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Original Article

Elucidating Production Bottlenecks in the Indian Pharmaceutical Industry for Enhanced Pandemic Preparedness Using a Combined Theory of Constraints and Six Sigma Approach

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ABSTRACT

Aim/Background: Early in the COVID-19 epidemic, the dire need for effective and readily available outpatient therapies became apparent as healthcare systems worldwide faced unprecedented strain. This study addressed the initial focus on medications with anecdotal evidence against COVID-19 and the emergence of Hydroxychloroquine (HCQ) as a potential therapeutic option due to its demonstrated *in vitro* activity and established safety record in treating autoimmune conditions. However, the surge in prescriptions and panic buying led to a significant imbalance in the supply and demand for HCQ, affecting pharmaceutical companies. Focusing on the Pharmaceutical Supply Chain (PSC), the primary objective was to present a new methodology for investigating production processes to identify potential improvements and mitigate the impact of bottlenecks on productivity. **Materials and Methods:** The study employed an integrated Theory of Constraints (TOC)-Six Sigma (SS) approach to pinpoint constraints within the PSC and proposed strategies to mitigate their effects. The case study presented in this research focused on the Indian pharmaceutical industry. **Results:** The results revealed that inventory status and production capacity were critical bottlenecks/constraints in the system. The integrated approach successfully identified these constraints and provided insights into potential improvement scenarios. **Conclusion:** This study presented a unique roadmap for industry practitioners to alleviate production bottlenecks and enhance the resilience of the PSC, especially in the face of pandemics. Implementing these findings could help pharmaceutical companies better navigate future disruptions and contribute to the development of robust therapeutic supply chains.

Keywords: COVID-19, Pharmaceutical supply chain, Production bottlenecks, Six sigma, Theory of constraints.

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INTRODUCTION

A quick glance into the COVID-19 outbreak

The World Health Organization (WHO) received reports of a pandemic outbreak on December 31, 2020.[1] The virus responsible for this pandemic is referred to as SARS-CoV-2 and the associated illness is known as Coronavirus disease. This infectious disease primarily spreads through saliva droplets released when infected individuals cough or sneeze. SARS-CoV-2 compromises the immune system and targets the respiratory organs, particularly the lungs, leading to severe respiratory illness.[2] In some cases, it can result in organ failure and, ultimately, death. India recorded its first COVID-19 case on March 02, 2020.[3] At that time, there was no specific cure for the disease,[4] and the only effective preventive measure was breaking the infection chain.[5] This involved practices such as maintaining distance from potentially infected individuals, implementing social distancing, quarantine protocols and the enforcement of lockdowns.[6] The Government of India (GoI) imposed a nationwide lockdown on March 24, 2020,[7] initially for 21 days, later extending it until May 17, 2020.[8] As of November 22, 2023, the World Health Organization

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received reports of 772,386,069 confirmed COVID-19 cases and 6,987,222 associated deaths worldwide.[9] Despite the invention of vaccines as a preventive measure for this disease, the outbreak had revealed weaknesses in the PSC across different countries globally.

Detrimental impacts of the Pandemic on the global supply chains

The global pandemic inflicted severe and detrimental impacts on the intricate web of global supply chains, disrupting the flow of goods and services on an unprecedented scale. Companies and business operations faced significant setbacks due to resource shortages, disruptions in supplies, labour shortages and transportation delays, causing a domino effect throughout the supply chain and impeding its smooth functioning.[10] The interdependent nature of supply networks accelerated this disruption across global businesses and international trade, leading to a substantial drop in demand. This upheaval contributed to escalating economic challenges amid the pandemic, with many enterprises reducing their supply chain activities.[11] Manufacturing plants faced closures, leading to a shortage of critical components and raw materials. The heightened demand for certain products, coupled with logistical challenges, resulted in bottlenecks and increased costs.[12] Around 75% of companies reported vulnerabilities in their supply chains due to lockdown restrictions, with almost half experiencing considerable delays in fulfilling orders.[12] China, often termed the "factory of the world," faced closures that rippled across the global supply chain.[13] The shutdown of Chinese factories raised concerns about sourcing components essential for a wide range of products, from nano-electronics to heavy machinery, indicating the complex challenges in supply chain management as the pandemic unfolded.[13] Additionally, the reliance on just-in-time inventory models left little room for flexibility in the face of disruptions, amplifying the consequences of the pandemic.[10] The fragility exposed in global supply chains has prompted a reassessment of resilience and contingency planning, urging businesses and governments alike to seek more robust and adaptable strategies to navigate future crises.[11]

Research Motivation

In the wake of recent global health crises, the imperative to fortify our pharmaceutical infrastructure against unforeseen challenges has never been more apparent. The unprecedented challenges posed by the COVID-19 pandemic underscored the critical need for swift and effective therapeutic interventions to counteract the devastating impact of the virus on global health-care systems.[14] The COVID-19 pandemic has underscored the vulnerability of the pharmaceutical industry to sudden surges in demand, exposing critical production bottlenecks that hinder timely response and exacerbate the impact of public health emergencies.[14] The initial stages of the epidemic illuminated the urgency of developing early outpatient therapies that are not only efficacious against the disease but also readily accessible.[15] Amid the urgency, HCQ,[16] an off-patent antimalarial with a well-established safety profile and promising *in vitro* activity against COVID,[17] emerged as a potential solution. However, the surge in demand for HCQ, driven by both healthcare providers' prescriptions and panic-driven consumer behaviour,[18] led to a profound demand-supply imbalance within the pharmaceutical industry.[19] The heightened demand for HCQ exposed vulnerabilities in the PSC,[19] revealing critical bottlenecks that impeded the industry's ability to meet the urgent and escalating needs. To address these challenges and chart a course towards enhanced pandemic preparedness, this manuscript introduces a TOC-based approach tailored to alleviate production bottlenecks in the pharmaceutical sector.[20] This study addresses the aftermath of this demand shock, focusing on the acute demand-supply imbalances faced by pharmaceutical companies and their consequential impact on production processes.

Research Objectives

Our primary objective is to introduce a novel methodology for scrutinizing production processes, with the aim of identifying improvement scenarios that can effectively alleviate bottlenecks and enhance productivity in PSC. We aim to provide a comprehensive framework for identifying and mitigating constraints, thereby fostering a more resilient and responsive pharmaceutical manufacturing ecosystem. This paper navigates the intersection of theory and practical application, offering insights and strategies crucial for optimizing production processes and ultimately safeguarding global health in the face of future pandemics. To achieve this goal, we adopt an integrated approach that combines the principles of the TOC,[21] and SS.[22] This integrated framework enables a comprehensive analysis of the PSC, highlighting constraints and proposing targeted strategies to mitigate their effects. Our investigation centres on a case study within the Indian pharmaceutical industry, where inventory status and production capacity emerge as pivotal bottlenecks within the system. Through this research, we offer a unique roadmap for industry practitioners, providing insights that can guide efforts to not only address the immediate challenges posed by demand-supply imbalances but also fortify the pharmaceutical production landscape against future disruptions, particularly in the context of pandemics. By synthesizing the principles of TOC and SS, our study aims to contribute valuable perspectives and strategies to enhance the industry's resilience and responsiveness.

The rest of the paper is garnished as follows: Section 2 proposes research framework, Section 3 validates the proposed model through a real-world supply chain disruption problem, Section-4 draws conclusion by discussing important issues and portraying further research avenues.

LITERATURE REVIEW

Pharmaceutical Supply Chain Management

The management of PSC is a vital aspect of the healthcare sector, encompassing the planning, execution and oversight of processes related to the manufacturing, distribution and overall management of pharmaceutical products.[19] Ensuring the timely production and distribution of life-saving medications, particularly during public health emergencies, relies heavily on efficient PSC Management (PSCM). Scholars like Vyas *et al.*,[23] and Yoo *et al.*,[24] have thoroughly examined the intricacies of PSC, underscoring the importance of adaptability and agility in addressing dynamic demands. The primary objective is to guarantee the prompt and effective delivery of safe medications to patients, upholding product quality and compliance with regulatory standards.[18] This intricate supply chain engages various stakeholders, including manufacturers, wholesalers, distributors, pharmacies and healthcare providers.[19] Key elements of PSCM involve the procurement of raw materials, manufacturing, packaging, distribution and inventory management.[14] Successful supply chain management within the pharmaceutical industry is essential for averting drug shortages, maintaining product integrity and responding to shifts in demand. Challenges in PSCM encompass regulatory adherence, quality control, traceability and the necessity to adapt to global market dynamics.[23] The industry is progressively embracing technology, such as blockchain,[25] Industry 4.0,[26] and data analytics,[27] to enhance transparency and traceability across the supply chain. As the industry undergoes continual evolution, PSCM remains a pivotal factor in ensuring timely and dependable access to essential medications for patients worldwide.

Previous Pandemics and Pharmaceutical Response

Previous pandemics throughout history have significantly influenced the evolution of pharmaceutical response strategies.[28-30] These global health crises have spurred research progression in medical domain,[31] vaccine development,[32] and public health practices.[33] The global response to previous pandemics offers valuable insights into the challenges faced by the pharmaceutical industry during health emergencies. Studies by Abay *et al.*,[28] and Samhale *et al.*,[29] have examined the industry's response strategies, emphasizing the importance of preparedness and adaptive manufacturing capabilities. Here's a brief overview of some notable pandemics and the corresponding pharmaceutical responses:

HIV/AIDS Pandemic: The HIV/AIDS pandemic emerged in the late 20th century and posed a substantial public health challenge.[34] Pharmaceutical companies played a pivotal role in developing antiretroviral drugs to manage HIV infections. The response highlighted the importance of ongoing research, public awareness and access to medications for global health crises.

H1N1 Influenza Pandemic (2009): The H1N1 pandemic prompted a rapid response in vaccine development.[35] Pharmaceutical companies collaborated with health authorities to produce and distribute vaccines globally. The pandemic emphasized the importance of timely vaccine production and distribution capabilities.

Ebola Outbreaks: Ebola outbreaks in Africa underscored the need for antiviral treatments and vaccines.[36] Pharmaceutical companies engaged in research and development efforts to create vaccines and experimental treatments. The outbreaks highlighted the challenges of addressing infectious diseases in resource-limited settings.

1918 Influenza Pandemic (Spanish Flu): The Spanish Flu pandemic was one of the deadliest in history.[37] Limited pharmaceutical interventions were available at the time. Vaccines were not developed and treatments were mostly supportive care. The pandemic highlighted the need for global cooperation in disease surveillance and response.

In each of these instances, lessons learned from previous pandemics influenced strategies for vaccine development, distribution and global collaboration. Collaborations, public-private partnerships and regulatory flexibility were key elements in the rapid response to the pandemic. The need for effective treatments, preventive measures and global cooperation has been a consistent theme. Advances in vaccine technologies, antiviral medications and pandemic preparedness have been critical outcomes of the pharmaceutical industry's responses to historical pandemics. These experiences continue to shape the industry's approach to emerging infectious diseases and public health challenges.

Pharmaceutical Industry's Response to COVID-19

The COVID-19 pandemic underscored the importance of a resilient PSC, prompting a re-evaluation of strategies to enhance flexibility, reduce lead times and improve collaboration among stakeholders. The onset of the COVID-19 pandemic catalysed research exploring the industry's response to sudden and unprecedented demand for specific medications. Works by Kochakkashani *et al.*,[38] and Lim *et al.*,[39] have examined case studies, illustrating the challenges faced by pharmaceutical companies in managing production and supply chains during such crises. The pharmaceutical industry played a pivotal role in responding to the COVID-19 pandemic,[32] demonstrating agility, innovation and collaboration to address the global health crisis.[33] Several key aspects highlight the industry's response:

Therapeutic Research: In addition to vaccines, the industry focused on researching and developing therapeutics to treat COVID-19 patients. Antiviral drugs, monoclonal antibodies and other treatments were explored to mitigate the severity of the illness.[29]

Supply Chain Resilience: The industry faced challenges in the supply chain, including disruptions to the production and distribution of medications. Efforts were made to enhance supply chain resilience, ensure the availability of essential medicines and address shortages caused by increased demand.[40]

Collaboration and Partnerships: Pharmaceutical companies collaborated with governments, research institutions and other industry partners to accelerate research, share data and increase manufacturing capacity. Public-private partnerships played a crucial role in scaling up vaccine production and distribution.[28]

Global Access Initiatives: Recognizing the need for global access to vaccines, several pharmaceutical companies committed to equitable distribution. Initiatives such as COVAX aimed to ensure that vaccines reached populations worldwide,[32] including those in low-income countries.[30]

Regulatory Flexibility: Regulatory agencies worked closely with pharmaceutical companies to expedite the review and approval processes for COVID-19-related drugs and vaccines. Emergency use authorizations were granted to speed up the availability of critical medical interventions.[41]

Investment in Research and Development: The pandemic underscored the importance of ongoing investment in research and development. Lessons learned from COVID-19 are likely to influence future approaches to vaccine and drug development, as well as strategies for managing global health emergencies.[42]

Vaccine Development: Pharmaceutical companies engaged in an unprecedented race to develop and distribute COVID-19 vaccines. Multiple vaccines were developed and authorized for emergency use in record time, utilizing various technologies such as mRNA and viral vector platforms.[32]

The pharmaceutical industry's response to COVID-19 showcased the sector's capacity for rapid innovation, collaboration and commitment to addressing global health challenges. The experiences gained during this crisis are likely to shape the industry's approach to future pandemics and healthcare emergencies.

Hydroxychloroquine Crisis and Demand-Supply Imbalances

HCQ attracted substantial attention and stirred controversy in the initial phases of the COVID-19 pandemic.[17] Recognized as an established antimalarial medication,[16] HCQ was investigated as a possible treatment for COVID-19.[18] The early period of the pandemic saw an unparalleled increase in the demand for HCQ, revealing weaknesses in PSC. Research by Meeus *et al.*,[43] and Tripathy *et al.*,[44] delves into the HCQ crisis, documenting the challenges faced by pharmaceutical companies in meeting the sudden and overwhelming demand,[18,19] thus setting the stage for our exploration of production bottlenecks. The crisis surrounding HCQ highlighted the complexities of managing drug availability during a global health emergency.

Demand Surge

In the early months of the pandemic, there were speculative claims about the potential effectiveness of HCQ in treating COVID-19. This led to a surge in demand as governments and healthcare providers sought to stockpile the drug as a potential treatment option.

Global Interest

The interest in HCQ was fueled by high-profile endorsements, including political Figures and media attention, contributing to a global demand spike.[45]

Supply Chain Challenges

Raw Material Shortages: HCQ is produced using raw materials and shortages in the supply chain for these materials further compounded the problem. Countries that were major suppliers of raw materials faced disruptions due to lockdowns and other pandemic-related factors.

Production Capacity: The sudden surge in demand for HCQ overwhelmed the existing production capacity. Pharmaceutical manufacturers faced challenges in scaling up production quickly to meet the increased requirements.

Export Restrictions: Some countries-imposed export restrictions on HCQ and its precursor materials to ensure an adequate domestic supply. This led to concerns about global availability, especially for regions heavily dependent on imports.

Regulatory Challenges: Regulatory agencies faced challenges in managing the increased demand for HCQ while ensuring safety, quality and appropriate use. This resulted in changes in regulations, emergency use authorizations and increased scrutiny of HCQ prescriptions.[46]

Global Cooperation and Controversies

The effectiveness of HCQ in treating COVID-19 became a subject of controversy, with conflicting studies and recommendations. This added complexity to the crisis, as decisions on stockpiling and distribution were influenced by evolving scientific understanding.[47]

The HCQ crisis underscored the need for international collaboration in managing the supply chain for critical medications during a pandemic. Discussions and negotiations between countries were initiated to address imbalances and ensure equitable access.

The HCQ crisis during the COVID-19 pandemic highlighted the delicate balance between public health needs, global supply chain dynamics,[48] and the importance of evidence-based

decision-making. It underscored the necessity of transparent communication,[49] international collaboration,[50] and robust supply chain management to navigate such challenges effectively.[51] The experience with HCQ has prompted discussions on improving preparedness for future health crises and ensuring a more resilient PSC.

Theory of Constraints in Manufacturing sector

The TOC, introduced by Goldratt,[52] has proven valuable in optimizing production processes in various industries. In the context of manufacturing supply chains, TOC was applied to identify and alleviate constraints that impede production efficiency.[53] Studies by previous authors illustrated the successful application of TOC principles in various industrial settings, providing a foundation for our integrated approach.[52-54] In the context of pharmaceutical manufacturing, the application of TOC can lead to enhanced efficiency, resource utilization and overall productivity. By applying the TOC in pharmaceutical manufacturing, companies can streamline their processes, reduce lead times and enhance the reliability of product delivery. This approach aligns well with the industry's need for precision, quality control and compliance with regulatory standards, contributing to improved overall performance and competitiveness. Despite the considerable potential for applying the TOC in PSC, no research has been conducted thus far to address production bottlenecks in the pharmaceutical sector through the utilization of TOC.

Six Sigma in Pharmaceutical Quality Management

SS is a data-driven methodology widely adopted in various industries, including the pharmaceutical sector, to enhance quality management, reduce defects and improve overall operational efficiency.[22] SS methodologies have gained prominence in pharmaceutical quality management, aiming to minimize defects and variations in production processes. Previous researchers highlighted the effectiveness of SS in enhancing the quality and reliability of pharmaceutical manufacturing.[55,56] In summary, SS offers a robust framework for pharmaceutical companies to systematically improve the quality of their products, enhance operational efficiency and meet regulatory standards.[57-59] The application of SS principles in pharmaceutical quality management contributes to the industry's commitment to delivering safe and effective medications to patients.

Research Gaps

The extensive literature reveals the following research gaps:

Despite the recognized significance of the TOC in optimizing production processes, there might be a research gap in its application within the pharmaceutical industry, particularly in the context of pandemic preparedness and response.

While SS method is widely employed for process improvement, there may be a research gap in the literature regarding their integration with TOC, specifically in the pharmaceutical sector's response to pandemics.

Existing studies may not provide a comprehensive framework that combines TOC and SS to address production bottlenecks specifically arising from pandemic scenarios in the pharmaceutical industry.

Many studies might focus on specific cases or industries without providing generalizable approaches. This research could fill a gap by offering a more widely applicable methodology for identifying and mitigating production bottlenecks in PSC during pandemics.

The literature might lack in-depth investigations into methodologies specifically designed for alleviating production bottlenecks in the pharmaceutical industry during pandemics, emphasizing the novelty of this research.

Previous studies may have focused more on immediate responses to pandemics rather than proposing strategies for long-term preparedness and sustained production efficiency in the pharmaceutical sector.

Collectively, the literature reveals a rich tapestry of research on PSC, production optimization, pandemic response and integrated methodologies. The literature might not sufficiently explore the global dynamics of PSC during pandemics, potentially overlooking the interconnectedness and dependencies that can exacerbate production bottlenecks. Our study builds upon this foundation, synthesizing insights to develop a targeted approach for identifying and mitigating production bottlenecks, with a focus on enhancing pandemic preparedness in the pharmaceutical industry. The literature surveyed underscores the urgency of fortifying PSC for effective pandemic preparedness. The integration of TOC and SS methodologies presents a promising avenue for identifying and mitigating production bottlenecks, as highlighted in both theoretical frameworks and practical industry applications. However, our study uniquely applies this integrated approach to the specific context of pandemic-induced demand shocks. Our integration of TOC and SS draws inspiration from previous works to address constraints and optimize pharmaceutical production processes.

MATERIALS AND METHODS

This section proposes a constraints-based approach to solve a real-life supply chain disruption problem and explore the necessary strategies to mitigate it. The study proposes an integrated TOC-SS approach. The methods are explained below:

Theory of Constraints (TOC)

The TOC, introduced by Eliyahu M. Goldratt in his book "The Goal," serves as a management philosophy and methodology. Its objective is to enhance organizational performance by pinpointing and managing constraints or bottlenecks that hinder

the achievement of goals. TOC employs a logical approach to identify the weakest link or limiting factor (constraint) that obstructs goal attainment. The methodology then focuses on improving constraints in a hierarchical manner until they no longer impede progress, thereby increasing an organization's throughput. In various operations, a constraint is often referred to as a 'bottleneck.' TOC fundamentally asserts that any system must possess at least one constraint that impedes the system from reaching its desired goal. It also suggests that the existence of constraints in a system presents an opportunity for further improvement. This methodology finds application across diverse industries, including manufacturing, services and project management, with the overarching goal of enhancing efficiency and productivity. The primary steps of the TOC are often referred to by the acronym "POOGI," representing the five focusing steps as shown in Figure 1.

Identify the Constraint (P-Identify the Problem): The 1st step involves recognizing the limiting factor or bottleneck that restricts the overall system's performance. This could be a resource, a process, or any element that hinders the organization from achieving its goals.

Exploit the Constraint (O-Optimize the System): After identifying the constraint, the organization concentrates on optimizing the utilization of the constraint. This entails ensuring that the bottleneck resource is fully used to its maximum capacity without interruptions or downtime. The goal is to extract the utmost efficiency from the constrained resource to enhance overall system performance.

Subordinate Everything Else to the Constraint (O-Optimize the System): The next step is to align and synchronize all other processes in the organization to support and enhance the performance of the identified constraint. Non-bottleneck processes are subordinated to the constraints to prevent them from causing disruptions.

Elevate the Constraint (G-Goal of the System): If the exploitation and subordination steps do not lead to the desired improvement, the organization considers investing in additional resources or upgrading the capacity of the constraint. This step involves removing or elevating the constraint to a higher level of performance.

Repeat the Process (I-Iterate): The final step in TOC is a continuous improvement cycle. After addressing one constraint, the organization goes back to the beginning and repeats the process, identifying the next constraint in the system. TOC is an iterative methodology and improvements are made incrementally.

Additionally, TOC recommends the use of buffers to manage variations and uncertainties in the manufacturing process. This could involve maintaining inventory buffers to accommodate fluctuations in demand, supply chain disruptions, or variations

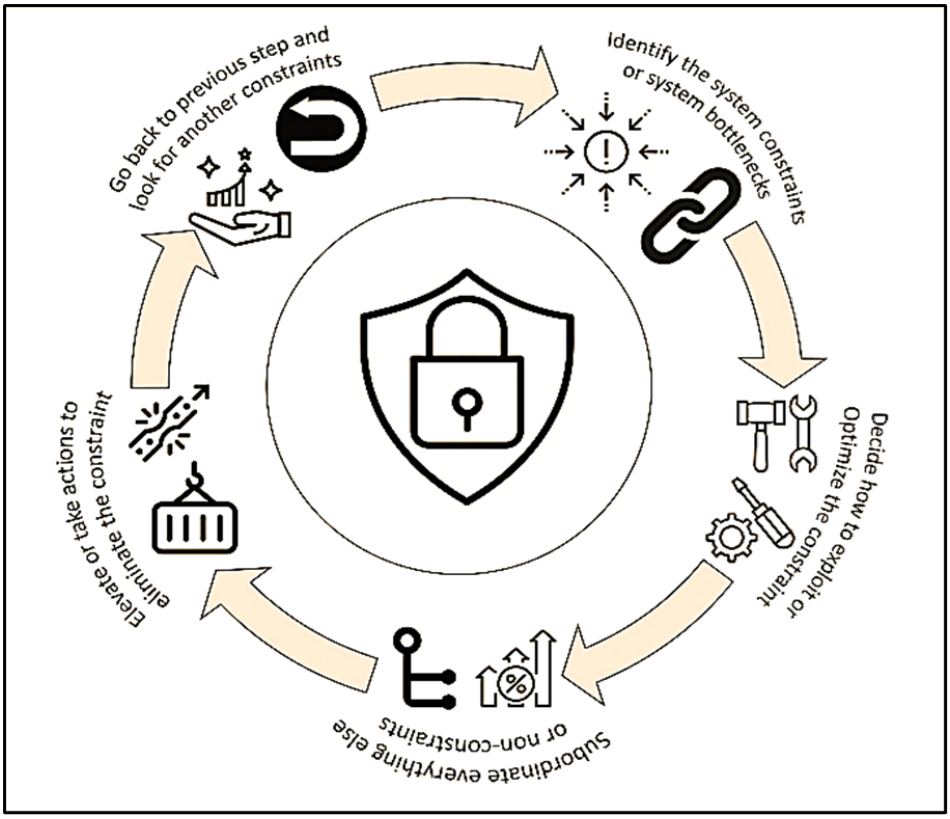

Figure 1: Five focusing steps of TOC.[60]

in production rates. TOC also advocates for the use of specific performance metrics, such as throughput and inventory turn, to measure the effectiveness of the manufacturing process. These metrics help assess how well the organization is optimizing its constraints and improving overall efficiency.

Six Sigma

It represents a data-driven statistical approach aimed at eradicating defects within products, processes, or services. Additionally, it functions as a continuous improvement methodology. Bill Smith initially introduced it in 1980 at Motorola.[22] The term "Sigma" denotes standard deviation, a measure of variation in a data set. In the context of SS, the process mean is positioned six standard deviations away from the nearest specification limit. Achieving SS accuracy implies a mere 3.4 defects per million products. Two predominant methodologies in SS are DMAIC and DMADV.

DMAIC, an acronym for Define, Measure, Analyze, Improve and Control, represents a structured approach with five phases for process improvement (Figure 2).

Define: The Define phase involves clearly outlining the goals and objectives related to quality management. This includes specifying critical quality parameters, regulatory requirements and customer expectations for industrial products.

Measure: SS places a strong emphasis on data-driven decision-making. During the Measure phase, manufacturing companies employ statistical tools to precisely quantify the existing quality state within their processes. This entails the collection and analysis of pertinent data to pinpoint areas that require improvement. The goal is to have a comprehensive understanding of the current quality performance, allowing for informed decisions and targeted improvements in subsequent phases of the SS methodology.

Analyze: The Analyze phase entails a meticulous examination of data to uncover the root causes of defects or variations in manufacturing processes. This step is pivotal in comprehending the factors that contribute to quality issues and deviations from established standards. By identifying the underlying causes, organizations can develop targeted strategies to address and rectify the issues, ultimately improving the overall quality and efficiency of their processes.

Improve: Building upon the analysis conducted in the previous phases, the Improve phase is dedicated to implementing solutions that address the identified root causes. This stage may encompass various interventions such as process modifications, technology upgrades, or alterations in operating procedures. The primary objective is to enact changes that enhance the overall quality of products and contribute to the elimination or reduction of defects in the manufacturing processes. Through targeted improvements, organizations aim to optimize their operations and deliver products that meet or exceed established quality standards.

Control: In the Control phase, the focus shifts to establishing controls and monitoring mechanisms to ensure the sustainability of the improvements implemented during the Improve phase. This involves setting up quality control measures, implementing standard operating procedures and continuously monitoring key performance indicators. The goal is to create a structured framework that prevents the recurrence of previous issues and ensures that the enhanced processes consistently meet the desired quality standards over time. Through diligent control and monitoring, organizations strive to maintain the gains achieved

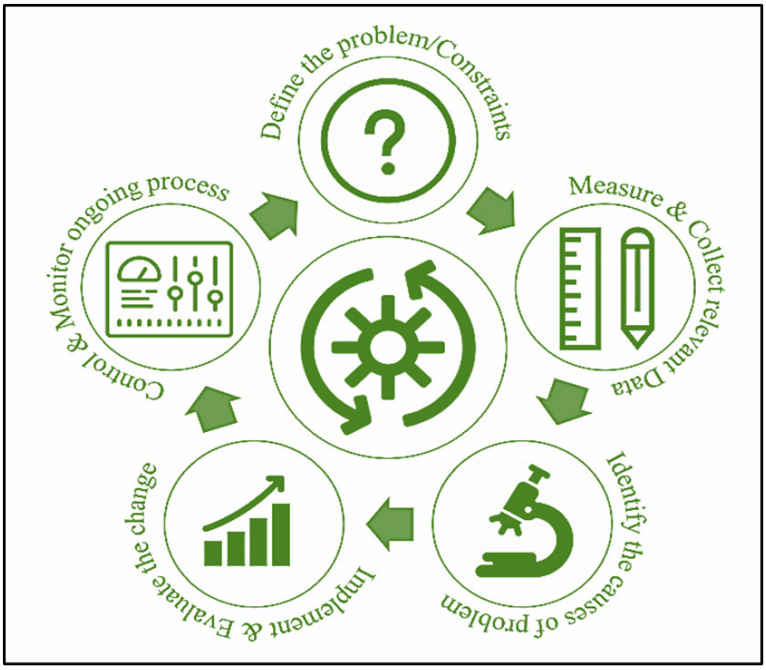

Figure 2: DMAIC methodology.[60]

during the SS improvement process and foster a culture of continuous quality excellence.

Additionally, SS aligns with the pharmaceutical industry's emphasis on regulatory compliance. By systematically improving processes and reducing variability, companies can enhance their ability to meet and exceed regulatory requirements, ensuring the safety and efficacy of products. Also, SS fosters a culture of continuous improvement within manufacturing organizations. It encourages teams to regularly assess and refine processes, driving a commitment to excellence in quality management.

Integrated TOC-SS methodology

The integration of the TOC and SS represents a powerful approach to process improvement, combining the strengths of both methodologies to achieve more comprehensive and sustainable results. Each methodology brings unique principles and tools to the table and their integration aims to address constraints, reduce variation and enhance overall system performance. The integration of TOC and SS recognizes the complementary nature of these methodologies. While TOC focuses on identifying and managing constraints that limit system performance, SS aims to reduce variation and improve process capability. The integration addresses both the capacity limitations identified by TOC and the variation issues targeted by SS, resulting in a more comprehensive approach to process improvement. By integrating these approaches, organizations can create a more holistic strategy for continuous improvement. The integration leverages data-driven decision-making from both methodologies, providing a robust foundation for informed and effective improvements. By aligning improvement efforts with constraints, organizations can optimize the use of limited resources, enhancing overall efficiency. Four focusing steps of the integrated methodology is as follows:

Identifying Constraints with TOC: TOC's Five Focusing Steps (POOGI) helps identify and address constraints systematically. The integration begins by applying TOC principles to identify and exploit constraints in the process.

Reducing Variation with SS: The DMAIC methodology is used to analyze and improve processes by reducing defects and minimizing variation. Statistical tools and techniques from SS are employed to enhance the stability and predictability of the process.

Alignment of Improvement Efforts: TOC emphasizes subordinating non-constraints to the constraints, ensuring that all improvement efforts align with the goal of optimizing the constrained resources. SS tools, such as control charts and process capability analysis, help monitor and maintain the gains achieved during the improvement process.

Continuous Improvement Loop: The integration encourages a continuous improvement loop where organizations repeatedly identify constraints, apply SS tools to reduce variation and optimize the overall system performance.

Figure 3 delineates the proposed research framework, which integrates TOC and SS approach. Initially, the most vulnerable parameter of the system is identified which put back the system form achieving its desirable objectives. SS yields relatively more throughput out of the constraint in order to eliminate variations. So, the first step identifies and defines the system bottlenecks. Secondly, the TOC method exploits the system constraints

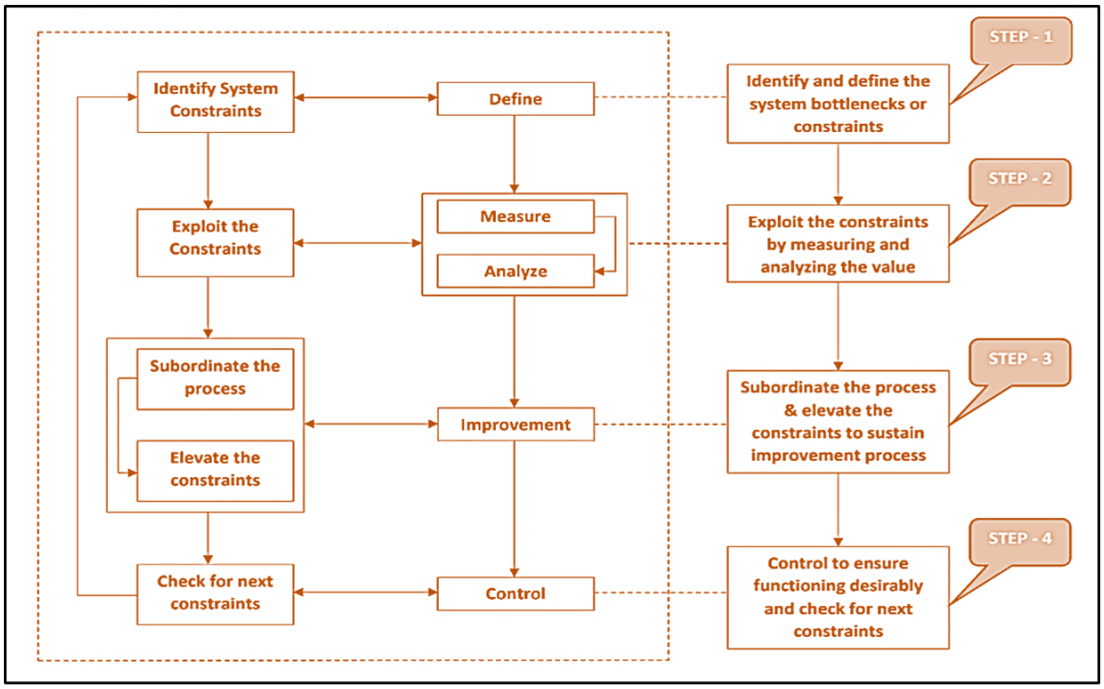

Figure 3: Integrated thinking process.

while SS facilitates this by measuring the values quantitatively and analysing this successively. "Analyze" step of SS helps in identifying the sources of variations. Root cause of the problem is identified using thinking tool-Current Reality Tree (CRT). In the next step, TOC philosophy subordinates the process under consideration. Necessary actions are taken to elevate the constraints to sustain the improvement process. This step ensures all preventive measures to elevate the constraints, are taken previously are implemented in the system successfully.

Finally, the system is controlled and monitored to ensure the methodology is functioning desirably. Thus, the pursuit of precision should be continued by following the initial step of TOC again, to explore new constraints in order to avoid inertia from the system.

A REAL-WORLD APPLICATION

This case study delves into the specific challenges faced by Indian pharmaceutical industry and the application of a TOC-SS integrated approach to alleviate its production bottlenecks. The following stanzas depicts a real-world application.

Motivation behind the case study

At the early and mid-pandemic period, there was no remedy for COVID-19.[4] Various laboratories worked tremendously towards the development of vaccines and drugs to cure this disease. Several studies found that HCQ performed well in preventing the severity of the infection to some extent and it was quite able to fight against COVID-19.[17] Therefore, HCQ was being used as a temporary cure for COVID-19.[18] Hence, the global demand for HCQ went on increasing enormously. Unfortunately, this medicine was produced only in a few countries like India. And the capacity of the existing HCQ manufacturers was still not sufficient to meet the large-scaled global demand. India manufactured 70% of the world's total supply of HCQ.[61] India tried to meet its domestic demand, in addition to that, it shipped this medicine to COVID-19 affected neighbouring countries.[62] Drug manufacturers faced many kinds of constraints due to ramping up their production on an emergency basis.[63] The surge in demand for essential medications, exacerbated by panic-driven consumer behaviour and healthcare provider prescriptions, exposed critical bottlenecks within the production system.[18] To tackle these adversities, the proposed framework in this research could be applied in this case to identify the possible constraints, exploit and elevate it and ultimately find a contingent way of improvement.

Industry Background

The Indian Pharmaceutical Industry boasts a rich and dynamic background, marked by significant growth and advancements. Recognized globally for its robust infrastructure and diverse capabilities, the sector has evolved into one of the key players in the international pharmaceutical landscape. With a focus on research and development, India has become a hub for the production of generic medicines, contributing substantially to global healthcare accessibility. The industry's journey has been characterized by innovation, strategic collaborations and adherence to stringent quality standards. As a vital contributor to the country's economy, the Indian Pharmaceutical Industry continues to play a pivotal role in addressing healthcare needs, both domestically and on the global stage. According to estimates, the pharmaceutical industry presently provides employment for approximately 550,000 to 570,000 individuals.[64] This rise can be credited to GoI initiatives. As per the 2021 annual report, the pharmaceutical sector in India made up 1.72% of the nation's GDP.[65] In the same year, the Indian pharmaceutical industry was projected to generate a domestic revenue of approximately 42 billion dollars and is estimated to reach $130 billion by 2030.[65] India holds the title of being the foremost contributor of generic medicines worldwide in terms of quantity, representing a 20% portion of the overall global pharmaceutical exports.[66] Additionally, it stands as the primary global supplier of vaccines based on volume, responsible for over 60% of the total vaccines produced globally.[66]

The Indian pharmaceutical industry faced unprecedented challenges during the early stages of the COVID-19 pandemic.

Detail about the case organization

XYZ Pharma, a prominent player in the Indian pharmaceutical landscape, stands as a stalwart in the production of generic medications. Renowned for its commitment to innovation, quality and affordability, XYZ Pharma has been a driving force in meeting the healthcare needs of a global clientele. Formerly recognized under a different name, the company rebranded as XYZ Pharma in adherence to its stringent privacy policies. As a leading pharmaceutical entity, XYZ Pharma has consistently demonstrated its prowess in developing and manufacturing a diverse range of pharmaceutical products, particularly specializing in generic medications. The company's commitment to quality is reflected in its adherence to stringent regulatory standards, ensuring that its products not only meet but exceed industry benchmarks. The onset of the COVID-19 pandemic brought about unprecedented challenges and XYZ Pharma found itself at the forefront, responding dynamically to the surge in demand for HCQ. The surge in demand highlighted two primary bottlenecks in their supply chain: inventory management and production capacity. The company struggled to maintain optimal inventory levels while simultaneously ramping up production to meet the escalating demand. This antimalarial drug, with its potential efficacy against COVID-19, became a focal point in global efforts to combat the pandemic. XYZ Pharma's swift response to this heightened demand underscores its adaptability and dedication to public health. Navigating through the complexities of an increased demand-supply imbalance, XYZ Pharma's

experience during this period serves as a compelling case study. The company's strategic decisions, operational challenges and innovative approaches in addressing the surge in HCQ demand provide a rich context for understanding the broader dynamics of PSCM, making XYZ Pharma an exemplary subject for in-depth analysis in the outlined research.

Formation of experts' committee

Given the compelling nature of this research, the formation of an expert committee became crucial to ensure the robustness and validity of the proposed approach. The expert committee consisted of 50 experienced professionals (with a 3:2 male and female ratios) from various domains such as PSCM, production processes and healthcare systems, offering diverse perspectives on the challenges posed by the COVID-19 pandemic. Engaging professionals with experience in TOC and SS methodologies, as well as individuals with a deep understanding of the pharmaceutical industry, contributed significantly to the credibility and effectiveness of this study. The expert committee's role encompassed advising on the selection of relevant case studies, validating the research methodology and providing critical insights into the identification of bottlenecks and proposed improvement strategies within the PSC. Their collective expertise not only enhanced the study's methodological rigor but also ensured that the proposed solutions aligned with industry best practices.

Identification of the bottlenecks in pharmaceutical supply chains

The identification of manufacturing bottlenecks within the PSC represents a critical endeavor, especially in the context of combating the challenges posed by the COVID-19 pandemic. Extant literature review coupled with insights garnered from expert consultations was instrumental in unveiling several key bottlenecks within this intricate system. The literature elucidated the emergence of demand-supply imbalances, particularly highlighted by the unprecedented surge in demand for medications like HCQ. This surge, triggered by panic buying and widespread prescriptions, exacerbated supply chain disruptions, showcasing the vulnerability of the pharmaceutical industry during crises. By synthesizing knowledge from scholarly articles, industry reports and case studies, the research aims to pinpoint recurring themes and common obstacles experienced by pharmaceutical manufacturers. Expert consultations have further accentuated the multifaceted nature of bottlenecks, emphasizing challenges in inventory management and production capacity as primary constraints. These insights, derived from seasoned professionals specializing in PSCM, production processes and healthcare systems, have corroborated the findings from existing literature while offering nuanced perspectives on the intricacies of these bottlenecks. The synergy between extant literature and expert consultations unveiled a comprehensive understanding of the manufacturing bottlenecks, emphasizing the urgent need to address inventory status and production capacity as pivotal areas requiring strategic intervention. This collaborative approach, amalgamating theoretical insights and practical expertise, serves as a cornerstone for devising effective strategies aimed at mitigating these bottlenecks and fortifying the resilience of the PSC against future disruptions.

Instrument development and data collection

In terms of data collection through questionnaires, it was prudent to design a survey instrument that captured the nuanced perspectives of professionals within the pharmaceutical industry. Questions were crafted in consultation with the expert committee to ensure relevance and depth, probing into areas such as challenges faced during the pandemic, the impact on production processes and the effectiveness of current methodologies in addressing bottlenecks. Additionally, the questionnaire sought insights into the perceived benefits and challenges of implementing TOC and SS strategies. A pilot testing phase with industry professionals further refined the questionnaire, enhancing its validity and reliability. Overall, the collaboration between the expert committee and the research team in crafting and implementing the questionnaire was integral to the success of this study.

Throughout the pandemic, significant focus was placed on government rules and limitations on travel. Experts were consulted through emails and phone conversations, while surveys and interviews were conducted using online meetings.

Stepwise application of the integrated TOC-SS framework

XYZ Pharma engaged in a comprehensive analysis of its supply chain using the TOC-SS integrated approach. The initial step involved identifying constraints within the system, focusing on inventory management and production capacity. Utilizing TOC principles, the company implemented measures to enhance real-time visibility into inventory levels, ensuring more accurate demand forecasting. Simultaneously, the SS methodology was employed to optimize the production processes. Process mapping and analysis revealed inefficiencies in the production line, leading to delays and increased lead times. By applying SS tools, such as DMAIC, XYZ Pharma addressed these inefficiencies, streamlining the production workflow and reducing cycle times. The implementation of the TOC-SS approach yielded significant improvements for XYZ Pharma. Real-time inventory visibility allowed for better demand anticipation, mitigating stockouts and overstock situations. Production processes were optimized, resulting in a more agile and responsive manufacturing system. The lead time for HCQ production was notably reduced, enabling XYZ Pharma to meet demand more efficiently. The stepwise application is shown below:

Step 1: Identify and define the system bottlenecks or constraints

The first and foremost procedure of the integrated approach was to identify the constraints that hindered the production operations. Numerous studies indicated that HCQ exhibited potent antiviral effects against the coronavirus disease. The US Food and Drug Administration had designated HCQ as a potential treatment for COVID-19,[67] and it was undergoing testing on numerous patients. At that time, there was no specific remedy for COVID-19, making HCQ the sole option for patients due to its effectiveness against the virus. Consequently, the demand for HCQ steadily increased in various countries. However, there was insufficient HCQ supply to meet the growing demand because it was only produced in a handful of countries worldwide. Moreover, Indian drug manufacturers had encountered procurement challenges. The president of the Pharmaceutical Manufacturer Association revealed,[68] "As the global demand for HCQ tablets continued to rise, small pharmaceutical manufacturers had ceased production due to a sharp increase in the cost of raw materials. The raw materials, which previously cost ₹9000 per kg, were being sold at ₹55000-75000 per kg because of the excessively high demand and relatively low supply in the market". He further explained, "The maximum selling price of the drug was regulated and it could only be sold at Rs. 5.61.[68] Therefore, it was not feasible for small companies in the MSME sector to manufacture it, as the manufacturing cost exceeded the MRP".

India emerged as a key global manufacturer of the anti-malarial drug, contributing to 70% of the worldwide supply of HCQ. The Indian Council of Medical Research (ICMR),[69] functioning under the Ministry of Health and Family Welfare, GoI, recommended HCQ for chemoprophylaxis in COVID-19 patients. The prescribed dosage involved 400 mg twice on day 1, followed by 400 mg once a week.[19] This recommendation was extended to asymptomatic healthcare workers treating suspected or confirmed COVID-19 cases, as well as asymptomatic household contacts of confirmed cases, as part of the collective efforts to combat the COVID-19 pandemic.

Considering the prevailing infection trends among the public and the affected patients in various states and union territories of India, the following issues warranted attention:

Inventory status of HCQ in India.

Production capacity of all the Indian Pharmaceutical Companies.

Uniform distribution and delivery of HCQ so that patients can access medicine easily across various regions in the country.

Step 2: Exploit the constraints by measuring and analysing the value

To leverage the constraint effectively, either a push system or a pull system could have been employed, contingent on the inventory status, production capacity and delivery of HCQ, among other factors. As per available sources, India was maintaining a substantial stock of HCQ and was proactively taking measures to prevent any shortages in the domestic market. Major HCQ producers in India had affirmed that the country possessed an ample supply to meet demand. The National Pharmaceutical Pricing Authority (NPPA) corroborated this, stating that HCQ stocks in India were sufficient.[70] Ongoing monitoring of demand, availability and production was in place, with necessary actions being implemented to avert any potential shortage of the drug in the foreseeable past.Top of Form CRT, stands as one of the five Thinking Process (TP) tools, alongside Evaporating Cloud, Future Reality Tree, Prerequisite Tree and Transition Tree. The primary function of CRT is to systematically trace all Undesirable Effects (UDE) linked to the root cause, ultimately revealing core conflicts within a system. The process commences with the identification of UDEs within the system. To pinpoint elements requiring modification, reliance is placed on cause-effect relationships. CRT visualizes interrelations and links between undesirable effects, concentrating on negative outcomes and barriers preventing the system from attaining its objectives. Typically, critical root causes are positioned at the diagram's base, while top sections progressively articulate principal conflicts, culminating in the constraint.

A CRT (Figure 4) comprises entities presented in round-cornered boxes, providing concise descriptions of present-tense facts. Entities may serve as causes, consequences, or both. Arrows connect entities, with the base indicating an 'if' and the tip signifying a 'then' relationship. When reading the CRT from top to bottom, linked entities can be interpreted as follows: 'Entity B (arrow pointing to it) exists because of Entity A (arrow starting from it).' If two or more arrows point to an entity, the entities at the arrow's base suggest possible causes. When arrows are enclosed by a circle or ellipse, it signifies a logical 'AND' relationship, indicating that all possible causes must be present for the effect to occur.

In this case study, the identified constraints included production capacity, inventory status and the availability of HCQ. The root causes behind the insufficient production of HCQ were multifaceted. Firstly, HCQ was produced in only a limited number of countries, with India being a significant producer. However, the number of pharmaceutical companies manufacturing this medicine was relatively low and their production capacity was insufficient to meet the increasing global demand for HCQ. The surging demand for HCQ was attributed to its perceived effectiveness in mitigating the severity of COVID-19, as suggested by some clinical trials. Given the absence of a definitive cure for COVID-19 and the limited success of HCQ in preventing the disease, health organizations and medical consultants recommended its use in the treatment of COVID-19. This high demand, coupled with the inadequate production

of HCQ, resulted in a significant demand-supply imbalance and conflict. Additionally, various lockdown measures, such as export-import bans and logistics restrictions, disrupted the supply chain of essential commodities, including food products and medicines. This disruption further compounded the issue, leading to an insufficient supply of medicines in retail shops. Individuals relying on emergency medicines, such as a person from the north-eastern state of India with hypertension, faced challenges in obtaining their required medications due to supply chain disruptions. The case highlighted a real-life scenario where a person, dependent on daily medication, was unable to access the required medicine due to supply chain failures. The fear and uncertainty surrounding the availability of essential medicines underlined the critical importance of maintaining a robust and uninterrupted supply chain for pharmaceuticals. It emphasized the need for preventive measures, including Injections (INJ), to address supply chain disruptions systematically. To address these challenges, the Ministry of Health and Family Welfare had reportedly placed a substantial order for around 10 crore tablets of HCQ,[70] reflecting the government's recognition of the urgency and significance of maintaining an adequate supply of this essential medication.

Step 3: Subordinate the process and elevate the constraints to sustain improvement process

The third step in the process was to subordinate all other activities related to the constraints and traditional metrics had to be adapted to ensure that all activities supported decisions aimed at exploiting these constraints. In the context of this case, India possessed an annual installed capacity to produce 40 metric tons of Active Pharmaceutical Ingredients (API) of HCQ. This capacity allowed leading pharmaceutical companies to manufacture approximately 200 million tablets of 200 mg and there was potential to increase this production capacity.[70] Pharmaceutical companies in India were actively working towards boosting the production capacity of HCQ by five times, aiming for 70 metric tons per month.[70] This expanded capacity would enable these companies to produce 35 crore tablets every month. The GoI had strategized to maintain a stock of 10 crore tablets for domestic requirements, with the remainder planned for export to neighboring countries.[71] The then chairman of Zydus Cadila had reported a tenfold increase in the processing capacity for manufacturing HCQ, reaching 30 metric tons (15 crore tablets of 200 mg) per month.[72] The company was actively assisting the government in creating a stockpile of 10 crore dosages of the drug.[72]

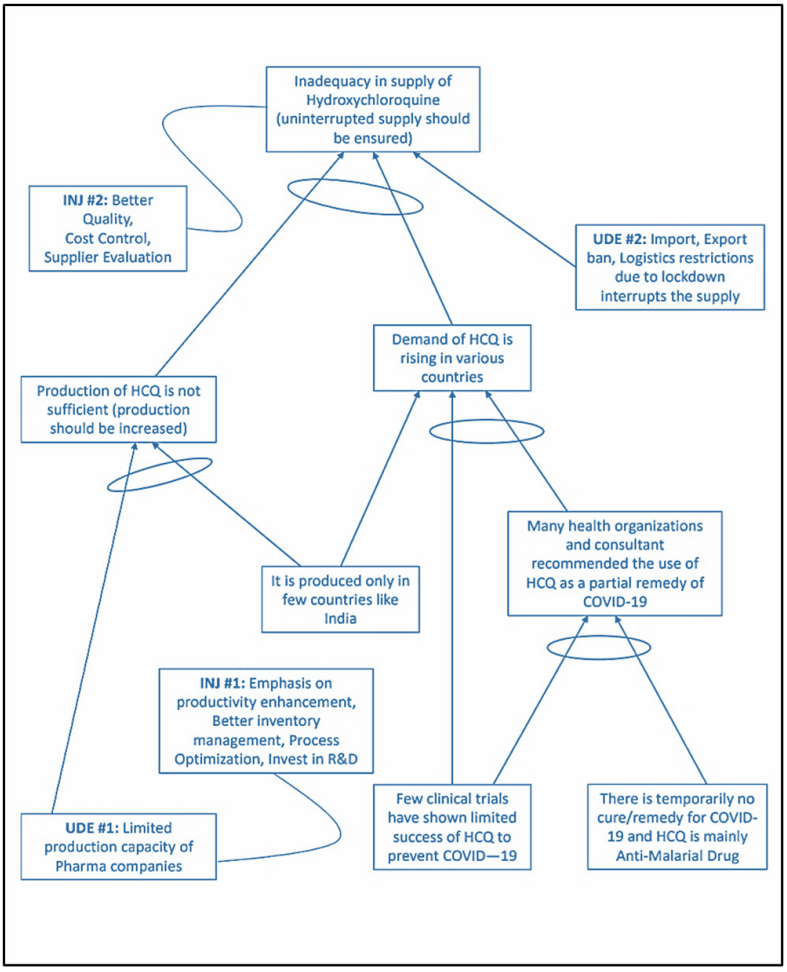

Figure 4: CRT Diagram.

India had become a key global supplier of HCQ, with shipments to 55 countries, including the United States, Brazil, Germany, Nepal, Bhutan, Afghanistan, Bangladesh, Maldives, Mauritius and the Dominican Republic. India was already supplying tablets to Russia, South Africa, UAE, Uruguay, Colombia, Ecuador, Jamaica, Peru, France, Jordan, Kenya, Nigeria, Oman, and others. In the second consignment, the United States had requested 48 lakh tablets of HCQ and India had approved 35.82 lakhs tablets.[71] India was set to export 285 million tablets of HCQ to other countries on a commercial basis.[71] Additionally, around 500 million paracetamol tablets were to be sent to 60 countries, with 1.32 million tablets being donated for free.[70] This substantial contribution showcased India's role in the global effort to combat the COVID-19 pandemic.Top of Form To enhance the capacity of constraints, manufacturers could have elevated their production capabilities through process reengineering. In the context of pharmaceutical companies producing HCQ, it was essential for them to focus on various aspects such as productivity enhancement,[73] improved inventory management,[74] process optimization,[75] and increased investment in Research and Development (R&D)[76] to augment production capacity.[77] Notably, many small pharmaceutical companies had halted production due to the sharp increase in raw material prices and low market supply. To address this, drug controllers from various states had petitioned the GoI to ensure the availability and supply of raw materials, assuring that production would resume promptly once raw materials were secured. The GoI responded affirmatively to the issue, assuring the availability of raw materials. Zydus Cadila and IPCA Laboratories emerged as the prominent HCQ manufacturers in the country among pharmaceutical companies.[70] While Intas Pharmaceuticals, McW Healthcare of Indore, Macleods Pharmaceuticals, Cipla and Lupin were also capable of manufacturing the drug,[71] only Zydus and IPCA possessed backward-integrated production capacity. This meant they could convert crucial raw materials into intermediates and, ultimately, into Active Pharmaceutical Ingredients (APIs), forming the final formulations. This intricate process involved approximately 12-15 steps. Other manufacturers relied on API suppliers, including Abbott India, Rusan Pharma, Mangalam Drugs, Unichem Remedies, Laurus Labs and Vijayasri Organics.[69] As China gradually returned to normalcy, the procurement of raw materials for HCQ production was expected to become less challenging. This highlighted the critical importance of a stable supply chain and collaborative efforts to ensure the availability of essential pharmaceuticals during a global health crisis.

The CRD (Figure 5), also known as the Evaporating Cloud, is a component of the TOC and serves as one of the five TP tools. It operates as a logical diagram specifically designed to address problems that lack an apparent solution. The CRD is particularly useful in handling dilemmas or conflicting situations where finding an acceptable solution poses a challenge. This diagram encapsulates a shared objective that precedes two or more conditions, all of which are vying to fulfil the overarching goal. The Evaporating Cloud provides a structured approach to analyse and resolve conflicts by identifying core issues and constraints in complex situations. In this scenario, a central conflict impacting the efficient supply and distribution of medicine within the supply chain performance revolved around the trade-off between ensuring patient access to medicine at a low cost and mitigating the risk of deterioration in perishable drug compositions. Simultaneously, there was a need to enhance productivity to ensure continuous sales and reduce the high risk of supply disruption. Efficient supply and distribution across nations necessitated easy patient access to medicine and effective pricing strategies. Additionally, minimizing waste was crucial for productivity improvement. To achieve this, the risk of deterioration in perishable drug compositions had to be minimized, requiring the maintenance of relatively low inventory levels. The TOC analysed the interplay between supply and demand in inventory management, with a particular focus on the supply side. While instant responsiveness to demand would eliminate the need for reliance on forecasts, in this case, maintaining the right amount of inventory in the supply chain was crucial for better availability of items at the consumption end. Despite the potential risks

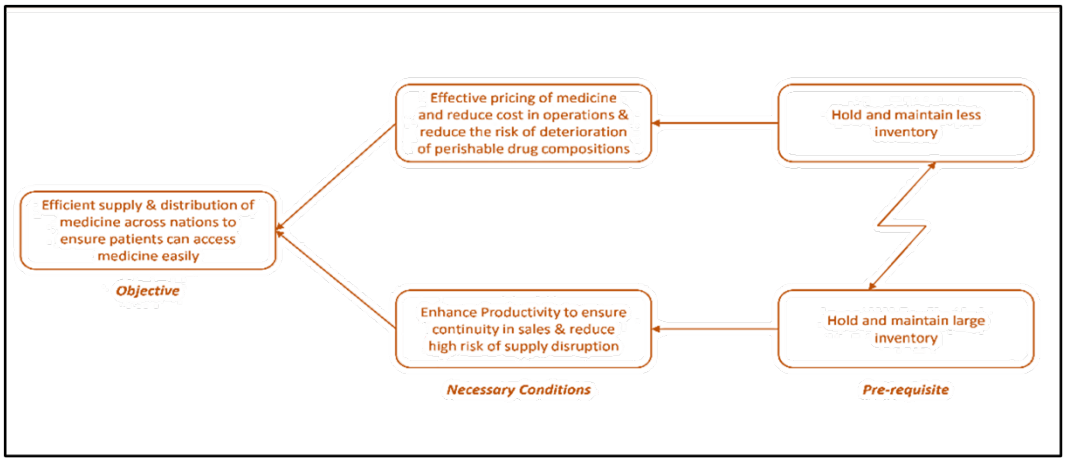

Figure 5: Conflict Resolution Diagram (CRD).

associated with excess inventory, especially for perishable items like chemical products, drugs and food commodities, TOC suggested consistent replenishment of decaying stocks to build a more resilient supply chain. This involved the following steps:

Keep stock buffers as close as possible to the source, such as the plant or warehouse. Periodically determine stock buffer sizes at all stock points, monitor inventory based on demand and supply and readjust them accordingly.

Facilitate the communication of production and consumption data throughout the nodes in the supply chain. Reduce the renewal time as much as possible.

By adhering to these principles, organizations could optimize their supply chain management, strike a balance between patient accessibility and cost-effectiveness and reduce the risks associated with perishable drug compositions. In contrast, ensuring an efficient supply of medicine necessitates that pharmaceutical companies augment their production capacity and reduce the elevated risk of supply chain disruptions. To achieve this goal, it becomes essential to stock and maintain a substantial inventory and buffer. However, there exists a fundamental contradiction between holding less inventory and maintaining a large inventory. Holding less inventory poses a threat to the productivity of companies and increases vulnerability to supply chain disruptions. Conversely, maintaining a high inventory level raises overall expenditure,[78] affecting the effectiveness of the pricing system and heightens the risk of deterioration of perishable items. To resolve this conflict, a continuous search for better ways to predict demand is imperative. Often, this challenge is addressed through mathematical modelling,[79] optimization techniques, decision-making processes and similar approaches. By adopting these methods, pharmaceutical firms can strive to predict demand more accurately, allowing them to maintain optimal inventory levels. This approach aims to strike a balance between productivity, cost-effectiveness and risk mitigation in the supply chain, acknowledging the dynamic and complex nature of the pharmaceutical industry.[80]

Step 4: Control to ensure functioning desirably and check for next constraints

The last step was crucial in preventing inertia from obstructing the continuous improvement process. Even if constraints had been successfully eliminated in the earlier steps, there was a possibility that new constraints might emerge elsewhere in the supply chain. This emphasized the importance of continuous attention from decision-makers to identify and address new constraints, leading to a repeated process. In the context of this case, the previous three steps involved identifying, exploiting and subordinating constraints to eliminate their negative impact on the system. The CRD was employed to identify undesirable effects and propose preventive measures. The successful implementation of this framework resulted in India no longer facing a deficiency in the supply of HCQ. However, there remained an insufficient supply of HCQ in various countries worldwide. Indian pharmaceutical industries committed to increasing their production capacity to meet both domestic and global demand for HCQ.[68] IPCA Labs, for instance, emphasized the need to continue the production of HCQ irrespective of the demand for COVID-19, as numerous countries, approximately 70-80, relied on the company for this essential medication for Rheumatoid Arthritis patients.[71] IPCA Labs was actively building sufficient stocks to cater to the domestic market. Government policies played a crucial role in exploiting all constraints and achieving a resilient supply chain, a process that continued until COVID-19 was eradicated from India. Given that the TOC is a continuous improvement process, monitoring and controlling the performance of the system remained essential. Regular checks for new constraints were imperative to ensure that the supply chain remained adaptive and robust. This ongoing vigilance aligned with the principles of TOC, emphasizing the need for sustained improvement and adaptability in response to evolving challenges.

MANAGERIAL INSIGHTS

The research outcomes presented in this study hold valuable insights for managers, policymakers and industry practitioners, offering potential benefits in the development of a resilient PSC. The following key recommendations can be derived from the analysis:

Developing Inventory Analysis: Companies can enhance the robustness of their supply networks by implementing efficient inventory analysis models. This includes incorporating risk management strategies and making informed decisions in supplier selection to optimize inventory levels effectively.

Extending Collaborative Networks: Reducing dependencies on a sole supplier is crucial. Instead, companies should diversify and extend their supplier networks. The research suggests that procuring raw materials from local sources can be financially advantageous. Companies should cultivate trusted networks that encompass suppliers, consumers, competitors and government sources, fostering collaboration for effective crisis management.

Implementing Proper Risk Mitigating Strategies: Collaboration with suppliers is essential for analysing and reducing exposure to hazards. Encouraging and incentivizing partner suppliers to establish multiple manufacturing or assembly sites in geographically separated regions can be a key strategy. Regularly measuring and assessing suppliers' performance is also vital for risk management.

Embodying Flexibility: Flexibility should be integrated into every aspect of the supply chain. Success stories from history emphasize the importance of companies responding rapidly to supply chain disruptions caused by hazards. Transparency in risk

information sharing and the development of risk assessment and quantification tools are imperative for building a resilient PSC.

Restructuring the Supply Chain: It is advisable to segment and regionalize the supply chain, aligning with resilient supply chain strategies tailored to the pharmaceutical products supply chain. Companies should focus on improving international and inter-organizational compatibility of resilience programs, ensuring adaptability and responsiveness to dynamic challenges.

By adopting these insights, stakeholders in the pharmaceutical industry can work towards building a resilient supply chain that can withstand disruptions and contribute to the sustainability and success of the overall pharmaceutical ecosystem.

CONCLUSION

In conclusion, this research presents a comprehensive exploration of the challenges posed by production bottlenecks in the pharmaceutical industry, particularly in the context of pandemic preparedness. The case study of XYZ Pharma in the Indian pharmaceutical landscape exemplifies the practical application of the integrated TOC and SS approach. By addressing specific constraints in inventory management and production capacity, the study demonstrates the efficacy of this methodology in enhancing supply chain resilience and responsiveness. The strategies employed by XYZ Pharma offer valuable insights for industry practitioners seeking to enhance resilience and responsiveness in the face of unforeseen disruptions, ultimately contributing to improved pandemic preparedness. The insights gained from this research contribute not only to the immediate concerns surrounding demand-supply imbalances, as highlighted by the surge in HCQ demand during the early stages of the COVID-19 pandemic, but also offer a strategic roadmap for industry practitioners to fortify their production processes against future disruptions. The synergistic application of TOC and SS provides a nuanced understanding of how a holistic approach to production management can mitigate bottlenecks and foster a more agile pharmaceutical manufacturing ecosystem. As the industry grapples with the evolving landscape of global health challenges, the findings of this research underscore the importance of proactive measures and strategic frameworks to navigate uncertainties and ensure a prompt response to surges in demand. This research, therefore concludes that in order to gain better risk management capabilities, organizations need to put more stress on making their supply chain resilient so that it can absorb unexpected shocks, responds immediately to disruptions and recover quickly form such type of distress. The study also found the real constraints that create hindrances in the way of improving the resiliency of PSC. In order to build resilient supply chain, pharma companies should follow the robust strategies that successfully helped various esteemed organizations in recovering effectively from past disasters.

LIMITATIONS AND FUTURE SCOPE

While this research provides valuable insights, it is essential to acknowledge certain limitations. Firstly, the case study focuses on a specific pharmaceutical company in the Indian context and the generalizability of the findings to different regions and company structures may vary. Additionally, the study predominantly addresses the challenges posed by a surge in demand for a specific medication (HCQ) during a specific period (early stages of the COVID-19 pandemic). The applicability of the proposed methodologies to other medications and different types of disruptions requires further investigation. Furthermore, external factors such as regulatory changes, geopolitical events and advancements in technology may influence the effectiveness of the proposed strategies. This research provides a snapshot of a dynamic industry and ongoing monitoring and adaptation of strategies are crucial to address emerging challenges.

Building on the findings and limitations of this research, several avenues for future exploration emerge. Firstly, extending the application of the TOC-SS approach to different pharmaceutical products and diverse industry settings would provide a more comprehensive understanding of its versatility and effectiveness. Comparative case studies across various regions and industry scales could offer insights into the contextual nuances influencing the implementation of these strategies. Additionally, future research could delve into the integration of emerging technologies, such as artificial intelligence and blockchain, to further enhance the efficiency and transparency of PSC. Exploring the impact of regulatory frameworks on the adoption of TOC-SS methodologies and understanding the role of government interventions in crisis scenarios would contribute to a more holistic analysis. Continuous monitoring and assessment of industry trends will be essential to refine and adapt strategies as the pharmaceutical landscape evolves. This research lays the foundation for ongoing dialogue and investigation, encouraging a proactive and collaborative approach to strengthen the pharmaceutical industry's resilience in the face of future uncertainties.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CRD: Conflict Resolution Diagram; **CRT:** Current Reality Tree; **DMADV:** Define-Measure-Analyze-Design-Verify; **DMAIC:** Define-Measure-Analyze-Improve-Control; **FRT:** Future Reality Tree; **GoI:** Government of India; **HCQ:** Hydroxychloroquine; **INJ:** Injections; **PCS:** Pharmaceutical Supply Chain; **SS:** Six Sigma; **TOC:** Theory of Constraints; **TP:** Thinking Process; **UDE:** Undesirable Effects.

SUMMARY

This study, conducted amid the early stages of the COVID-19 pandemic, delved into the challenges faced by global healthcare systems in securing effective outpatient therapies. Focusing on HCQ as a potential solution, the research addressed disruptions in the pharmaceutical supply chain due to heightened demand. Employing an integrated TOC-SS approach, the study identified critical bottlenecks, emphasizing inventory status and production capacity. The integrated methodology provided actionable insights for industry practitioners, offering a strategic roadmap to mitigate production challenges and enhance pharmaceutical supply chain resilience, particularly in the context of pandemics.

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