increase side effects.^{53,54} As patients adjust to alternative treatment plans, they may require additional care to manage symptoms or side effects, which, in some cases, can include extended hospitalization or rehospitalization.^{51, 53, 55}

Intangible Costs: Shortages can decrease quality of life as patients grapple with issues such as the return of symptoms,^{52, 55} withdrawal,^{56,57} or stress caused by delayed or extended treatment.^{45, 51, 58} Furthermore, caregivers and families can face increased stress and caregiving workloads as they help patients manage untreated symptoms and navigate the logistics of obtaining treatment.^{52, 54, 59} This is particularly true when shortages affect conditions that require long-term care and these stressors can occur regardless of the severity of the condition.

Costs for Health Care Systems

In addition to negatively affecting patients, shortages affect the health care systems and clinicians who are delivering care (Figure 4C).

Direct Costs: In the immediate response to a shortage, clinicians expend additional time and resources to formulate alternative treatment plans.^{51, 58, 61} These plans may involve extensive coordination among pharmacists, physicians, and nurses in addition to purchasers, clinical coordinators, risk management teams, and legal representatives.⁶²

“It’s one of those things that you don’t know when it’s going to occur again. Your guard is up, if you hear anything you still are ready to go crazy trying to get the product. Talk about changed practice—what I’ve had to do is drop everything else. My whole job becomes obtaining that drug.”

Community Hospital Pharmacist⁶⁰

Indirect Costs: There are several critical tasks that support the delivery of care. These tasks span multiple categories, including updating IT systems, adjusting inventory, managing budgets, shifting staff assignments, coordinating with other health care systems, performing risk assessments, updating prescription

“About 5 years ago it was disruptive enough, actually, maybe even 7 years ago that we started to add it to [our meeting agendas]—it was a standing agenda topic of our management team meeting on a weekly basis.”

Academic Pharmacist⁶⁰

practices, training staff (e.g., on the use of alternative therapies), communicating with patients, and managing patient side effects from alternative treatments.^{62, 63} Prolonged shortages expand the list of indirect costs as providers develop and implement long-term plans for the delivery of alternative or rationed care. This can involve further coordination with risk management teams, legal representatives, patients, and families.⁶² Beyond the effects of a given shortage, health care systems often dedicate resources to planning for future shortages. This can include designating a drug shortage committee and having regular discussions about shortage management.^{60, 63, 64} Estimates for the annual cost of labor to manage drug shortages in the United States range from \$216-359 million. However, given the far-reaching effects of drug shortages, not every component can be quantified. Furthermore, these costs are likely underestimates due to the lack of systematic data collection and the focus on hospital systems (rather than all types of health care facilities).^{61, 65}

Intangible Costs: Clinicians face increased stress in addition to potential damage and strain to their relationships with patients and other staff.^{61, 66} This stress is

compounded when shortages are exacerbated by events such as pandemics.^{67, 68} In addition to the emotional toll on clinicians, shortages can also cause intangible costs through the disruption of critical medical practices, including clinical trials⁵⁸ and antibiotic stewardship.^{69, 70}

Costs for Society

Beyond the immediate costs of drug shortages, there are long-term societal ramifications of both the drug shortages themselves and the poor quality management practices that can cause them. Although these costs are not easily quantified, they pose significant medical, ethical, economic, and environmental risks (Figure 4D).

Intangible Medical Costs: Recent shortages of the chemotherapy drugs cisplatin and carboplatin necessitated the use of alternative treatments for a broad range of cancers.⁷² This dependence on less-than-optimal alternatives impacted patient outcomes in ways that were difficult to anticipate and quantify, including lower “quality of life.” Additional medical risks can result from the spread of infectious disease and the emergence of treatment-resistant infectious disease. These concerns have been reported for fungal,⁷³ bacterial,^{69, 74-77} and viral infections.^{70, 78} Beyond the intangible medical costs of shortages, there are significant medical costs associated with poor quality management practices in pharmaceutical manufacturing. Inefficient manufacturing leaves less funding available for the development of innovative lifesaving treatments. A 30% increase in manufacturing efficiency could potentially generate \$1-12.3 trillion in social value through reinvestment of savings into research and development for new treatments.³³

“We know that about two thirds of medicine supply chain challenges begin as a quality issue. Shortages of medicines only exacerbate the quality issues that have been there all along. This is particularly dangerous in the case of antimicrobial medications because of the deadly global public health consequences of resistance.”

Ronald T. Piervincenzi, PhD, U.S. Pharmacopeia CEO⁷¹

Intangible Ethical Costs: During drug shortages, limited supply creates ethical dilemmas in the distribution of medical care. When the supply of medicines is insufficient, health care systems must decide how to allocate care and which patients to prioritize.^{79, 80}

“You know, it just feels professionally like we’re not doing our job for the patient...It’s hard to say...‘we just don’t have the drug to treat you,’ I never would think I would have to say that. It doesn’t feel very good.”

Academic Hospital Pharmacist⁶⁰

Intangible Environmental Costs: Furthermore, poor quality management practices in pharmaceutical manufacturing can create environmental hazards. Inefficient supply chain design can increase greenhouse gas emissions.^{81, 82} In addition, suboptimal manufacturing processes and waste management practices can lead to higher levels of pollution from pharmaceutical manufacturing.⁸²⁻⁸⁴ This pollution can affect local ecology and human health.^{84, 85}

Summary of Quality Management's Return on Investment for Public Health

Investing in quality management gives pharmaceutical companies the opportunity to turn the tide against the far-reaching impacts of drug shortages and poor quality management practices. Through investments in quality management initiatives, companies can strengthen the health care system and improve the lives of patients and consumers. Furthermore, these investments can have broad societal ripple effects for medical, ethical, and environmental considerations. With the chance to prevent the far-reaching costs of drug shortages, investments in quality management initiatives have the potential to yield substantial returns for public health.

Conclusion

From mitigating public health risks and stabilizing the supply of essential medications to fostering innovation and supporting economic growth, mature quality management practices produce far-reaching benefits. As outlined in Part I, strategic investments in quality management initiatives can yield economic returns, including lower costs associated with defects, waste, and recalls. Standard economic principles and examples from pharmaceutical manufacturing demonstrate that even incremental investments in quality management initiatives can yield returns. Investing in quality management initiatives can be an incremental process tailored to a company's specific situation, and companies can customize their strategies as they optimize their level of investment.

As outlined in Part II, strategic investments in quality management initiatives can also yield returns for public health. When pharmaceutical companies invest in quality management initiatives, they can increase supply chain reliability and create a stable supply of critical medicines. This is particularly important during crises such as drug shortages or pandemics when pharmaceutical companies need to respond to increased demand. These investments can safeguard patient welfare and prevent the extensive costs of poor quality that are faced by society and health care systems.

Thus, in this ever-evolving global landscape, the costs of investing in quality management initiatives are outweighed by the far-reaching economic and societal benefits. Whether companies are implementing their first quality culture initiatives or embracing new technologies, there are opportunities for companies at every stage of quality management implementation. Along the way, companies can participate in programs that measure and promote mature quality management practices. With the return on investment for both companies and public health, investing in quality management initiatives is an opportunity that pharmaceutical companies cannot afford to lose.

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