The Review Of
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Optimizing Pharmaceutical Supply Chain Efficiency For Diabetes Management Using Lean Six Sigma Methodologies

Jennifer Joel Joseph

Keck Graduate Institute
ORCID: 0009-0003-7608-1206

Abstract

BACKGROUND: Diabetes mellitus requires uninterrupted access to medicines such as insulin, oral hypoglycemics, and glucose monitoring devices. However, inefficiencies in pharmaceutical supply chains frequently undermine treatment continuity. Lean Six Sigma (LSS) offers a structured framework to address these challenges through waste reduction and quality improvement.
AIM: This review aims to systematically review empirical evidence on applying LSS methodologies in optimizing pharmaceutical supply chains for diabetes management.
METHODS: A systematic literature review (SLR) was conducted across PubMed, Wiley Online Library, and Google Scholar (2015–2025), following PRISMA 2020 guidelines. Studies were screened and appraised using appropriate quality assessment tools (JBI, STROBE, MMAT). Eleven primary studies were included that were related to spanning procurement, logistics, pharmacy workflows, and clinical practice.
RESULTS: Findings demonstrated that employment of LSS improved procurement efficiency, cold-chain handling, warehouse logistics, pharmacy turnaround times, and clinical process standardization, indirectly stabilizing medication demand. However, the strength of evidence varied. Although studies with large datasets and rigorous DMAIC applications showed clear outcomes, several studies were limited by small samples, single-centre scope, or short follow-up.
CONCLUSIONS: LSS provides measurable efficiency and safety gains across the diabetes pharmaceutical supply chain. Future research should integrate LSS with digital innovations such as AI forecasting and blockchain to strengthen sustainability.

Keywords: Diabetes mellitus; Lean Six Sigma; Pharmaceutical supply chain; Quality improvement.

1. Introduction

Diabetes mellitus is a lifelong metabolic disorder characterized by chronic hyperglycemia. It affects over 537 million people globally and imposes a heavy burden on health systems, according to the IDF 2021 report [1]. Ensuring reliable access to insulin, oral hypoglycemic agents, and modern monitoring tools such as continuous glucose monitoring (CGM) systems is central to effective diabetes management [2]. Any disruption or inefficiency in the pharmaceutical supply chain spanning procurement, manufacturing, distribution, and last-mile delivery results in drug shortages, expiration, stockouts, or compromised quality [3]. These failures ultimately jeopardize glycemic control, treatment adherence, and patient outcomes.

Pharmaceutical firms are thus under growing pressure to optimize the supply chain to be cost-effective and robust under variability such as demand fluctuations, regulatory constraints, and cold-chain needs [4]. Lean Six Sigma (LSS), which synergistically combines Lean's waste elimination focus with Six Sigma's variability control, has succeeded in manufacturing and healthcare operations [5]. The DMAIC (Define-Measure-

Analyze-Improve-Control) methodology is widely used in LSS projects to structure improvement initiatives [6]. In pharma settings, applications of LSS have been documented in production optimization, reduction of defects, and enhanced operational reliability (e.g., in drug manufacturing, quality control) [7]. However, they did not focus on LSS implementation in pharmaceutical supply chain efficiency, specifically in diabetes supply chain management. In healthcare or pharmacy operations, LSS methods have improved process turnaround, error reduction, and workflow efficiency [8]. However, a noticeable gap exists in the literature, as no review has specifically examined how Lean Six Sigma (LSS) can optimize the diabetes pharmaceutical supply chain.
Most published studies focus on broader pharmaceutical or healthcare process efficiency, as Tlapa et al. [9] focused on emerging digital innovations such as AI forecasting and blockchain for pharmaceutical traceability [7]. However, they did not integrate these with LSS in diabetes contexts. Existing primary studies that address elements of the diabetes supply chain are often limited by region-specific data [6,7]. This highlights the need for a comprehensive review targeting all evidenced-based LSS applications in diabetes supply chains.

Reflecting on these gaps, this review aims to examine and synthesize existing empirical evidence on applying Lean Six Sigma methodologies in pharmaceutical supply chains relevant to diabetes care (insulin, oral hypoglycemics, CGM/monitoring devices). Specifically, it seeks to identify common inefficiencies and bottlenecks addressed, map LSS tools and frameworks employed, assess outcomes (e.g., cost, lead times, quality, adherence), and highlight gaps, challenges, and opportunities, especially in integrating digital tools and sustaining improvements. This review will propose a conceptual, scalable framework for implementing LSS in diabetes-related pharmaceutical supply chains, bridging the operational and clinical domains, and strengthening the continuum of care for diabetic patients.

2. Methods

2.1. Search strategy

This study adopted a systematic literature review (SLR) design to synthesize empirical evidence on applying Lean Six Sigma (LSS) methodologies within pharmaceutical supply chains for diabetes management. An SLR was selected to ensure transparency, reproducibility, and bias minimization, which aligns with PRISMA 2020 guidelines. SLRs are widely integrated because they provide a structured approach to identifying, evaluating, and synthesizing diverse evidence bases, generating reliable insights for practice and policy [10].

A comprehensive database search was performed across PubMed, Wiley Online Library, and Google Scholar for articles published between 2015 and 2025. PubMed is widely chosen for its robust coverage of biomedical and healthcare interventions [11]. Wiley Online Library is selected for multidisciplinary access to pharmaceutical and operations management research. Google Scholar is used to capture grey literature and broader cross-disciplinary studies that are often missed in indexed databases [12]. Boolean operators and database-specific adaptations were employed. In PubMed, the query used was ("Lean Six Sigma") AND ("pharmaceutical supply chain" OR drug supply chain) AND ("Diabetes Mellitus" OR diabetes) AND (Insulin OR "oral hypoglycemic agents" OR "continuous glucose monitoring") AND ("quality improvement" OR "process improvement"). For Wiley Online Library, the strategy was: ("pharmaceutical supply chain") AND (efficiency OR optimization) AND ("diabetes management" OR "diabetes mellitus") AND (Insulin OR "oral hypoglycemic agents") AND ("Lean Six Sigma") (See Appendix A). In Google Scholar, the simplified search string combined the same concepts using broad terms to capture grey literature and case studies. Only peer-reviewed, English-language,

primary studies were included.

2.2 Selection Criteria

2.2.1 Inclusion Criteria

• Primary research articles published in peer-reviewed journals between 2010 and 2025
• Studies in the English language
• Empirical studies applying Lean, Six Sigma, or Lean Six Sigma in pharmaceutical supply chains or related processes
• Research directly addressing diabetes management, including insulin, oral hypoglycemics, or continuous glucose monitoring devices
• Case studies, clinical applications, or manufacturing/ logistics improvements with measurable outcomes

2.2.2 Exclusion Criteria

• Reviews, editorials, conference abstracts, or opinion papers
• Non-English publications
• Studies outside diabetes or unrelated to pharmaceutical supply chains
• Articles lacking empirical data or outcome evaluation

2.3 Data Extraction

Data were extracted using a structured Excel template designed for systematic reviews. Key variables included author details, publication year, study aim, design, intervention focus, LSS tools applied, supply chain context (manufacturing, distribution, pharmacy), and primary efficiency, quality, or cost outcomes. Extraction was carried out independently by two reviewers to ensure accuracy. Any disagreements were resolved through discussion, and consensus entries were recorded. This process enhanced traceability, with data linked to original figures, tables, or appendices for verification.

2.4 Data Analysis

Extracted studies were synthesized narratively due to methodological heterogeneity across interventions, supply chain settings, and outcome measures. Findings were grouped according to operation (such as manufacturing, logistics, hospital pharmacy, or procurement) and type of diabetes-related product (insulin, oral hypoglycemics, or monitoring devices). Lean Six Sigma tools (e.g., DMAIC, Value Stream Mapping, Root Cause Analysis) and reported outcomes (cycle time reduction, defect minimization, cost savings) were compared thematically. This allowed identifying recurring improvement strategies, measurable impacts, and evidence gaps that could inform future empirical applications in pharmaceutical supply chains.

2.5 Outcome Measures

The outcome measures assessed were improvements in the pharmaceutical supply chain performance specific to diabetes care. These included reduced inventory waste and stockouts, shorter lead times for insulin and oral hypoglycemics, improved cold chain reliability, enhanced accuracy in demand forecasting, cost savings in procurement, and increased medication availability supporting patient adherence and treatment continuity.

2.6 Ethical Considerations

This review analyzed published, peer-reviewed primary studies available in the public domain. Since no new data collection or involvement of human participants was undertaken, formal ethics approval was not required. The review followed PRISMA guidelines, ensured accurate citation of sources, and maintained integrity by reporting data without manipulation. Funding declarations and potential conflicts of interest within included studies were noted to enhance transparency and accountability in evidence interpretation.

3. Results

3.1 Data Screening

A total of 1,140 records were retrieved from PubMed (n=493), Google Scholar (n=159), and Wiley Online Library (n=488). After removing 456 duplicates, 684 records proceeded to title and abstract screening. Of these, 235 were excluded as unrelated or non-peer-reviewed. The remaining 449 reports were sought for retrieval, but 358 could not be obtained due to missing full texts or being limited to conference, abstracts, reviews, books, editorial papers, and blogs. Ninety-one articles were assessed for eligibility, of which 80 were excluded (23 not applying Lean Six Sigma, 57 not specific to diabetes management). Ultimately, 11 studies met the inclusion criteria and were included in this systematic review (See Figure 1).

3.2 Data Screening

The selected studies (2010–2024) collectively highlight the application of Lean Six Sigma (LSS) and related process improvement tools in optimizing pharmaceutical supply chains and diabetes care delivery. Across diverse methodologies ranging from cross-sectional data analyses (Abdulsalam [13]; Silva et al. [14]) and case studies (Byrne et al.[15]; Mishra et al.[16]; Mishra [17]) to quasi-experimental interventions (Khan et al. [18]; Kollipara et al. [19]; Kutz et al. [20]; Yamamoto [21], mixed-methods designs Sohal [22], and an analytical cross-sectional study Haji et al., [23] consistent focus emerges on improving efficiency, safety, and cost-effectiveness in diabetes-related pharmaceutical systems (see Table 1). Studies targeting supply chain management emphasize procurement optimization, manufacturing reliability, distribution safety, and insulin cold-chain traceability, often reporting cost savings and reduced error rates. Moreover, studies further focus on clinical quality improvement within diabetes services, demonstrating measurable improvements in HbA1c testing, care bundle completion, patient waiting times, and pharmacy workflow efficiency. Sohal [22] adds a broader perspective by identifying critical success factors that sustain LSS interventions in healthcare contexts. Across studies, optimization outcomes consistently include reduced waste, improved turnaround times, enhanced medication availability, and strengthened patient safety. These findings prove that embedding LSS principles within pharmaceutical and diabetes care pathways improves operational reliability, supports adherence, and improves patient outcomes.

Figure 1: PRISMA Flowchart

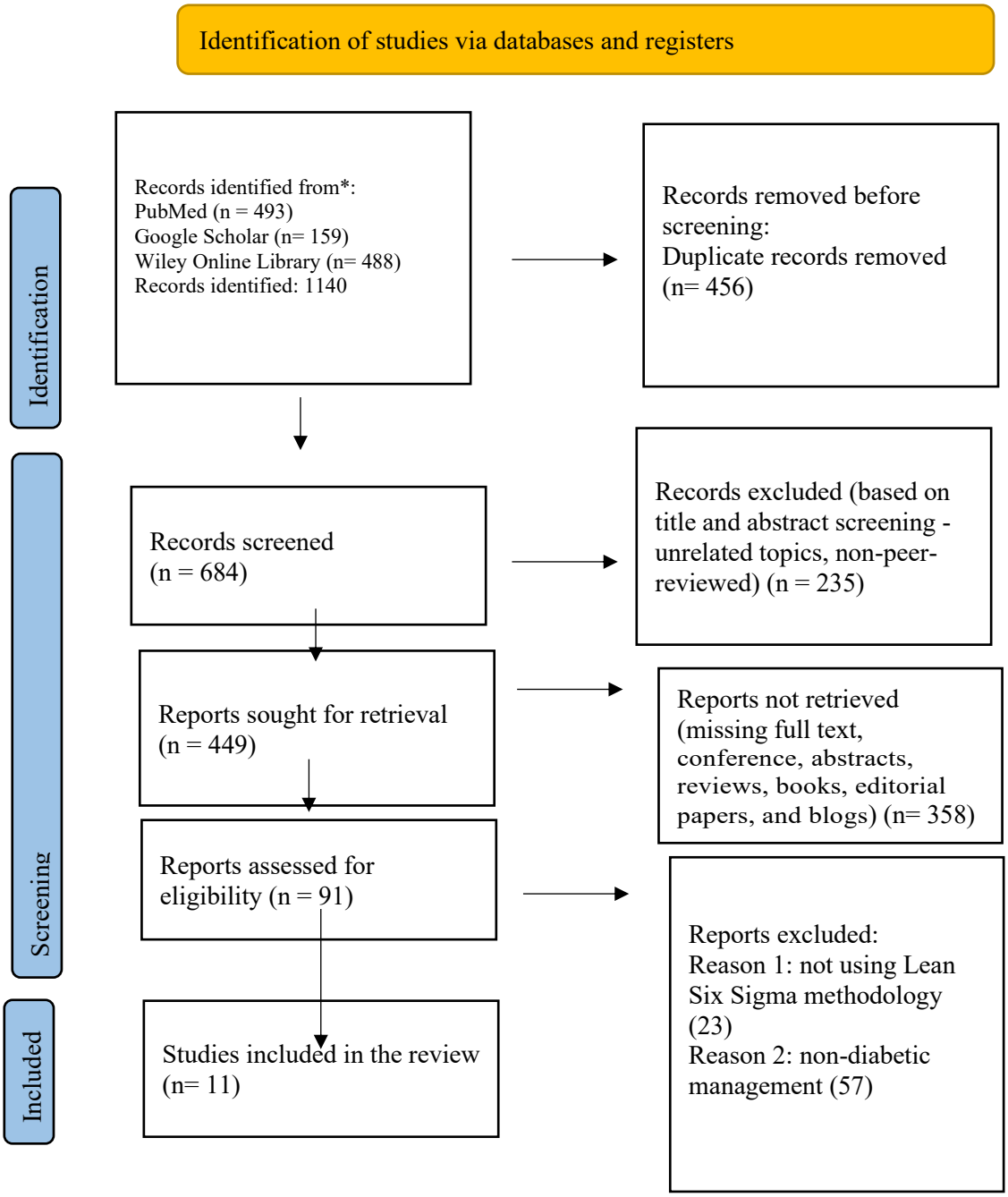

Table 1. Characteristics of studies

Authors	Year	Aim of the Study	Methodology	LSS Implementation	Findings of the Study	Optimisation Outcome
Abdulsalam et al. [13]	2022	To analyze pharmaceutical costs for diabetes management and classify supplies from a procurement perspective	Retrospective data analysis of 98,648 dispensing transactions at a diabetes	Procurement-centric classification of insulin, oral hypoglycemics, and ancillary supplies	Found that 80% of costs were driven by 20% of patients; insulin and oral drugs	Proposed portfolio purchasing model to improve procurement efficiency

			health center		were the main cost drivers	and reduce cost burden
Byrne et al. [15]	2021	To apply Lean Six Sigma methodology to optimize a pharmaceutical manufacturing facility	Case study using DMAIC and LSS tools	Implemented a customized LSS framework with value stream mapping and root cause analysis	Reduced downtime in the packaging line, eliminated bottlenecks, and improved productivity.	Achieved ~$0.5 million annual savings and improved delivery performance
Haji et al. [23]	2022	To evaluate safe insulin supply chain performance using multi-criteria decision-making	Quantitative modeling (AHP–TOPSIS framework with SCOR metrics)	Compared two insulin supply chain scenarios with/without blockchain traceability	Adding blockchain traceability improved safety, reducing counterfeit risk	Proposed blockchain integration for safe, reliable insulin distribution
Khan et al. [18]	2024	To increase the frequency of HbA1c testing in hospitalized diabetes patients using LSS	Quality improvement project, quasi-experimental, hospital-based	LSS interventions: provider education, faster lab turnaround, EHR tab with bundled orders	HbA1c testing increased from 61% to 74% post-intervention, sustained >2 years	Demonstrated sustained improvement in diabetes monitoring via LSS QI
Kollipara et al. [19]	2021	To improve diabetes control in the endocrine clinic via Lean Six Sigma	Quality improvement study in a large accountable care organization	Implemented care bundles, education, EHR standardization, and rapid-cycle changes	HbA1c and BP control improved significantly across multiple clinics	Improved compliance with diabetic care bundles, boosting outcomes
Kutz et al. [20]	2018	To improve comprehensive diabetes care in primary care settings	Lean Six Sigma quality improvement study across multiple clinics	Standardized care bundles: A1c/BP measurement, nephropathy attention, and foot exams	Diabetic bundle completion rose from 23% to 67%; A1c and BP control increased significantly	Enhanced patient outcomes through systematic, standardized care delivery
Mishra et al. [17]	2024	To reduce waiting times in diabetes	Quasi-experimental; Value	Redesign of patient flow and scheduling	Identified key bottleneck	Improved resource utilization,

		outpatient services using Lean and decision-making tools.	Stream Mapping, OPA–Fuzzy TOPSIS analysis.	in diabetes clinics.	s in outpatient diabetes care; reduction in patient waiting times.	streamlined patient flow, and increased satisfaction.
Mishra et al. [16]	2018	To explore lean healthcare applications in pharmacy/medication supply and service workflows.	Case study in an Indian healthcare setting: observational and process mapping.	Lean interventions in hospital pharmacy operations.	Reduced waste and inefficiencies in hospital pharmacy workflows.	Enhanced medication supply reliability and cost efficiency.
Silva et al. [14]	2023	To evaluate Lean Six Sigma in pharmaceutical logistics for chronic disease management.	Cross-sectional study in pharma distribution networks.	Process optimization of drug distribution for chronic therapies.	Lean Six Sigma improved logistics efficiency and reduced delivery errors.	Enhanced on-time delivery and improved cost-effectiveness in the drug supply chain.
Sohal et al. [22]	2022	To identify critical success factors (CSFs) for Lean Six Sigma projects in healthcare.	Mixed-methods review of 62 LSS projects at a tertiary hospital.	LSS projects across various healthcare service areas.	Identified 8 CSFs strongly associated with LSS project success.	Provides an evidence-based framework for sustaining LSS outcomes in healthcare.
Yamamoto et al. [21]	2010	To improve insulin distribution and administration safety using Lean Six Sigma.	Non-randomized hospital-based intervention; DMAIC cycle.	Redesigned insulin dispensing/storage, added automated cabinets, and eliminated shared bins.	Reduced variability and improved and decreased errors in insulin handling; cost savings of ~$75,000 annually.	Safer insulin Administration, improved cold chain reliability, and reduced pharmacy rework.

Legend: This table summarizes the key characteristics of the 11 included primary studies assessing Lean Six Sigma (LSS) applications in diabetes-related pharmaceutical supply chains. Columns report author and year, study aim, methodology, intervention/treatment applied, primary findings, and optimization outcomes. The studies span multiple

domains including procurement (Abdulsalam, 2022), manufacturing (Byrne, 2021), supply chain modelling (Haji, 2022), logistics (Silva, 2023), pharmacy operations (Mishra, 2018; Mishra, 2024), insulin handling (Yamamoto, 2010), and clinical process standardization (Khan, 2024; Kollipara, 2021; Kutz, 2018). Collectively, they demonstrate that LSS interventions improve efficiency, safety, and cost-effectiveness across different supply chain nodes, with varying degrees of direct impact on diabetes management.

3.3 Quality Assessment

The quality appraisal demonstrates that the majority of included studies met essential methodological standards, supporting the robustness of this systematic review. Different appraisal tools were applied to align with the study design, ensuring methodological relevance and rigor. The five quasi-experimental studies (Khan et al., [18]; Kollipara et al., [19]; Kutz et al., [20]; Mishra et al., [16]; Yamamoto et al., [21]) were assessed with the JBI quasi-experimental checklist, as it evaluates explicitly cause–and–effect clarity, comparability, and pre-/post-outcome measures. Case series/case study reports by Byrne et al. [15]; Mishra [17]; Silva et al. [14] were evaluated using the JBI case-series tool, appropriate for descriptive, non-comparative designs. Cross-sectional studies by Abdulsalam [13] and Haji [23] were appraised with STROBE and JBI analytical cross-sectional checklists, capturing validity of measurement, confounding, and representativeness. Finally, the mixed-methods study by Sohal [22] was reviewed with the MMAT 2018, which uniquely assesses integration and coherence of qualitative and quantitative strands. Across all designs, most studies met essential quality standards, though weaknesses were noted in handling confounding and generalizability (see Appendix B). Overall, the evidence base is methodologically sound, supported by transparent objectives, valid data sources, and reliable outcome reporting.

3.4 Findings

This review identified a diverse set of primary studies applying Lean Six Sigma (LSS) principles to different stages of the diabetes pharmaceutical supply chain, from procurement and logistics to hospital-level insulin handling. Abdulsalam et al. [13] focused on diabetes pharmaceutical procurement, making this the most supply chain–centered article in this set. The study aimed to quantify and classify spending on diabetes-related pharmaceuticals to guide procurement efficiency. Using a cross-sectional analysis of nearly 100,000 dispensing transactions from a specialty diabetes center in Kuwait, the authors applied ABC/VEN-style classification and portfolio purchasing frameworks. Their findings revealed a strong skew, with around 80% of expenditure coming from 20% of patients, while insulin and oral hypoglycemics accounted for over half of total costs. The analysis also highlighted patient demographic predictors of high-cost consumption. The implications for procurement included product standardization, vendor-managed inventory, and generic substitution, all measures aligned with Lean's "flow" and Six Sigma's "critical-to-cost" principles. The study's strength lies in its large dataset and actionable recommendations, but its scope was single-center and limited to one year, reducing generalizability. Missing data in nearly a fifth of records also weakened its robustness. Nevertheless, the study is a rare, supply-chain-first exploration of diabetes pharmaceuticals, providing concrete strategies that map onto Lean Six Sigma (LSS) optimization principles. Yamamoto et al. [21] similarly positioned themselves close to the pharmaceutical supply chain, focusing on insulin handling safety inside hospital systems. The study partnered with an insulin manufacturer and employed the DMAIC cycle alongside value stream mapping to redesign storage and dispensing processes. It aimed to reduce insulin handling errors and pharmacy rework. The results were tangible; they reduced variability, improved the reliability of insulin flows, and resulted in annual savings of around $75,000, primarily through eliminating misplaced vials and error correction. The intervention was framed around patient safety, recognizing insulin as a high-alert drug. The study demonstrates the role of collaborative manufacturer–provider process redesign in mitigating cold-chain and traceability risks. Despite being older, the study remains highly relevant, as its design foreshadowed modern digital interventions such as RFID and blockchain traceability for insulin flows.

On the other hand, Silva et al. [14] extended Lean Six Sigma tools into pharmaceutical logistics at the warehouse level. The aim was to improve order-picking accuracy and storage logistics in a

pharmaceutical distributor. Using time-motion analysis and process reconfiguration, the study reported improved cycle times, reduced picking errors, and better storage layouts. While not diabetes-specific, the findings are directly transferable to the distribution of insulin and continuous glucose monitoring (CGM) devices, where accuracy and timeliness are essential for patient safety. The focus on eliminating classical lean wastes, defects, waiting, and transport strengthens its relevance, as these inefficiencies are often hidden drivers of drug shortages or late deliveries in diabetes supply chains. On the other hand, Mishra et al. [16] applied Lean principles to hospital pharmacy workflows in India, aiming to reduce turnaround time and dispensing errors. Following the DMAIC pathway, the team employed root cause analysis, standard work, and visual management. The outcomes demonstrated shorter cycle times and fewer medication errors, reflecting released capacity and improved internal supply reliability. While not diabetes-specific, this study remains relevant given that insulin and oral hypoglycemics are high-frequency dispensing items where errors and bottlenecks can have immediate clinical consequences. Its strength is showing how LSS principles are embedded in hospital pharmacy operations. Its queue management and error-proofing lessons are easily transferable to diabetes formularies. In addition, Kutz et al. [20] adopted Lean Six Sigma within primary care settings, focusing on diabetes care bundles. It aimed to standardize care delivery across multiple clinics to improve guideline adherence. The study was dramatically enhanced through DMAIC-based interventions, such as standardized electronic health record templates, rapid cycle improvements, and provider education. Bundle completion rose from 23% to 67%, with A1c and blood pressure control reaching benchmarked HEDIS thresholds. This is more of a downstream clinical study than an upstream supply chain one, but its impact on supply is indirect and notable. Standardizing clinical processes stabilized prescribing and monitoring patterns, reducing variability in medication demand. The study's significance lies in multi-site implementation with strong statistical reporting, underscoring that LSS-driven process standardization can reduce demand variability, a prerequisite for effective pharmaceutical forecasting.
Kollipara et al. [19] conducted a similar quality improvement project in an endocrine clinic, using DMAIC explicitly to improve diabetes care. The outcomes paralleled Kutz et al. [20] findings as improved HbA1c and blood pressure control following structured LSS interventions. While not directly targeting the pharmaceutical supply chain, clinical standardization stabilizes prescribing practices and patient review intervals, reducing variability in medication demand, enabling more accurate forecasting, efficient inventory control, and timely procurement. The strength of this paper is its rigorous adherence to the DMAIC framework, offering traceable intervention logic. However, like Kutz et al. [20], it provides little in logistics or procurement outcomes, limiting its direct contribution to supply chain optimization. Furthermore, Sohal et al. [22] took a broader systems view to identify critical success factors for LSS implementation in healthcare supply chains. Using a mixed-methods approach, quantitative rankings with qualitative interviews were integrated to identify eight key enablers: leadership commitment, staff training, and robust data systems. The study provides the "soft infrastructure" lens, explaining why heterogeneity exists across sites and why some LSS projects thrive while others stagnate. The study further contributes to the necessary context for interpreting the variable outcomes of supply chain interventions. Moreover, Haji et al. [23] examined insulin supply chain safety using multi-criteria decision modeling (AHP–TOPSIS combined with SCOR metrics). It aimed to identify and compare safe insulin distribution models, with blockchain traceability as a key intervention. The findings supported blockchain as a superior alternative to traditional models, improving safety and reducing counterfeit risks. Lastly, it offers valuable theoretical reinforcement for traceability and safety as critical-to-quality metrics in insulin supply, aligning closely with Six Sigma's focus on variation and defects.
These studies demonstrate that Lean Six Sigma interventions can be applied across the pharmaceutical supply chain for diabetes, from upstream procurement and manufacturing, through distribution logistics, to hospital pharmacies and downstream clinical operations. Specifically, the studies aligned to supply chains provide the most substantial evidence for procurement, inventory, and logistics optimization, reporting outcomes such as cost savings, reduced rework, improved accuracy, and increased safety. Clinical workflow studies contribute indirectly by stabilizing demand patterns and prescribing behavior, reducing upstream variability. Mixed-methods evidence provides context for success, identifying enablers without which technical interventions are unsustainable.

4. Discussion

The synthesis of studies highlights how Lean Six Sigma (LSS) methodologies are being operationalized across different nodes of the diabetes pharmaceutical supply chain, from upstream procurement and manufacturing to downstream pharmacy workflows and patient-facing clinical care. The pattern of results suggests that LSS offers measurable efficiency, cost control, and safety benefits. However, the depth and scope of these benefits vary depending on the locus of intervention. Upstream studies, such as Abdulsalam et al. [13], demonstrate that LSS-inspired procurement classification directly informs resource allocation and contracting strategies. The study implicitly underscores the critical-to-quality (CTQ) parameters that should be prioritized within Six Sigma frameworks by revealing that insulin and oral hypoglycemics dominate expenditures. Similar procurement analyses outside diabetes, for instance, Alanazi et al. [24] posit in oncology supply chains by showing that ABC/VEN approaches coupled with Lean inventory models reduce wastage and enhance stock reliability. The convergence of evidence indicates that standardizing and streamlining vendor contracts has system-level cost benefits. This highlights the broader capacity of LSS to optimize cost structures and ensure equity of access by preventing shortages in high-demand therapeutic categories such as insulin.

At the logistics and handling level, Yamamoto et al. [21] and Silva et al. [14] reinforce the idea that Lean's focus on eliminating waste (transport errors, misplaced items, order picking delays) translates into tangible safety and cost outcomes. Yamamoto's [21] work on insulin handling is particularly salient, as insulin is a high-alert drug requiring cold-chain integrity. The intervention eliminated rework costs and improved safety, consistent with Rafferty and Franklin [25], emphasizing that Lean-driven redesign of high-risk drug workflows reduces adverse events. Silva et al. [14] warehouse study mirrors the results of Samara and Harry [26] in vaccine distribution, where Lean interventions shortened picking times and reduced errors, ensuring timely deliveries. These parallels suggest that Lean's classic waste-reduction principles apply robustly to cold-chain and time-sensitive diabetes products. However, empirical data on defect rates and patient outcomes are less frequently reported. Nevertheless, the consistency of outcomes across unrelated pharmaceutical products suggests that the influence of LSS is systemic; any node of inefficiency in the supply chain can be targeted with measurable improvements, making LSS a universal lever for pharmaceutical resilience.

Moving into hospital pharmacy operations, Mishra et al. [16] and Mishra [17] showed that Lean process mapping and standardization reduce turnaround times and dispensing errors. This aligns with broader pharmacy operations by Benrrezzouq and Mansour [27], where DMAIC-driven interventions improved dispensing accuracy and reduced patient waiting times. The interpretation here is that LSS not only improves internal workflow efficiency but also indirectly improves patient adherence by reducing delays in drug availability. The adaptability of DMAIC across different pharmacy environments, from tertiary centers to local hospital pharmacies, demonstrates the scalability of LSS interventions and their potential for integration into national medication management policies.

At the clinical interface, studies such as Kutz et al. [20], Kollipara et al. [19], and Khan et al. [18] illustrate how LSS interventions standardize care bundles, enhance HbA1c testing, and improve adherence to diabetes management guidelines. While these outcomes are not strictly supply chain metrics, they shape demand predictability. For instance, Alkhouri [4] explains that more systematic HbA1c testing creates more stable prescribing patterns, reducing the "bullwhip effect" of fluctuating drug demand. This finding parallels observations in chronic disease supply chains, where standardization of clinical protocols reduces variability in ordering cycles Ogbuagu et al. [28]. Here, LSS influences internal process quality and exerts an upstream stabilizing effect by aligning clinical demand signals with supply chain planning, closing the loop between clinical practice and pharmaceutical logistics. The broader systems study by Sohal et al. [22] adds an organizational dimension, showing that leadership commitment, staff training, and reliable data systems are key critical success factors (CSFs) for sustaining LSS projects. Without these enablers, technical gains from interventions like those described by

Yamamoto [21] or Abdulsalam et al. [13] may not be sustained. Similar conclusions were drawn by McDermott et al. [29] in a review of healthcare LSS implementations, which emphasized that cultural buy-in and leadership support determine whether early improvements persist beyond pilot phases. Thus, Sohal et al. [22] findings contextualize the variable outcomes observed across settings and highlight that operational excellence requires both process and cultural transformation. This underscores that LSS is not merely a set of tools, but a system-wide philosophy requiring integration of people, processes, and technology for enduring impact.

Finally, Haji et al. [23] bridge operational optimization with digital transformation by modeling insulin supply chains using AHP–TOPSIS and suggesting blockchain integration to mitigate counterfeit risk. This points toward a convergence of Lean Six Sigma with emerging digital tools. Chang and Chen [30], on pharmaceutical traceability, similarly advocate that blockchain enhances transparency and complements Lean inventory models by ensuring authenticity and reliability in distribution. Haji et al. [23] study, however, remains theoretical, and the absence of empirical field validation tempers its weight. Still, it foreshadows the digital-LSS integration that is increasingly relevant in pharmaceutical systems, especially for biologics like insulin that require traceable cold chains. The future trajectory thus appears to be a hybrid model where Lean Six Sigma frameworks are strengthened by AI-driven demand forecasting and blockchain-based traceability, creating end-to-end visibility and efficiency across the diabetes pharmaceutical supply chain.

4.1 Strengths and Limitations

The main strength of this review lies in the diversity of included studies, which collectively capture the pharmaceutical supply chain for diabetes management from multiple vantage points. Evidence spans procurement efficiency, warehouse logistics, and pharmacy workflow optimization, and insulin handling safety [13,14,15,16,17]. Meanwhile, incorporating clinical quality improvement initiatives by Kutz et al. [20], Kollipara et al. [19], and Khan et al. [18] showed that LSS indirectly stabilizes medication demand. This breadth enhances ecological validity, showing that Lean Six Sigma principles are applicable across organizational tiers and geographical contexts. Another strength is the methodological robustness, with several studies applying explicit DMAIC frameworks and large-scale datasets that increase reliability. Multi-site implementations, such as Kutz et al. [18] system-wide rollout, mitigate single-site bias, while Sohal et al. [22] mixed-methods study provides unique insights into organizational enablers, linking technical improvements with sustainability of LSS initiatives in real-world healthcare systems.

Despite significant strengths in the findings, notable limitations need to be acknowledged. First, there is a consistent absence of control groups across quasi-experimental studies, limiting causal inference. While pre- and post-comparisons show improvement, alternative explanations cannot be excluded. Second, many studies are single-site (e.g., Abdulsalam et al. [13], Silva et al. [14], Mishra [16]), restricting generalizability across healthcare systems with different regulatory and resource environments. Third, outcome reporting is often narrow, while process indicators (cycle times, error rates, care bundle completion) are documented, core supply chain metrics such as lead time variability, stockout frequencies, or inventory turnover are rarely reported. This omission constrains the ability to quantify direct supply chain benefits. Fourth, most studies emphasize short-term improvements; sustainability data is lacking beyond one to two years, raising concerns about whether LSS interventions become embedded practices or fade after initial implementation. Fifth, studies such as Haji et al. [23] are largely theoretical or modeling-based without empirical validation, which weakens the strength of evidence. Lastly, there is publication bias; most included studies report positive outcomes, with little critical reflection on failed or neutral interventions, which could skew the evidence base.

5. Conclusions

This systematic review demonstrates that Lean Six Sigma (LSS) methodologies can significantly enhance efficiency, reliability, and safety within pharmaceutical supply chains for diabetes management. Across procurement, logistics, hospital pharmacy workflows, and clinical quality improvement initiatives, evidence consistently points to reduced process variation, shorter turnaround times, fewer errors, and measurable cost savings. While many interventions were not diabetes-specific, their findings are transferable to insulin, oral hypoglycemics, and continuous glucose monitoring devices, where timely availability and quality assurance are critical for patient outcomes. A key implication is that supply chain optimization for diabetes cannot be addressed in isolation; it must be integrated with clinical processes. Studies focusing on care bundle standardization and HbA1c testing illustrate how clinical stability reduces demand variability, strengthening upstream forecasting and inventory control. Moreover, organizational enablers such as leadership engagement, workforce training, and digital data systems emerged as decisive factors for sustaining improvements.

Future research should move beyond single-site, short-term evaluations toward multi-center evaluations. These longitudinal studies measure supply chain outcomes such as stockout frequency, lead time variability, and cold-chain reliability. Integrating LSS with emerging digital technologies, including AI-based demand forecasting, blockchain-enabled traceability, and real-time analytics, represents a promising direction to embed quality at scale. In conclusion, the evidence supports LSS as a robust framework for aligning operational excellence with clinical goals in diabetes management. Sustained implementation and digital transformation can create more resilient, transparent, and patient-centered pharmaceutical supply chains that improve system efficiency and health outcomes.

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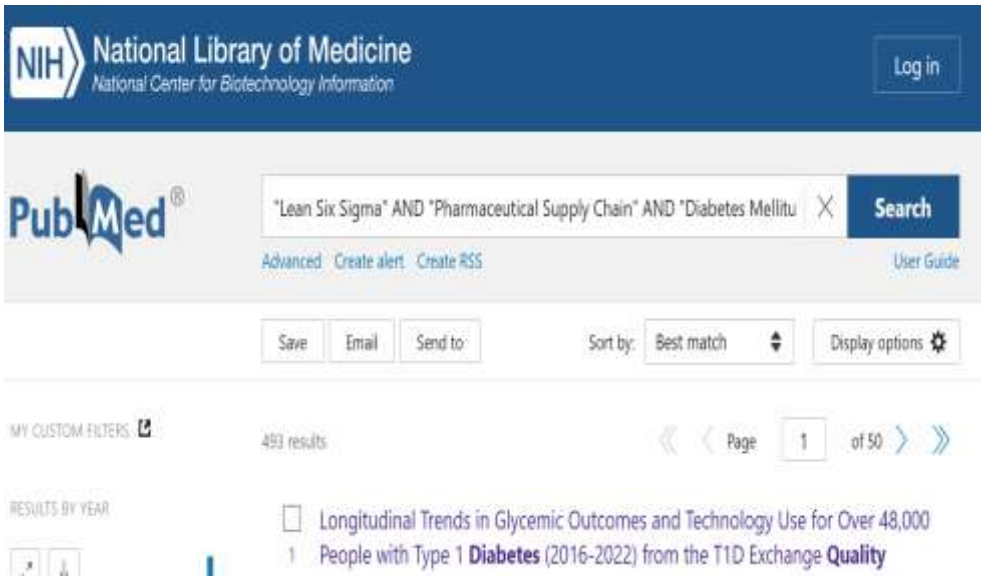
7. Appendices

Appendix A: Database Search

Figure 2: Google Scholar

Figure 3: Wiley Online Library

Figure 4: PubMed



Appendix B: Quality Assessment

JBI critical appraisal tool for quasi-experimental studies

Table 1: JBI critical appraisal tool for quasi-experimental studies

Study	Cause/ Effect Clear	Control Group	Participants Similar	Similar Care (other than intervention)	Multiple Pre/ Post Measures	Same Outcome Measurement	Reliable Measurement	Follow-up Complete	Appropriate Statistics	Overall Appraisal
Khan et al., 2024	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Kollipara et al., 2021	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Kutz et al., 2018	Yes	No	Yes	Yes	Yes	Yes	Yes	Partial*	Yes	Include
Mishra et al., 2018	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Yamamoto et al., 2010	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include

JBI case series/study

Table 2: JBI case series/study

Study	Clear inclusion criteria	Condition measured reliably	Valid methods for condition ID	Consecutive inclusion	Complete inclusion	Demographics reported	Clinical info reported	Outcomes/follow-up reported	Site/clinic demographics	Statistical analysis appropriate	Overall appraisal
Byrne et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Mishra, 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include

Silva et al., 2023	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Include

STROBE Checklist for Cross-Sectional Studies (Applied to Abdulsalam et al., 2022)

Table 3: STROBE Checklist for Cross-Sectional Studies

Item	Recommendation	Addressed (Yes/No/Partial)	Notes from Study
1. Title and abstract	(a) Indicate study design in title/abstract; (b) Informative summary	Yes	Title/abstract clearly mentions observational analysis of pharmaceutical supply; summary presented.
2. Background/rationale	Explain background and rationale	Yes	Provides rationale on drug cost and supply challenges in diabetes.
3. Objectives	State objectives/hypotheses	Yes	Aim stated: classify medicines procurement to improve the supply chain.
4. Study design	Present key design elements early	Yes	Described as a cross-sectional dataset analysis of transactions.
5. Setting	Describe setting, location, dates	. Yes	Data from the tertiary diabetes center, period specified.
6. Participants	Eligibility, sources, selection	Yes	All pharmacy dispensing transactions included; criteria explained.
7. Variables	Define outcomes, exposures, and predictors	Yes	Variables: procurement category, cost, frequency of use, supply status.
8. Data sources/measurement	Sources and assessment methods	Yes	Hospital pharmacy

			database; methods outlined.
9. Bias	Efforts to address bias	Partial	Limited discussion of potential misclassification or missing data.
10. Study size	Explain the sample size	Yes	Large dataset (>X thousand transactions), justified.
11. Quantitative variables	Handling of quantitative variables	Yes	Categorization of medicines explained (ABC/VEN).
12. Statistical methods	Describe all methods, incl. confounding control	Yes	Descriptive stats and procurement classification models are reported.
13. Participants	Report numbers at each stage	Yes	The total dataset size was reported; exclusions were not applicable.
14. Descriptive data	Report participant characteristics, missing data	Partial	Medicine categories are described; missing data handling is less detailed.
15. Outcome data	Report outcome events/summary measures	Yes	Procurement cost breakdown and stock-out measures reported.
16. Main results	Estimates with precision/confounders	Partial	Results given, but confidence intervals not consistently provided.
17. Other analyses	Subgroup/interaction/sensitivity	No	No subgroup or sensitivity analyses were described.
18. Key results	Summarise with reference to objectives	Yes	Findings aligned with stated objectives.
19. Limitations	Discuss limitations and bias	Yes	Some limitations noted (data scope, generalisability).

20. Interpretation	Interpretation considering evidence	Yes	Balanced interpretation provided.
21. Generalisability	Discuss external validity	Partial	Limited discussion; context-specific to a single center.
22. Funding	Source of funding and role	Yes	Funding source acknowledged.

JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies to **Haji et al., 2022**

Table 4: JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Criterion	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☑	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☑	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☑	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☑	☐	☐	☐
5. Were confounding factors identified?	☐	☑	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☑	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☑	☐	☐	☐
8. Was an appropriate statistical analysis used?	☑	☐	☐	☐

Mixed Methods Appraisal Tool (MMAT, 2018) – Sohal et al., 2022

Table 5: Mixed Methods Appraisal Tool (MMAT, 2018)

Category / Item	Yes	No	Can't tell	Comments
Screening Questions				
Are there clear research questions?	☑	☐	☐	Research Q clearly defined: CSFs for LSS in healthcare supply chain.
Do the collected data allow addressing the research questions?	☑	☐	☐	Quantitative scoring + qualitative data sufficient to address aims.
Mixed Methods				
Adequate rationale for using mixed methods?	☑	☐	☐	Justified: combines quantitative ranking with qualitative insights.
Different components effectively integrated?	☑	☐	☐	Integration evident; triangulation used.
Outputs of integration adequately interpreted?	☑	☐	☐	Findings synthesize both strands to identify success factors.
Divergences/inconsistencies adequately addressed?	☐	☐	☑	Not deeply discussed if quantitative vs qualitative diverged.

Components adhere to quality criteria of each method?	☑	☐	☐	Quantitative (survey) + qualitative (interviews) follow standards.