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Digital Transformation in the Pharmaceutical Industry: A Systematic Review of Agile and Hybrid Project Management Success Factors for Pharma 4.0

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Patras, Greece, July 2026

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Abstract

The Pharmaceutical industry is aiming to shift from the traditional way of operation to the new Pharma 4.0 digital transformation which integrates IS technologies such as Big Data, AI, Digital Twins, Industrial Internet of Things (IIoT) in to the drugs lifecycle through a harmonized ecosystem. Additionally, the operation process of the pharmaceutical industries are highly regulated of strict rules such as GXP, CFR 21 and Annex One which often creates bottlenecks in the project management teams especially in combination with the traditional project management "waterfall" by leading the project in to failure. This thesis presents a systematic review of the transition from the Traditional to the Agile project management by focusing/emphasizing to the Hybrid Project management which is the proper method for the Pharmaceutical industries in order facilitate the digital transformation and present the Success Factors. The scope of this research is to evaluate how the adaptive project management methods and especially the Hybrid model which blends the Agile's flexibility and the strict but robust Waterfall structure have a successful impact on the Pharma 4.0 implementation projects by identifying the Critical Successful Sectors (CSFs) which are mandatory to undertake the complexity and the fast pace of digital transformation projects in a dynamic improved environment in contrast with the organizational culture, cross-functional collaboration and data integrity design. In addition, will emphasize to the Hybrid model value and efficient because allows at the same time the iterative and waterfall model to cooperate by maintaining a dynamic flow stream, respecting the strict regulatory frame and delivering the project's outcomes on time which is translated in business management model as the opportunity of extra creation of social and commercial value for the industry.

Keywords

Pharma 4.0, Digital Transformation, Agile Project Management, Hybrid Project Management Models, Systematic Review, Critical Success Factors.

Περίληψη

Η φαρμακευτική βιομηχανία στοχεύει στη μετάβαση από τον παραδοσιακό τρόπο λειτουργίας στον νέο ψηφιακό μετασχηματισμό Pharma 4.0, ο οποίος ενσωματώνει τεχνολογίες Πληροφορικής όπως τα Μεγάλα Δεδομένα, την Τεχνητή Νοημοσύνη, τα Ψηφιακά Δίδυμα, το Βιομηχανικό Διαδίκτυο των Πραγμάτων (IIoT) στον κύκλο ζωής των φαρμάκων μέσω ενός εναρμονισμένου οικοσυστήματος. Επιπλέον, η διαδικασία λειτουργίας των φαρμακευτικών βιομηχανιών ρυθμίζεται από αυστηρούς κανόνες όπως το GXP, το CFR 21 και το Annex One, οι οποίοι συχνά δημιουργούν παγίδες στις ομάδες διαχείρισης έργων, ειδικά σε συνδυασμό με τον παραδοσιακό μοντέλο «καταρράκτη» διαχείρισης έργων, οδηγώντας το έργο στην αποτυχία. Αυτή η διατριβή παρουσιάζει μια συστηματική ανασκόπηση της εναλλαγής από την παραδοσιακή στην ευέλικτη Διαχείριση έργων, εστιάζοντας/δίνοντας έμφαση στη διαχείριση έργων μέσω του υβριδικού μοντέλου, το οποίο έχει την κατάλληλη μέθοδο για τις φαρμακευτικές βιομηχανίες, προκειμένου να διευκολυνθεί ο ψηφιακός μετασχηματισμός και να παρουσιαστούν οι παράγοντες επιτυχίας. Το πεδίο εφαρμογής της παρούσας έρευνας είναι η αξιολόγηση του τρόπου με τον οποίο οι προσαρμοστικές μέθοδοι διαχείρισης έργων και ιδιαίτερα το υβριδικό μοντέλο, το οποίο συνδυάζει την ευελιξία του “Agile” και την αυστηρή αλλά στιβαρή δομή “Waterfall”, έχουν επιτυχημένο αντίκτυπο στα έργα υλοποίησης του Pharma 4.0, προσδιορίζοντας τους Κρίσιμους Επιτυχημένους Τομείς (CSFs) που είναι υποχρεωτικοί για την ανάληψη της πολυπλοκότητας και του γρήγορου ρυθμού των έργων ψηφιακού μετασχηματισμού σε ένα δυναμικό, βελτιωμένο περιβάλλον σε αντίθεση με την οργανωτική κουλτούρα, τη δυσλειτουργική συνεργασία και τον σχεδιασμό ακεραιότητας δεδομένων. Επιπλέον, θα δοθεί έμφαση στην αξία και την αποτελεσματικότητα του υβριδικού μοντέλου, επειδή επιτρέπει ταυτόχρονα τη συνεργασία του επαναληπτικού μοντέλου και του μοντέλου waterfall, διατηρώντας μια δυναμική ροή, σεβόμενο το αυστηρό κανονιστικό πλαίσιο και παραδίδοντας τα αποτελέσματα του έργου εγκαίρως,

γεγονός που μεταφράζεται στο μοντέλο επιχειρηματικής διαχείρισης ως την ευκαιρία για επιπλέον δημιουργία κοινωνικής και εμπορικής αξίας για τον κλάδο.

Λέξεις – Κλειδιά

Φαρμακευτική 4.0, Ψηφιακός Μετασχηματισμός, Ευέλικτη Διαχείριση Έργων, Υβριδικά Μοντέλα Διαχείρισης Έργων, Συστηματική Ανασκόπηση, Κρίσιμοι Παράγοντες Επιτυχίας.

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List of Abbreviations & Acronyms

AC: Alternative Current.

AI: Artificial Intelligence.

APC: Advance Process Control.

APIs: Active Pharmaceutical Ingredient.

AR: Augment Reality.

BOD: Board of Directors.

CAPEX: Capital Expenditures

CD: Continuous Delivery / Continuous Deployment.

CDMO: Contract Development and Manufacturing Organization.

CFR: Code of Federal Regulations

CI: Continuous Improvement.

CMP: Certificate of Medicinal Product

COBOTS: Collaborative Robots

CPPs: Critical Process Parameters.

CPS: Cyber Physical Systems.

CPV: Continuous Process Validation.

CQAs: Critical Quality Attributes.

CSFs: Critical Success Factors.

CSV: Computerized System Validation.

DC: Development Cycles.

DC: Direct Current.

DIGas: Digital Health Applications.

DNA: Deoxyribonucleic Acid

DT: Digital Tranfromation.

EAV-Model: Enhance Agile V Model.

EMA: European Medicines Agency.

ERP: Enterprise Resource Planning

FDA: Food and Drug Administration

GAMP: Good Automated Manufacturing Practice

GxP: Good Practice ("x" is is a placeholder variable).

IDMP: Identification of Medicinal Products.

IIOT: Industrial Internet of Things.

INDUSTRY 4.0: Fourth Industrial Revolution.

IOT: Internet of Things.

IQ: Installation Qualification.

IRR: Internal Rate of Return.

ISPE: International Society for Pharmaceutical Engineering.

IT: Infrastructures Technology.

LIMS: Laboratory Information Management System

LLMS Large Language Models

MDS: Medical Device Software.

MES: Manufacturing Execution System

ML: Machine Learning.

MVP: Minimum Viable Product

OPEX: Operational Expenditure.

OQ: Operational Qualification.

PAT: Process Analytical Technology

PHARMA 4.0: Pharmaceutical Industry 4.0.

PICOS: Pharmaceutical Inspection Co-operation Scheme

PLCs: Programmable Logic Controllers.

PLM: Product Lifecycle Management

PQ: Performance Qualification.

PQS: Pharmaceutical Quality System

QA: Quality Assurance.

QbD: Quality by Design

QMS: Quality Management System.

QoD: Quality of Design.

R&D: Research and Development.

RAG: Retrieval Augment Generation.

RFID: Radio Frequency Identification

ROI: Return of Investment.

RQs: Research Questions.

RTRT: Real Time Release Testing.

SFs: Success Factors.

SLR: Systematic Literature Review.

SOPs: Standard Operating Procedure.

TPM: Traditional Project Management.

V&V: Validation and Verification.

VR: Virtual Reality.

XP: Extreme Programming.

1. Chapter 01: Introduction

1.1 Background

Historically the industrial landscape has proceeded with four fundamental technology revolutions which each redefined the boundaries of what was possible to be manufactured or not. The need to swift from traditional manufacturing process to a more sophisticated and data driven ecosystem of the modern technologies was a major change regarding the value creation. In each period of the industrial revolutions the needs for higher production speed, increased quantity and enhance product quality could be considered as common and timeless market push sectors. The customers and the markets demanded via an indirect way these features to be embed in the products that wish to buy and the innovators alongside with the industries replied to this call by creating a great positive and significant impact to the humanity.

Through these industrial revolutions multiple inventions were applied to commercial and domestic level such as steam, electricity and computers by enhancing the life quality of humanity and increasing the lifetime. It could be assumed that each industrial revolution has offered priceless value to all categories by breaking the limits and creating new barriers as the next challenge for the next industrial revolution. Generally the manufacturing sectors are focusing in the efficacy and the cost while in the pharmaceutical industry in the balance between these factors and the stringent regulatory compliance and the moral imperative of patient safety.

To understand the current digital revolution of Pharma 4.0 we need to proceed with a more detailed historical review of the mechanical and electronic foundation laid over the last two centuries and its evolution.

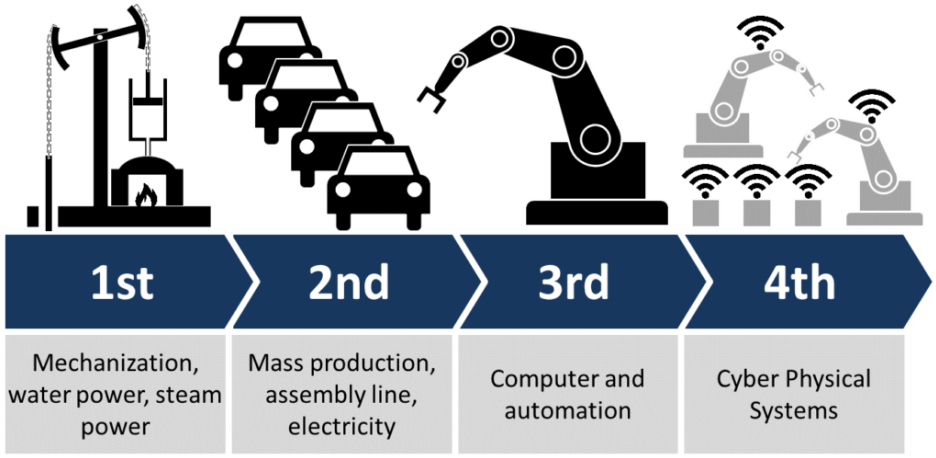

Figure 1.1: The Four Generations of Industrial Evolution (Source: Christoph Roser at AllAboutLean.com)

The industry 1.0 (Mechanization 1780s -1870s) was the first industrial revolution which took place on the 18th century. This was a fundamental shift for human history because replaced the hand production methods with machines. This wasn't just a change in tools or production methods but it was a radical transformation of society and way of living. The core of this industry revolution was the introduction of steam and water as power to supply and support facilities. The invention of first steam engine that could practically support steam power for industrial use was made by Thomas Newcomen in 1712 an English blacksmith in order to solve the problem of flooded coal mines and used approximately between (1712 - 1760). The evolution of Thomas Newcomen steam machine was undertaken by James Watt who significantly improved equipment by reducing the consumption about 75% and introducing the rotary motion. This new feature was more than enough to powering factories, steam boats, steam trains, mechanize the textile industry, transition the agriculture to industrial and be the fundamental technology of the 1st Industrial Revolution with duration (1760 – 1840). There was also a negative impact on urbanization because the cities grew too fast by becoming overcrowded and the working condition changed by including long working hours and child labor before regulations were established.

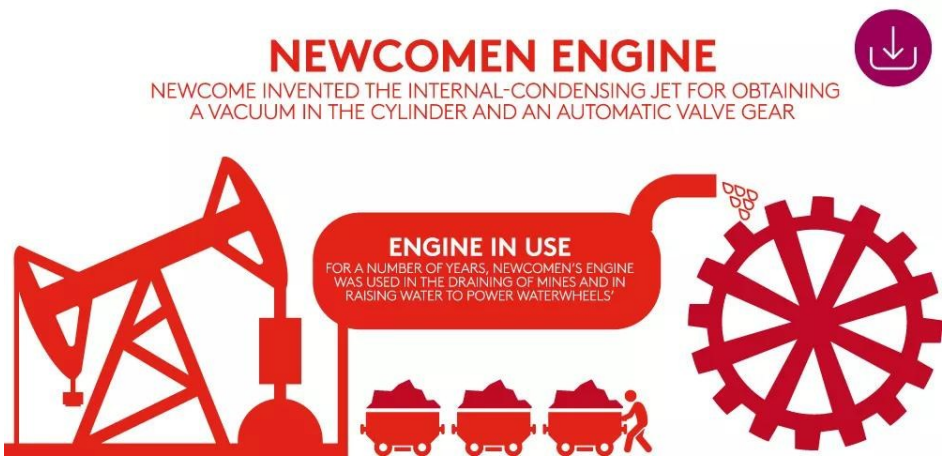

Figure 1.2: Industry 1.0: the power of steam (Source: essentracomponents 2020).

The industry 2.0 (Mass Production 1870s – 1960s) was the second and most fundamental industrial revolution which took place on 19th Century as a complementary asset of the first industrial revolution. While the previous technology of the steam and water use was dominating in multiple sectors the second revolution introduced a new era by reconstructing and accelerating the modern world. The core inventions which lay behind were the Electrical Power by opening a crucial fundamental innovative horizon for inventors, industries and commercial life. Inventors such as Michael Faraday who discovered the electromagnetic energy which is the operation foundations for the electric motors, Thomas Edison who developed the incandescent light bulb/ direct current (DC) system to power cities/factories and Nikola Tesla who developed the alternative Current (AC) by allowing electricity to be transferred over long distances to remote buildings/factories. The above mentioned innovations and the new era gave the opportunity to entrepreneurs/factory owners such as George Westinghouse to exploit the value of Nikola's Tesla innovation and support the making of large-scale industrial electrification commercially viable and Henry Ford by using the power of electricity to create the first automated mass production cars assembly lines and offer affordable cars to all social classes by placing himself to the level of mass productions industry 2.0 architect which its principles are applied to this day.

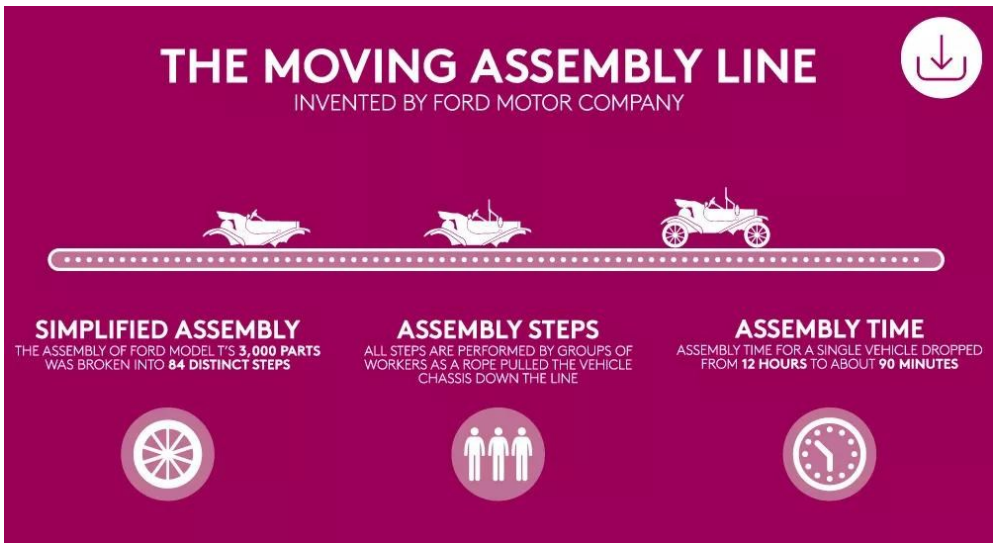

Figure 1.3: Industry 2.0: the growth of production automation (Source: essentracomponents 2020).

The industry 3.0 (Automation 1970s – 2010s) was the third industrial revolution which took place in the late 1960s and was the second most important after the industry 2.0 because was as shift from the purely mechanical/electrical systems to electronics and information technology by putting the "machine" in the "working machine." This wasn't just an industrial revolution just about making things faster but was about making them programmable by introducing the customization of operations by also opening a new way for further innovation and improvements with significant impact to industries and domestic life. The core innovations behind this revolution were the PLC Programmable Logic Controller which was invented in 1968 by letting factories to automate their process/machines, the large-scale computers like IBM system/360 began automating business data and personal computer which was invented in 1970s/80s by Steve Woznial (Apple I & II) and Bill Gates (Microsoft) by introducing the computing accessibility to individuals, the robotics (especially robotic arms) which were invented ultimately in 1970s by Stanford Arm and MIT Arm by adding more movement degrees of freedom and were used primarily for heavy lifting, welding, and repetitive tasks that were dangerous for humans and the Internet which was fundamentally invented/improved between 1969 – 1983 via a US Department of Defense project designed to allow computers to share

information across a network (ARPANET) but ultimately known World Wide Web we are using today was invented by Tim Berners-Lee in 1989 by making the internet accessible to general public. This revolution could be characterized as the bridging between Industry 2.0 and Industry 4.0 principles by providing the required fundamental complementary assets to the latter.

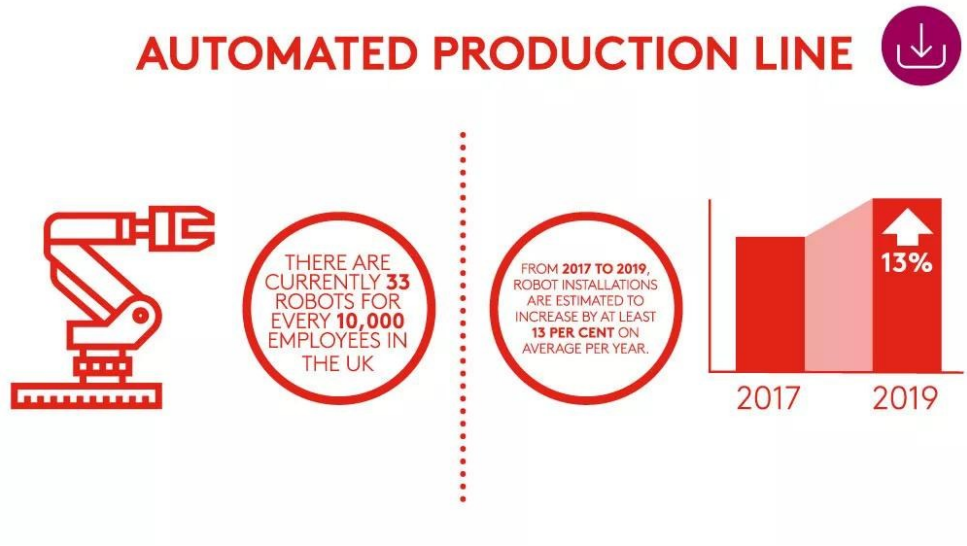

Figure 1.4: Industry 3.0: intelligent automation (Source: essentracomponents 2020).

The industry 4.0 (Connectivity/Decision Making Ecosystems 2010s - Present) was the fourth industrial revolution by merging the technologies of industry 3.0 via creating smart technological ecosystems in order to shift the machines from "automated to "smart by communicating each other and exchanging useful data. This is not just a communication method between machinery but is the ability of the machines to "talking" to each other without the humans to play the intermediate connection link. The main representative core technologies behind the industry 4.0 are clustered in four pillars. Firstly the Interoperability Pillar by integrating technologies such as IoT (Internet of Things) – DT (Digital Twins) – Cloud Computing by providing the ability to machines to communicate and readapting their operation module. Secondly the pillar of Information Transparency by integrating technologies such as Big Data Analytics – Artificial Intelligence (AI) – Edge

Computing – Block chain by providing the ability to collect, store and analyze data in real-time by helping in the decision making process. Thirdly the pillar of Technical Assistant by integrating technologies such as Augmented & Virtual Reality (AR/VR) - Collaborative Robots (Cobots) - Wearable Technology & Exoskeletons by contributing in everyday problem solving process and undertaking routine task which are non-valuable for humans. Fourthly the pillar of Decentralized Decisions by integrating technologies such as Edge/Fog Computing - Agented AI and Multi-Agent Systems (MAS) - Industrial IoT (IIoT) & 5G/6G Connectivity by providing control, speed, flexibility and failure risk mitigation at every day chaotic data driven life.

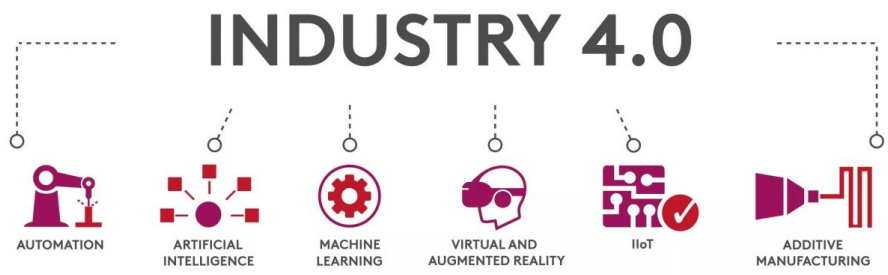

Figure 1.5: Industry 4.0 the Pure Digitalization (Source: essentracomponents 2023).

The Pharma 4.0 is a core part of Industry 4.0 by being more focused and specialized for the pharmaceutical industries. It aims to cover and solve the same problems but via a different framework which is driven by strict quality regulations – restrictions. The key technologies that have been a standard is the Digital Twins (Virtual replication of manufacturing lines used to simulate "what if" scenarios in real time production and re-adjust operation without wasting actual batches), the AI & Machine learning (Useful for predictive maintenance and continues Quality Monitoring) and the Block Chain (Creating a systematic audit trail for supply chain which is vital for preventing counterfeit drugs). The above mentioned technologies are crucial for the pharmaceutical industries in order to proceed and implement the Continues Manufacturing Framework (moving away from the classic usual "batch" processing to the non-stop dynamic flow with real time data evaluation by reducing the wastes/footprint) and the Quality 4.0 (is the automated dynamic

quality compliance testing which is built-in the operational process rather than at the end of the line).

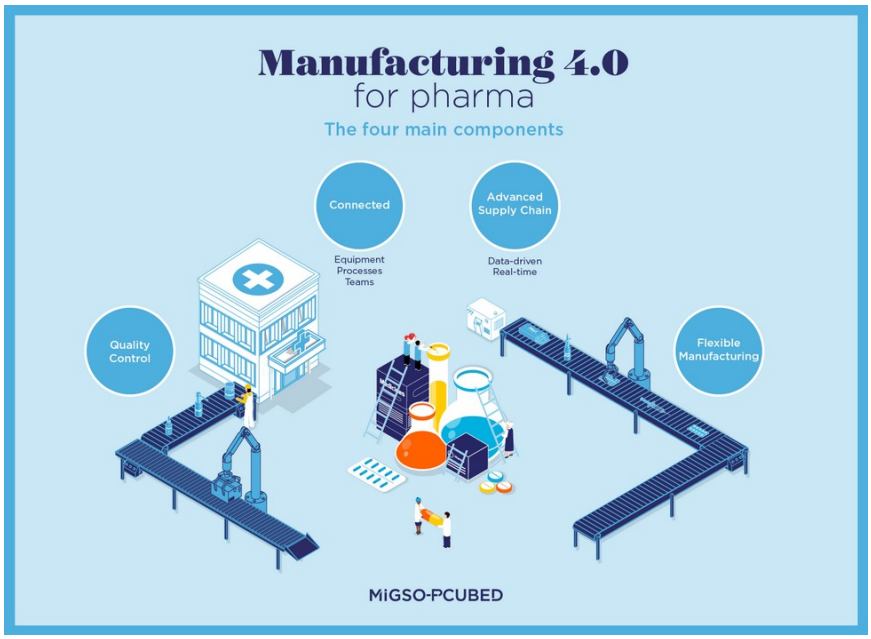

Figure 1.6: Pharma 4.0 The Four Main Components For The Modern Pharmaceutical Industry (Source: migso-pcubed).

1.1.1 The shift from traditional manufacturing to Pharma 4.0

The shift from traditional manufacturing to Pharma 4.0 is more than mandatory for the modern pharmaceutical industry because it represents more than a technological improvement to the already existing facilities and operation model. This fundamental Digital Transformation which is integrated in the way the medicines are researched, developed, produced and distributed focusing on creating a robust "smart" ecosystem to solve the known major problems such as Pharma Complexity, Cost Pressure and Quality Compliance. While the traditional manufacturing relies on data silos and reactive proves the Pharma 4.0 enhancing the Industrial Internet of Things (IIoT) by providing the tools for more efficient operation with higher quality compliance to entire product life cycle.

The advantage of real-time monitoring and continues processing provide the ability to Pharma manufactures to have a great level of predictability and adaptability by avoiding deviations which may occurred with the traditional manufacturing methods and have significant negative impact in their reputation and more critically to human life in case of malfunctioned products. Moreover, the failure and human error is mitigated in high degree by abandoning the huge load of paper work and the product release process is faster and more accurate that before by empowering the market and patients demand for drugs. These automated processes abstract non-valuable routine tasks from employees by creating a human resources pool which could be allocated wisely by the organization to support other more valuable tasks or these tasks which require more critical thinking process.

For these reasons and more the Pharmaceutical industries trying to adapt and integrate these technologies within their organization via Pharma 4.0 projects in order or create enhance Commercial-Social Value and significantly accelerating the time-to-market for life-saving treatments.

Figure 1.7: Comparison of Operational Models: Traditional Pharma versus Pharma 4.0 (Source: M. Kulkarni, 2023 linkedin.com)

1.1.2 The role of digital Transformation (DT)

The role of digital Transformation (DT) is far more than a simple upgrade of a Company's infrastructure because if represent the fundamental pathway on how an organization operates, produce and deliver value to its customers. The integration of technologies such as Artificial Intelligence (AI), Cloud Computing, and the Internet of Things (IoT) into each sector of the organization replace the traditional culture by introducing the new culture of continuous innovation, agile methodologies, adaptiveness and flexibility in a very challenging environment which are crucial sustainability assets as Vial (2019) argue that DT is a process where digital technologies create disruptions triggering strategic responses from organizations that seek to alter their value creation paths.

The primary role of DT is to bridge the gap between the human nature and the automated operational capabilities by increasing consumer expectations in an interconnected world. This venture requires digital maturity culture within the organization as Westerman et al. (2014) argue that digitally mature companies are those that combine digital activity with strong leadership to drive the change beyond the known limits and significantly create more profitable than their competitors. This means that by integrating this model the organization has the ability to be more flexible and open to personalize customer's experience. That has a great positive impact by underline the value of the DT role because allows the businesses to anticipate to customer's needs via predictive operational models and delivering the value both proactive and relevant to user needs.

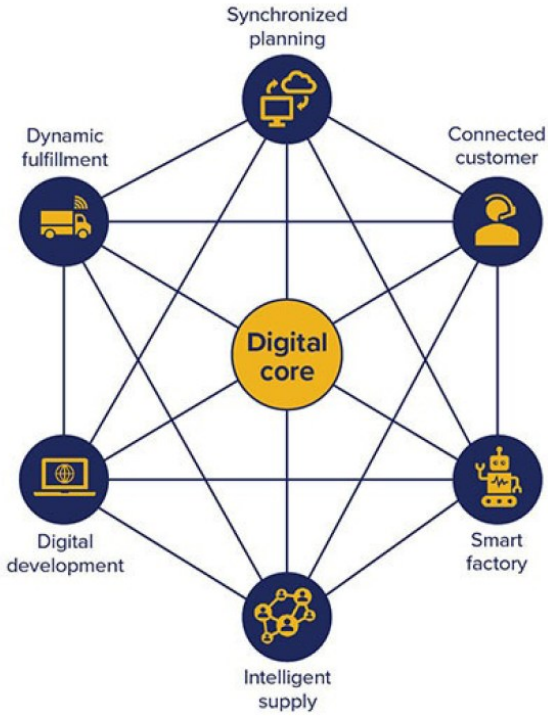

Figure 1.8: Digital Transformation Core Important Pillars (Source: Sinha, Amit 2020).

Beyond the significant efficiency and value gains, the role of DT is to ensure that the organization will operate within the proper way by ensuring long-term sustainability. The strong point of digital transformation is that creates a "digital culture" to the organization and introducing the strategy that encourage the risk-taking and continues improvement because this process is structured and has low risk of failure. The real-time visibility and the data analytics contribute positively to high hierarchy management levels because provide reliable and accurate data for the next strategic decisions. This survival mechanism via digital transformation creates a secure environment and competitive advantages that allow organizations to thrive and dominate in a "digital driven" landscape by differentiated them.

1.1.3 Differentiation of Pharma 4.0 from Industry 4.0

Despite the fact that Pharma 4.0 and industry 4.0 share common foundations regarding digitalization and interconnectivity they differ significantly on how are applied and the targeted objectives. The industry 4.0 focused on the integration of the Cyber-Physical Systems (CPS), the Internet of Things (IoT), and Big Data to maximize manufacturing efficiency and cross-sector flexibility while the Pharma 4.0 which is a term was coined by the international Society for Pharmaceutical Engineering (ISPE) in 2017 (ISPE 2017) is focused on the specialized extension of these technologies tailored to the unique regulatory constrains of life science by transforming the term “Smart Factory” into a concept of “Smart Quality Framework“ with primary driver not just the productivity but the absolute patient assurance and products compliance within a highly regulatory environment.

The most critical difference is the role of regulatory compliance and data integrity in each activity without exceptions. While the industry 4.0 prioritize the agility and cost reduction the Pharma 4.0 must operate within the strict boundaries of the Good Manufacturing Practice (GMP) by creating unique support frameworks like "Data Integrity by Design" and "Validation 4.0". Moreover, the Pharma 4.0 leverages the real time data in order to support the Continuous Process Verification (CPV) and Real-Time Release Testing (RTRT). Both ensure that each produced batch of product meets the strict quality standards without the need of retesting by being aligned with global health authorities like the FDA and EMA.

Table 1-1: Comparison between Industry 4.0 and Pharma 4.0 core features (Source: Adapted from Industry 4.0 baseline models vs. ISPE Pharma 4.0 guidelines).

Feature	Industry 4.0	Pharma 4.0
Main Goal	Efficiency & Speed	Compliance + Speed
Sector	General Manufacturing	Life Sciences Only
Focus	Productivity	Product Quality & Patient Safety
Regulation	Low	High (GxP, FDA, EMA)

Additionally the framework of the Pharma 4.0 emphasizing to a more agile-holistic "operation model" which include four main key pillars Resources, Information Systems, Organization and Processes, Culture by supporting strongly the Human Factor and the organizational culture in order to manage the complexity of drug development while the Industry 4.0 focuses heavily on technological "Horizontal and Vertical Integration". The collected data not only used for predictive machine maintenance but also for the Quality by Design (QbD) and Product Lifecycle Management (PLM) in order to provide a more precise drug development but also to build a mature pathway beyond the standard requirements of general Industry 4.0 applications. In essence, the Pharma 4.0 is a more specialized and agile model of digital transformation which was built not only to introduce the technologies of industry 4.0 but also overtake the emerged boundaries in pharmaceutical industries due to regulation and makes the Pharma 4.0 projects feasible.

1.2 Problem Statement

The pharmaceutical industry has long been focused on the Waterfall (Traditional) project management due to the nature of the drug manufacturing which is historically a linear process which ensures that the regulatory requirements are met for audit organizations

such as FDA and GMP. Therefore, this process requires completing successfully the previous scheduled production step in order to proceed to the next one by ensuring product quality/patient safety and is rooted deeply to the culture of pharmaceutical industries because is also supported by the Quality System. The transitioning to the Agile or Hybrid Project which presents agile and iterative actions is a fundamental change for this robust, tested and trusted operating project management model by creating at the first look and metaphorically speaking “huge earthquake” in the whole model of pharmaceutical organization. This required change will create fundamental problems and will be stopped immediately by the quality department because of potential risks and also from the executives because in business perspective this is a total reconstruction of the operation model of the business. The decision making process as is structured based on traditional pharmaceutical hierarchies which often require multiple layers of executive sign-off by creating bottlenecks that negate the speed benefits of Agile project management which is intended to provide. Additionally, the transition of the traditional project management to Agile or Hybrid requires two more significant complementary changes; in the culture of the organization and in the resources management which is also create barriers.

The pharmaceutical industries support the culture of the strict regulatory and compliance landscape which present a significant structural barrier. The regulatory documentation and Quality Assurance (QA) protocols which are applied vertically to all operation actions are designed for a specific sequence of process by supporting the Waterfall (Traditional) model. The requirements are fixed upfront while the Agile or Hybrid model supports the fast/adjustable requirements set up and continues audit readiness. This automatically states an administrative problem by creating synchronization problems and breaking the system's seals which is not acceptable without been strongly evaluated and validated. The disconnection between the rapid pace of software or digital health teams in combination with the slow and inflexible timelines of manufacturing departments may lead the organization to resource silos and "organizational friction" (Rigby et al., 2020).

The resource management and technical debt is another issue that poses substantial barriers during transition. The traditional pharmaceutical budget process is typically based on an annual project fixed basis with extremely low flexibility while the Agile model requires flexibility, instant cash flow capability in order to fund each department individually when is needed. Especially, in case of CDMO the huge Capitalized Investments (CAPEX) is strongly relied on external financial contribution via their customers which is not always an easy achievement for the DB department. Therefore, the agile project management in terms of financial perspective often meets strong resistance from the financial department by reducing or allocated the available funds to cover more important expenses such as operational. This financial resources management could lead to projects cancellation such as Pharma 4.0 despite the high technological/innovative characteristics and the overall future value because the operation process and the product delivery on time with total quality compliance is the first priority for the pharmaceutical industries.

1.2.1 Impact of Traditional Project Management in Pharma 4.0

The integration of Pharma 4.0 creates a paradox phenomenon for the traditional project management (TPM) methodologies, such as the Waterfall model due to the highly regulated landscape in the pharmaceutical industries. Despite the fact that the TPM is s accepted and valuable for the pharmaceutical operations and fully aligned with strict regulatory framework at the same time is creating multiple barriers for the modern digital technology Pharma 4.0 projects.

The TPM is still accepted and valuable for the pharmaceutical operations because of its linear, disciplined structure which is totally aligned with GxP (Good Practice) standards and Rigorous Validation Life Cycles. The audit organization such as FDA and EMA has prerequisites such as extensive documentation, clear stage-gate process models and predicted outcomes that could strongly support-ensure the patient safety and product

quality. The TMP frameworks link the user requirements directly to the functional core sector in order to create reliable specifications and validation testing processes by providing the required traceability and risk management essential features for quality compliance. The TPM could be assumed as the golden medal standard for the pharmaceutical industries by maintaining the validation state and providing a stable foundation upon due to pharmaceutical complex operations structure.

However, the TPM's non flexible process that ensures the compliance makes this project method a challenging foe for the to the agility project management method which is required for Pharma 4.0. The digital transformation of pharmaceutical industries relies on edge technologies such as Big Data, IoT, Digital Twins, Block Chain and AI all of which are requiring the iterative development and rapid fast action cycles in order to exploit the maximum value that TPM simply cannot accommodate. In traditional models any setup requires a formal documented time-consuming Change Control process by creating a bottleneck for the continuous integration and deployment (CI/CD) cycles typical of modern software. This process leads to significant impact of speed to market process which requires long time of Pharma 4.0 projects to be delivered even for years before the final validation by underlining that the specific digital technology may already be obsolete and not valuable for the organization anymore. Therefore, while the TPM protects the data integrity of the process, this core characteristic acts as a barrier to the agile method for Pharma 4.0 which requires real-time responsiveness and innovation that define the fourth industrial revolution in pharmacy.

1.2.2 Project Management team Structural Problems

The internal engineering teams which consist the core of the project management teams often operates with the traditional project management mindset which is characterized by a preference for establishment, linear methodologies like waterfall model and is contradicts with the needs of Pharma 4.0 projects which requires iterative and dynamic

processes in combination with high-tech integration. While the members of these teams are high experienced engineers with deep institutional, practical experience and core mechanical competency they strongly lack of adaptability to high –tech projects such as AI, Iot and Cloud computing. This could be considered as «digital illiteracy» by having a direct significant negative impact to the whole process. This structural rigidity often leads to the creation o a fundamental gap between the project management team and the project's goals implementation because the engineers may prioritize the long term stability and risk mitigation instead of the rapid prototyping and agile pivots required in modern tech-heavy initiatives. Consequently, if the project management teams don't shift towards to the Agile-Lean integrated project management it may fail to be synchronized with the fast-paced life cycles of the emerged digital health technologies (Kerzner, 2017).

In the pharmaceutical industries the term "bootstrapping" refers to the core operational foundations such as Good Manufacturing Practice (GMP) and Quality Management Systems (QMS) which are the regulatory constrains that rule the boundaries of engineering flexibility. This strict structure based on the pharmaceutical strict regulation ensures the safety and quality compliance but at the same time creates strong obstacle to the implantation of new innovative and non-standardized high-tech technology solutions. Within this strict landscape the project teams struggling to find the golden mean between two different frameworks, the Quality driven one in which the constantly moderated by Validation and Verification (V&V) protocols are mandatory for each change by requiring time/creating delivery delays and the Project one in which the time is limited and the high-end technology nature during implementation requires agility, fast decision making process and undisrupted synchronization between sections. Therefore, each technical change requires rigorous documentation and regulatory approval and the engineering's team mindset often adopts a more passive stance to avoid the "compliance debt" associated with radical innovation (Wysocki, 2019).

This approach points out the necessity of the project management team strategy to be extremely agile and have high adaptability by balancing the need of technological

advancement with the strict regulatory uncompromising safety standards of the pharmaceutical industry.

1.2.3 Strict Pharmaceutical regulations against Pharma 4.0 Projects

The integration of Industry 4.0 technologies into the Pharmaceutical Industry sector known as Pharma 4.0 is frequently stifled by the strict and historical risk-averse regulatory framework of Good Manufacturing Practices (GMP) and validation protocols which are mandatory for each action's change. Regulation protocols which are under the umbrella of GMP is the FDA 21, CFR Part 11 and EudraLex Volume 4, Annex 11 which are primarily designed and structured for static – linear process rather than for agile and dynamic driven environment which are required of smart factories. These regulations require exhaustive documentation and "static" process in order to ensure that the product's safety and production tractability to record possible defects.

Therefore, for Pharmaceutical industries who attempt to implement Pharma 4.0 projects by integrating technologies for autonomous systems such as Machine Learning (ML) algorithms/Digital twins by evolving the real time data process collection and analysis instantly the required Validation process will be a "deterrent wall". The traditional way of managing the re-validation process after every significant change in software or process it may create a prohibit administrative barrier to all involved organization's departments which often make unfishable to exploit the promised agility and continuous improvement value via Pharma 4.0 projects (Yingjie Chen,2022).

This regulatory friction has a measured significant impact on the progression of Pharma 4.0 projects which often leads to proceed with pilot phase project by applying the new technologies in a smaller area than was planned but unfortunately the innovation solutions fail to scale up beyond the initial testing. Especially, the support of strict compliance with Quality by Design (QbD) principles which are essential for patient safety while often lacks

the flexibility to support the unknown field of advanced Pharma 4.0 technologies such as Artificial Intelligence or the decentralized architecture of Block chain in supply chain creates a complex environment with negative impact to projects implementation. In more detail, the required high costs of compliance and the fear of regulatory non-conformity during inspections discourage the stakeholders from investing in disruptive technologies in terms of Financial and Human Resources.

This inactivity not only creates project delivery delays but also widen more the gap between the technological capabilities of Pharmaceutical industries and the "outdated in terms of technology" traditional compliance standards which are maintained by the global health authorities

1.2.4 Challenges for Pharmaceutical Industries during Pharma 4.0 Projects

The implementation of Pharma 4.0 projects and the integration of Industry 4.0 technologies like IoT, AI, and big data into pharmaceutical manufacturing industries face significant technical and financial challenges.

The primary challenge is the financial expenses nature which is widely used for special projects like Pharma 4.0 and is under the umbrella of the CAPEX which requires always a good ratio of ROI and IRR in order to be approved by the BOD. The problem is that the ROI and IRR of this kind of technological investments is not based on short term profits but on long term profits and usually their investment ratio is low and not attractive. May Business Units were designed for rapid production with fast delivered profits and relied on paper-dependent batch processes by making both costly and complex the transfer to the next technological field of Pharma 4.0 by creating automatically a serious challenge for the industries.

Furthermore, the technical challenges such as data fragmentation and a lack of interoperability between different systems which also require high expenses to be solved, creates a communication barrier regarding the information exchange among departments which is essential for achieving the full benefits of a digitalized environment (Tetteh-Caesar et al., 2024).

The secondary challenge but crucial as well, is the profound organizational and regulatory difficulties which often creates a huge “skill gap” where the existing workforce lacks the required expertise to operate high-end technologies or are not familiar. This obstacle create the need of re-skilling training and recruitment of new skilled workforce outside of the organization by increasing the OPEX cost and the tech maturity preparation time of the organization. The general challenge is the organizational resistance to change, training and adoption of the new Digital thinking mind set from the bottom to the top of hierarchy by excluding the middle management and experienced staff that may be hesitant to abandon traditional, validated methods (Tetteh-Caesar et al., 2024). In the spectrum of regulatory perspective the complex nature of the new Pharma 4.0 technologies and its core of software and algorithms point out a huge validation dilemma due to the lack of interoperability.

This lack creates difficulties regarding the satisfaction of stringent transparency and traceability standards which are required to ensure patient safety and Good Manufacturing Practice (GMP) compliance standards (Silva et al., 2020).

1.3 Research Objectives

1.3.1 Evaluation of Agile and Hybrid project management model in Pharma

The evaluation of the Agile and Hybrid project management models in the pharmaceutical industries reveals not only a transition from the traditional model to the new one but also a strategic shift toward by balancing innovation with strict regulatory compliance.

The pure agile method often adopts a fast track and aggressive approach which could shake the foundations of the existing applied traditional waterfall method. The Agile method could be a great strategic decision for small scale projects with specific areas such as early –stage of R&D (Research and development) projects and digital initiative where the rapid hypothesis testing and has as output the faster time-to-value is allowed by reducing the "discovery-to-trial" timelines. Due to the fact that the agile method provides flexibility but at the same time lack of formal structure at the late-stage of the project could be less accepted from the quality department. Anyhow, the project teams can utilizing short fast tracks to validate hypothesis by identifying the diffusion criteria for the non-viable sections much earlier by preventing the sunk-cost sunk-cost fallacy often associated with long-term linear planning and avoid the implementation of a project based on past, unrecoverable investments (time, money, or effort) rather than current benefits (PMC, 2025).

In contrast, the Hybrid model has emerged as the golden mean for the pharmaceutical industry for the large-scale drug development by introducing the bridge between the required agility/flexibility for innovation and the Quality standard compliance which is a prerequisite. This model combines the Agile iterative when ever is applicable such as trials, testing and data management while maintaining the Traditional model "Waterfall Stage-Gate process" structure for the high-demand Pharma regulatory milestones without creating deviations and negative impacts. Additionally, the Hybrid models are more

effective in the complexities of modern supply chain and digital initiative while the pure Agile model may lack the Audit trail required analysis during final validation process.

The Hybrid model and its combined principles can manage efficiently the valuable complementary assets from Traditional and Agile model for the Pharma industry by providing a powerful balanced blend of adaptive capabilities. This methodology ensures that, speed/flexibility does not come at the expense of safety/efficiency while balancing the demand for rapid technical/scientific pivots with the strict requirements of GxP documentation (Planta, 2024).

1.3.2 Critical Success Factors (CSFs) of Agile and Hybrid models

The successful implementation of Pharma 4.0 digital transformation projects for pharmaceutical industries via the high-edge technologies such as IoT, AI and big data analytics requires strategic planning and the shift from the Traditional model to a more flexible such as Agile and Hybrid model. The decision making regarding which model will be chosen is strongly linked with the project's complexity and the regulatory constrains impact which should be covered. Both models have its own unique Critical Success Factors by contributing actively to successful implementation of Pharma 4.0 projects by exploiting its value for the organization.

The following analysis introduces the main representative CSFs, both for Agile and Hybrid models.

The Agile model which uses methodologies such as Scrum, Kanban usually is used in software Pharma 4.0 projects because the requirements and the milestones needed to be evolved rapidly.

The first CSFs is the Management commitment which requires especially from the senior management to switch from the authoritarian management “command and control” to the supportive leadership. This switch is crucial and vital for securing that the required high-budget expenses needs for the Pharma 4.0 projects will be provided without delays or financial cut downs.

The second CSFs is the Team Capability by creating robust and cross-functions structured teams such as (IT, Quality, Production, Technical Services) by empowering and exploiting a multi-skill environment full of complementary assets with the most important the “Data integrity by Design” knowledge.

The third CSFs is the Agile culture which must me “cultivated” to the organizations structured from the top to the bottom and vise versa. This new mindset provides the shift from the “fail-safe” with high-end impact to a “fail-fast” with low impact because the identification of something that is not working in an earlier stage protects the organization to invest time, human resources and funds to something that will not create value.

Despite the fact that is difficult to apply in a regulatory environment is essential for the iterative process of digital innovation. The fourth is the Active Stakeholder Engagement which is a complex process but extremely important because creates the fundamental communication stream flow. The continuous feedback from end-users such as laboratory technicians, technical services and operators provide all required data to the project management team in order to evaluate and ensure that the digital tools are effective or not by adapting their strategy accordingly. The Agile’s strong point in Pharma 4.0 is the provided stability to manage the uncertainty because many technologies are in experimental level without long term feedback and the iterative process provides a constant realignment with "Validation 4.0" standards (ISPE, 2025). This type of model could be chosen in the case of Pharma 4.0 when there is high variability (the ideal process isn’t known), low manufacturing risk (low intervening in existing machinery) and demand

for fast delivery of Minimum Viable Product" (MVP) for internal decision-making process.

The Hybrid model which combines the structured planning process from the Traditional "Waterfall" model and the iterative process execution of the Agile model, creates the Industrial Standards for the Pharma 4.0 project management by involving multiple sectors of an organization in a harmonized way to a common target.

The first CSFs is the Alignment with Strategy which is a crucial factor because the Hybrid projects must bridge the gap between the strict regulatory road maps of an organization and the short-term digital delivery times in order avoid the technology outdated effect.

The second CSFs is the Regularity Compliance because have to incorporate with Quality Risk Management process and Quality of Design by integrating these features in their initial strategy and ensure that validation is a deliverable target.

The third CSFs is the Technological Infrastructure by creating and integrating a "Digital Thread" with a seamless data flow stream across the product lifecycle in order to be collected, analyzed and evaluated (Vimachem, 2025).

The fourth CSFs is the Defined Governance which is a fundamental factor by creating clear roles/responsibilities in a complex project management model by strategically creating sub-teams to handle the structured "Waterfall" milestones (construction, hardware installation) and the "Agile sprints" (software configuration, data integration). The Hybrid model is the golden mean for complex system integrations which require high-edge technology and proven documentation while allowing flexibility.

This type of model could be chosen in the case of Pharma 4.0 when there is high regularity impact (projects involving GxP), physical dependencies (installation of equipment on existed validated machinery) and complex collaboration (among multiple departments).

1.3.3 Process framework phases for digital transformation Pharma 4.0 Projects

The implementation of Pharma 4.0 projects requires a holistic organizational strategy, team members with vision-adaptation in new technologies and technological ecosystems which will support the digital transformation by bridging the gap between the traditional pharmaceutical quality systems (PQS) and the technological enablers of Industry 4.0. This specialized framework which was proposed by the International Society for Pharmaceutical Engineering (ISPE) focused on the integrated operating models with first priority to provide balance in to four key elements Resources, Information Systems, Organizational Structure, and Culture. The Digital Maturity and the Data integration by design are the major pre-requisite enablers to start the process framework for digital transformation in Pharma 4.0 projects. This process methodology is distinguished in four main pillars.

The first phase is the Assessment & Governance by involving the analysis and the identification of possible operational/technological gaps by using the industry 4.0 maturity index framework in order to assess the current state of “computerization” status and interconnectivity across all organization’s departments. This phase is fundamental because provides the actual status of the organization by giving all necessary information to the project team to build up a tailor-made strategy and ensures that the organization has the required maturity. Moreover, the vision and priorities defining the exact business case and goals demand by helping in the process of sequential road map creation will transform the data into actionable intelligent and mature path for the stakeholders. This structural but at the same time addictive process is crucial in order to create clear coals and processes by avoiding deviations during venture. The visibility and transparency is the main focus by breaking down into smaller parts the data silos through real time feedback by creating the process mapping.

The second phase is the Design by including the Validation 4.0 process from the beginning and be aligned with quality regulations or in other words implement the Quality of Design (QoD). This holistic control strategy is very crucial because instead of performing testing at the finalization stage of the product, the system is initially designed to continuously monitoring the whole process through the high-end digital technologies based on (Process Analytical Technology - PAT). Additionally, the fact that the initial design integrates the quality fundamentals and is respecting the GAMP (Good Automated Manufacturing Practice) principles, projecting a high level of risk based approached which will be accepted by Quality Department and ensures that the digital system is compliant and validated for its intended use.

The third phase is the Execution & Integration by involving multiple departments and sectors and is the interconnection stream flow between different systems, machinery and departments in and out of the organization. This phase could be considered as the data and information translator between departments or machines and is distinguished in Vertical and Horizontal Integration. The Vertical integration provides the function to connect the internal operations with the management level such as the shop floor via the installation of (sensors/PLCs) to its machinery via using programs such as (MES/ERP). This data thread provides the live tracking and status of the business plant operations by giving the opportunity to the managers to take quick and precise decisions in order to adjust and enhance the operational value. The Horizontal integration provides the competitive advantage to connect the internal sectors of the organization with the external world by creating collaboration networks between strategically selected organizational departments such as supply chain with raw material suppliers up to the patients. This direct communication provides speed, agility and direct feedback by helping the organizations to re-adjust and evaluate their process and products and exploit the benefits of fast market adaptiveness.

The fourth and final phase is the Monitoring & Scaling which including a crucial step for the sustainability of the applied technology by verifying the success digital transformation.

The continuous verification process (CPV) uses the generated data and technologies in order to apply the periodic re-evaluation and provides the required documentation by ensuring that the systems were tested and monitored continuously and all identified emerged deviations or malfunctions were been solved. Moreover, this process provides the opportunity to the organization for Continuous Improvement (CI) and open the path way for further scalability. Due to the fact that, the most of the Pharma 4.0 technologies are applied as pilot phase projects in order to be tested and validated with the minimum operational impact the next step is the move from the successful (monitored& validated) pilot "Lighthouse" project to full-site implementation by exploiting the core value of Pharma 4.0 technology via a robust centralized ecosystem.

1.4 Significance of the Study and contribution to Life Science

1.4.1 Theoretical contribution

The theoretical contribution of this study is relied on the conceptual synthesis of traditional project management with the engineering requirements of Pharma 4.0. While the existing literature often treats the digital transformation projects/methodology as distinct silos which are hard sometimes to be implemented it bridges this gap by mapping the Agile and Hybrid project management Success Factors. It also illustrates how the organizational agility acts as a crucial sector by providing to firms the systems to interconnect data-driven manufacturing environments.

Additionally the systematic review provides a theoretical approach to digital transition and its benefits. It contribute by identifying the specific boundary conditions under which a hybrid project management approach outstand versus a purely Agile or Waterfall project management methodology within a strict and highly regulated industry by isolating the "quality-by-design" (QbD) constraints and the non-negotiable nature of GxP compliance and providing the hierarchy of the Success Factors which are required in the high-

compliance digital ecosystems. This framework provides the relationship testing between project structure management and the long-term sustainability of digital transformation in pharmaceutical industries.

1.4.2 Practical contribution

The practical contribution of this study is to provide the required strategic road map for the pharmaceutical industries by providing the important milestones for the complex transition toward to Pharma 4.0. The synthesizing of Success Factors of Agile and Hybrid project management offers to the project leader and stakeholders a validated and tested framework via which they have the ability to enhance operational flexibility while maintaining the rigorous compliance standards characteristic of the industry. The project teams can utilize the findings in order to identify the specific bottlenecks of their organization and process with the proper hybrid methodology which is suitable for their needs by balancing the speed and iterative project management cycles with the structured documentation required by regulatory bodies like the FDA or EMA.

Additionally, the study provided the methodology which could be used as a decision tool by allocating wisely the resources and mitigating the potential risk during digital transformation. It also highlights the critical Success Factors which are mandatory for the organizations by adopting the hybrid models identifications specialized for the pharmaceutical industries by reducing the risk of failure and accelerating time-to-market process through more efficient, digitized manufacturing and distribution ecosystems.

2. Chapter 02: Literature Review

The Pharma 4.0 is more that a key word when referring to the digital transformation at pharmaceutical industries. It represents the new governance system of physical pharmaceutical manufacturing industries which are equipped with advanced digital ecosystems by creating autonomous systems. These ecosystems are equipped with high end industry 4.0 technologies and the most common key driver technologies for pharmaceutical industries are the Artificial Intelligence for predictive maintenance/generative AI, the Digital twins for live time simulation/continuous monitoring of Quality by Design (QbD), the industrial internet of Things using edge computing and the advanced robotics for vertical automations with low human-error contamination.

Despite the benefits there are possible barriers which may emerge during the digitalization process by preventing the adoption across the industry such as Validation Complexity (every digital system must be validated under the GMP regulations), Resistance to Change (the fear that the automation will replace the human roles), Data Silos (organizations may have fragmented old software non-compliance with modern platforms), High Investment Costs (Capital requirements for new technology with non attractive ROI) and the lack of talents (critical lack of professionals who can understand both data science and pharmaceutical process chemistry).

2.1 Pharma 4.0 Foundations via ISPE Framework

The adoption of the smart factories and the introduction of Lighthouses (advance manufacturing sites) is an important representative paradigm regarding the digital transition in the pharmaceutical industry by abandoning the classical operation way which

is consisted of bureaucracy and paperwork. The interconnected digital ecosystems in accordance with International Society for Pharmaceutical Engineering (ISPE), Pharma 4.0 is not just a simple process of new technology implementation but us a vertical and holistic (operating model) which is structured around a "4x2" matrix consisted of four structural elements the foundations (pillars): Resources, Information Systems, Organization Processes, Culture and two enablers (act as activators) Digital Maturity and Data Integrity by Design (ISPE, 2017). The smart factories utilize the combination of cyber-physical systems and Internet of Things (IoT) by creating a digital flow stream of real-time data by enhancing the decision making process. The increased productivity of these types of factories is a crucial for the profitability by ensuring at the same time the quality compliance without crating any negative impact and the complexities of personalized medicines and global disruptions.

The ISPE Pharma 4.0 guidelines are set up in a specific way by providing a structured roadmap for this transformation venture via a six-stage Digital Maturity Model by providing the mandatory guidelines to the companies from basic computerized systems up to the high-end technology systems (ISPE, 2021). In contrast with the general industry 4.0 initiatives the Pharma 4.0 emending the health regulatory best practices into its framework by ensuring that from the first step the innovation will be compliant with GxP regulatory. The strategy emphasize and endorsing the holistic control approach in which the real-time data are integrated with Management Systems (LIMS) and Enterprise Resource Planning (ERP) by providing flourished silo of valuable historical data. The maintaining and the analysis of these data allowing the manufactures to identify and solve the occurred problems in combination with technologies such as digital twins and mitigating production risk. Finally, the ISPE framework point out that the Pharma 4.0 is an essential enabler for the next level of pharmaceutical products production process by shifting the industries from the traditional production process to the fully digitalized oriented architecture where the patient safety, product quality, operational agility and on time delivery is the first priority.

2.1.1 Pharma 4.0 via ISPE Framework (Four Element Pillars)

The ISPE Pharma 4.0 operating model is a strategic framework which is designed in a specific way in order to bridge the gap between the traditional manufacturing processes with the new digitalized ecosystem by exploiting the value of industry 4.0 technologies. This framework has the four following structural elements in order to endure that the transition via digital transformation it's not only an upgrade but a holistic organizational shift.

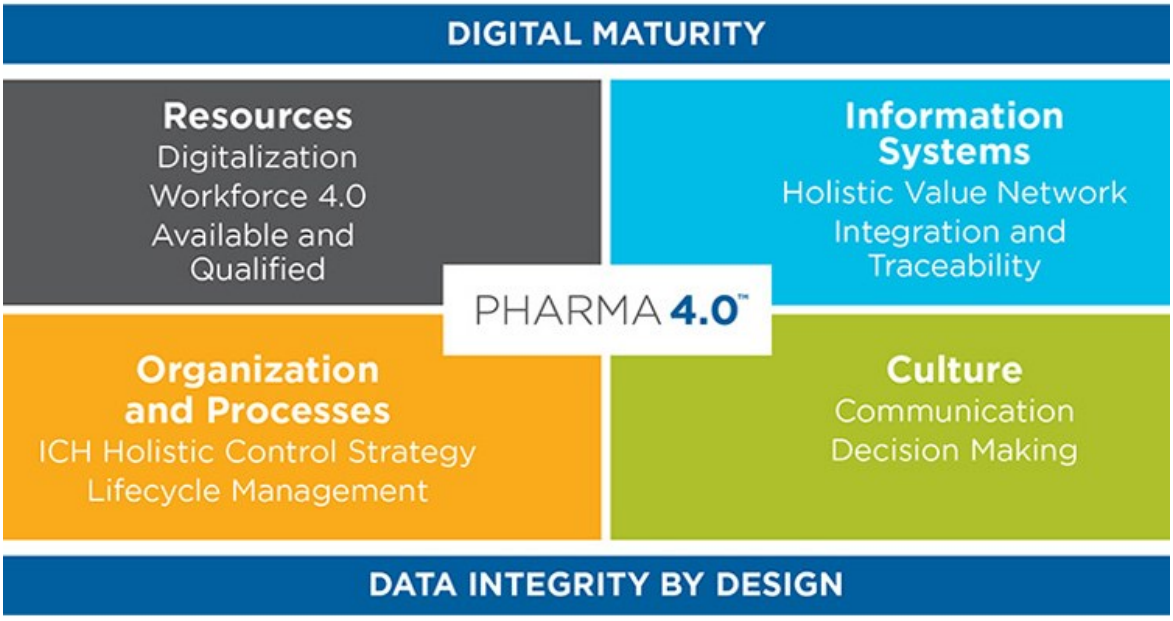

Figure 2.1: The ISPE Pharma 4.0 operating model (Source: ISPE Baseline Guide Vol 8: Pharma 4.0 2023)

1. **Resources:** It represent the physical and existing assets of an organization and in case of Pharma 4.0 have been transformed from static "tools" into "smart" entities by having the ability to generating and sharing data such as:

1.1. **Human resources** which are interconnected digitally by using AR for live support during operation, AR for equipment use training without loss impact or mobile tablets for paperless operations.

1.2. **Machinery & Equipment** which are equipped with smart sensors and interconnected via IoT by creating and sharing valuable operational data which could be uses for predictive maintenance plan.

1.3. **Physical materials** by utilizing technologies like block chain and advanced RFID scanning process by ensuring the end-to-end encryption/traceability of APIs and finished product for the complete life cycle.

2. **Information Systems**: It focus on the core of the digital infrastructure by capturing the process, sharing data accordingly to specific receivers and help the organization ot move from static data "Silos" to dynamic data source "Single source of truth" such as:

2.1. **Connectivity capabilities** by integrating vertically the shop floor to ERP systems and horizontal to supplier to patient systems.

2.2. **Data integrity by Design** is a crucial systemic element which ensures that the data is attributable, legible, contemporaneous, original, and accurate from the start of the process.

2.3. **Advance Analytics** by using Big Data and AI technologies to move from descriptive to predictive analytics by enhancing the operation stability.

3. **Organization and Process:** It redefines how the tasks could be allocated and how the organization's processes are managed in a digital environment such as:

3.1. **Process Mapping** by shifting from standard operating procedures (SOPs) to digital workflow systems by adapting real time.

3.2. **Agile Governance** by replacing the classical decision making process by integrating the new era of Agile cross functional department collaboration by responding quickly to data-driven insights.

3.3. **Holistic Control Strategy** by ensuring that all digital processes are integrated with the traditional Quality Management System (QMS).

4. **Culture:** It represents the most difficult sector to be mastered while trying to share values and behaviors alongside the organization in order to create a digital operational approach such as:
   4.1. **Digital mindset** is a shift via it's the employees at all hierarchy levels have to embrace the new technology and data management as an improvement for everyone rather than as a job security threat.
   4.2. **Knowledge Management** by prioritizing the undisrupted and continuous information sharing and learning's by conducting dynamic training.
   4.3. **Change Management** by managing actively the human factor mindset regarding the digital transformation process by mitigating the resistance and creating a secure environment in order to exploit the maximum value by fostering innovation.

2.1.2 Pharma 4.0 via ISPE Framework (Two Enablers)

While the four structural elements provide the foundations and the robust structure for the digital transition the two enablers (as following) are mandatory in order to "detonate" the process and drive the digital transformation forward (ISPE, 2020).

1. **Digital Maturity:** It refers to the organization's capability to empower, support and leverage the digital technologies in order to achieve the business objectives and deliver the Pharma 4.0 project requirements. In this case it's not the case for an organization just to own the latest or the most advanced software but it is how this technology will be integrated and how much the operations smart will be by enhancing the value. This process including six sequential stages which are adapted for the pharmaceutical industry in order to activate and unlock the required digital maturity level such as:

1.1. **Computerization:** The manual processes are replaced with the automated via using digital tools.
1.2. **Connectivity:** The equipment interconnection through IoT ecosystems by braking down the old static data silos.
1.3. **Visibility:** The capability to collect and archive all real-time data which are produced from equipment and processes by providing a crystal clear picture of the live current status.
1.4. **Transparency:** The capability to analyze the collected data by identifying the root causes and provides to all engaged levels the exact-evaluated the understanding and reasoning of the causes.
1.5. **Predictability:** The capability to use simulation tools like digital twins, AI and ML algorithms to simulate and forecast future status and what will happen in order to be proactive.
1.6. **Adaptability:** The capability for the systems to analyze its operation progress and proceed with decision making process by making autonomous decisions to optimize the output “smart & autonomous self-optimized factories).

The digital maturity can create a “roadmap” in order to bridge the gap between "Paper-based" and "Pharma 4.0 but requires the shift from reactive to proactive data drive optimization process.

2. **Data Integrity by Design**: It refers to the proactive integration of the data into the organization’s process by controlling throughout the entire lifecycle from the initial planning up to the decommissioning of the system. This framework is a preventive action by checking through the system architecture the data while being created instead of focusing on final check after the data are created and is distinguished in four main key pillars such as:

2.1. **Risk-Based Approach:** Using quality risk management methods in order to identify which data are the most vulnerable and need more attention.

2.2. **ALCOA++Principles:** Applying a comprehensive framework by ensuring that the data integrity is valid and not disrupted throughout its lifecycle.

2.3. **Critical Thinking:** The engineers and the quality teams have to map out the data flows streams wisely and methodically by identifying the bottleneck stages via automated systems instead of applying traditional checklists.

2.4. **Knowledge Management:** The method of treating the data as a valuable and strategic asset for the organization in order to ensure patient safety and product quality.

The enablers could be considered as a safety zone in Pharma 4.0 demanding environment due to the massive data and required standard manual checks at each stage of operation. The digitalization and the data integrity should be embedded in the organization's core mindset and "DNA" by ensuring the all automated decisions been made via the correct and quality approved process and create a robust/trustworthy outcome regarding the applied software/hardware.

2.2 Project Management Methodologies

2.2.1 Traditional model in Pharmaceutical Industry (Waterfall)

The traditional project management (Waterfall) in the pharmaceutical industry respects and follows the linear sequential flow which is a systemic and strict structured flow by requiring the completion of the current stage in order to proceed to the next one. This approach is classical for this kind of industry and is rooted back to the principle of distinguishing the progression in to distinct main phases: Requirements, Design, Implementation, Verification and Maintenance. In the strict regulatory environments like the pharmaceutical industries this structure ensures that every stage upon completion has meet all predefined benchmarks before moving to the next stage which is an accepted

procedure for the regulation auditors (Wysocki, 2014). The core mechanism is the stage – gate process in which the senior stakeholders review the main phase principles of the project against strict quality and safety criteria before approving the investment. This created a clear project road map with clear fixed and evaluated milestones by allowing the correct budgeting progress and resources allocation.

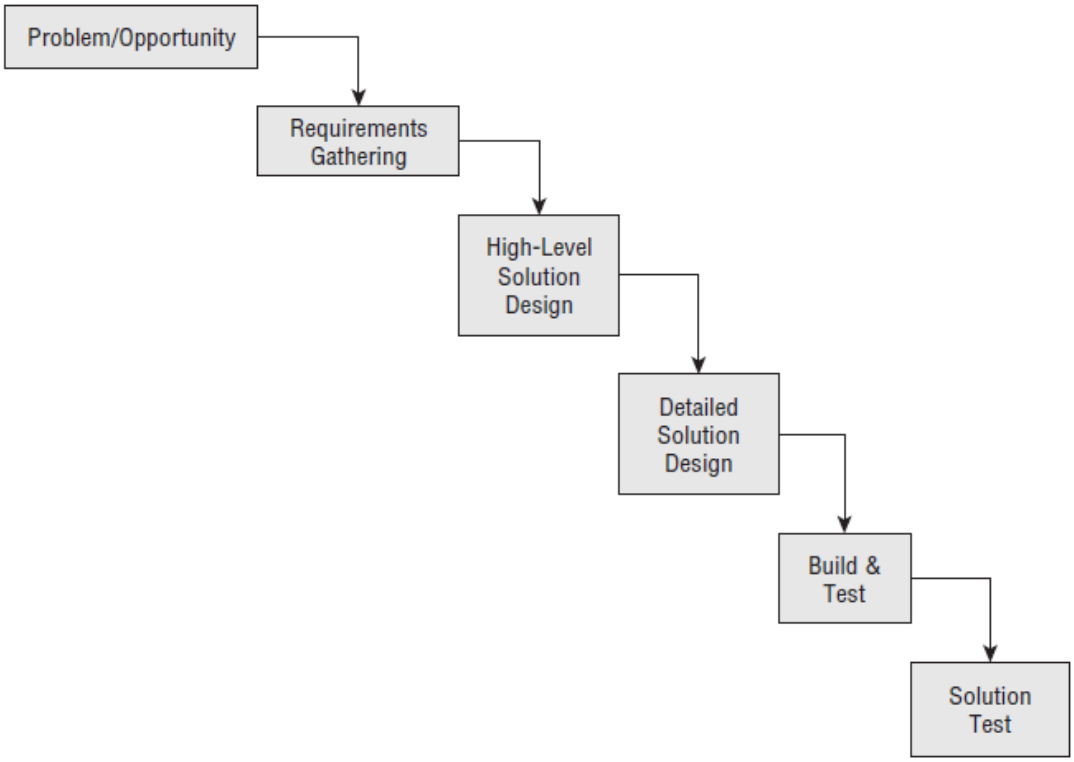

Figure 2.2: The Standard Waterfall model (Source: Wysocki, 2013, Effective Project Management 7nth Edition)

Despite the early adaption of Agile projects the Traditional project management is a standard must for the pharmaceutical industries due to the inflexible and structured regulatory requirements. In contract with the software where a feature could be modified without impact in the drug production each modification or formulation or process requires, testing, validation and regulatory approvals like FDA or EMA. The high cost of a potential failure in Pharma Industry and the impact on patients make the predictability and the structural base of the traditional project management extremely attractive due to the

ability to provide a robust audit trail and documentation framework and ensure the process traceability and verification which is essential for for GxP compliance (Kerzner, 2019).

2.2.2 Agile model in Pharmaceutical Industry (Dynamic)

The Agile project management in Pharmaceutical industry represents a fundamental shift from the traditional project management to a new dynamic and flexible approach which includes iterative, cross functional collaboration vertically within the organization. Historically the pharmaceutical industries relied on the traditional management in terms of drugs research, development, productions and clinical trials by exploiting the value of this structured stage gate process. The core mechanism of the agile project management is based on flexibility and iterative by repeating the same or previous steps as much time is required in order to produce the required result. This agility provides the capability to the project management teams to test and trial before deliver the tasks. The use of Agile project management can provide a speed improvement more than 20%, reducing testing by 50%, and boost patient satisfaction by 50 points in some cases by breaking the data silos in smaller parts and perform multiple iterative tasks at the same time in order to manage the complex regulatory environment fast and precise (McKinsey & Company 2024).

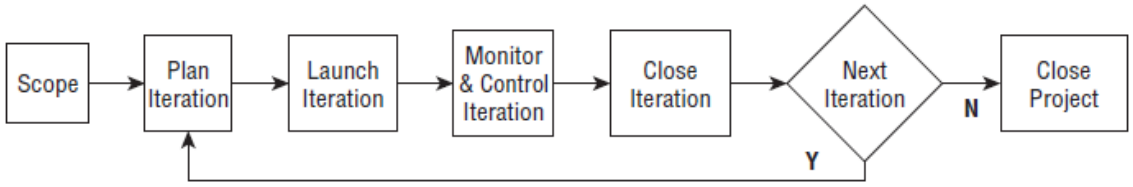

Figure 2.3: The Agile model (Source: Wysocki, 2013, Effective Project Management 7nth Edition)

Additionally, the teams have the ability to allocate the resources and create dedicated specialized small teams to each task without disrupt the quality compliance and ensuring that each process is strictly evaluated and performed as it was planned. The major agile principles emphasize to transparency empirical control and continuous improvement by

utilizing frequent processes of inspection and adaptation cycles by refining the protocols and engaged strategies. The shift from traditional to agile project management does not by pass regulation requirements but instead integrates the quality assurance compliance directly into the process development flow by ensuring that always that the projects will be aligned with global health authority standards and can be performed via the Agile Manifesto process.

The Agile Manifesto in pharmaceutical industry represent the strategic process shift from the sequential stage-gate waterfall process towards to an iterative cross functional approach which is designed to accelerate innovation while maintaining strict regulatory compliance. Originally was adapted from the software sector by emphasizing on its core values individuals-interaction over procedures and immediate respond to changes via iterative fast pace actions. This approach in Pharma is utilizing short quick actions regarding data analysis and continuous stakeholder feedback by providing the opportunity to the organizations to identify the “fail-fast” scenarios in an earlier stage during the drug development/production and ultimately reducing the high cost of negative impact and reschedule fast the next corrective actions.

2.2.3 Comparison of Agile VS Waterfall Model in Pharmaceutical Industry

The Choice between the Agile and the Waterfall model in the Pharmaceutical industry often has to deal with the emerged dilemma conflict between the need of speed to deliver fast and exploit the value and the non-negotiable strict quality requirements which must be meet. The Waterfall model historically has been the gold standard because its linear stage-gate process is aligned perfectly with the quality regulations and the industry’s V-Model regarding validation process. Specifically, during drug development a mistake will have an enormous negative impact by making the Waterfall model the strictest and controlled method by emphasizing on validated documentation and fixed non-negotiable milestones

which is a great fit for high-stakes environments where the thought of moving fast in parallel directions is not an option.

However, in the modern and technology driven pharmaceutical industries the landscape has changed by adopting slowly the Agile project model and supporting the data-driven operations. In contrast with the Waterfall model, the Agile model focus on dynamic iterative cycles, testing & trial and continuous two-way feedback from each stakeholder by collecting and evaluating in real time each situation by empowering the fast decision making reaction. This provides flexibility for quick adaptation and micro modifications in a fast and high demanded environment. The key point is that this model shows a new multiple roadmaps without bypassing the stringent quality gates required by global health authorities like the FDA or EMA.

Table 2-1: Comparison table of Waterfall model Versus Agile model Principles

Feature	Waterfall Model	Agile Model
Approach	Linear and Sequential stages.	Iterative and incremental dynamic cycles / test and trial.
Flexibility	Low capabilities and changes are costly and difficult.	High capabilities and fast changes at early stage are cheap and easy.
Documentation	Extensive with a lot of paper work and bureaucracy.	More control due to demand break down and integrated in the product.
Risk Management	Initially identified and fixed later with high impact.	Evaluated and mitigated continuously with less impact.
Validation	Occurs at the end of the lifecycle before final approval.	Integrated into every action and iteration by ensuring the compliance in real time.

The adoption of Agile method in pharmaceutical industries facing significant barriers due to unique and strict regulatory landscape despite the fact that offers new valuable features. These barriers could be the required fixed compliance targets, the traceability risks and the safety criticality. The golden mean is the Hybrid Model which is considered ad the most effective way by combining the traditional model for strategy-compliance and the Agile for execution actions.

2.2.4 Hybrid Model in Pharmaceutical Industry

The Hybrid model in the Pharmaceutical industry represents a wise strategic decision by using a framework which combines the structured, sequential discipline of the Waterfall methodology with the iterative, flexible nature of Agile in order to create an adaptive multi-speed project management process flow which depends on each need. The core strong point of the Hybrid model is the ability to partitioning the project tasks based on risk and volatility.

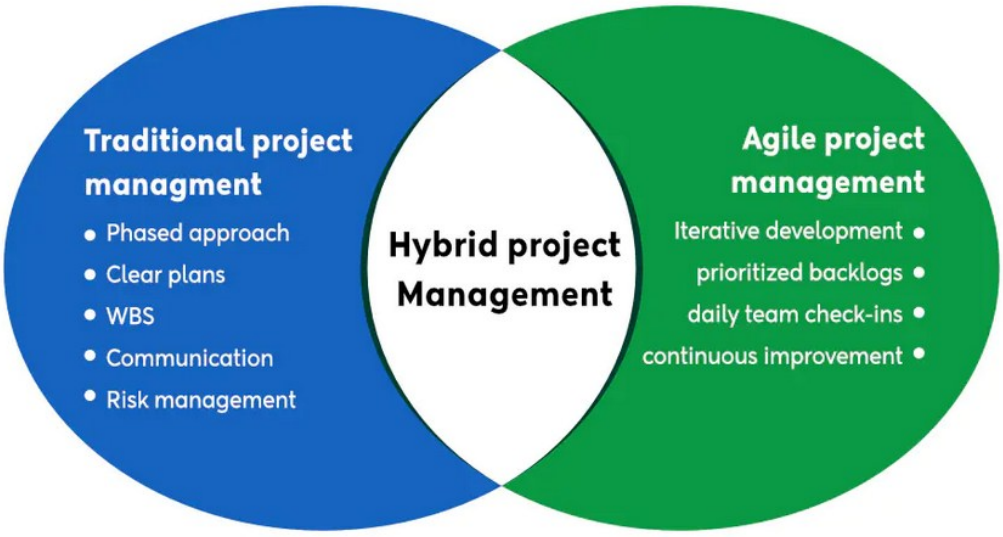

Figure 2.4: The Composition of Hybrid Project Management Frameworks (Source: S. Kashyap ProofHub 2026)

The model leverages the major principles of the Waterfall linear model in order to create a structural road map by ensuring that that Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) meet strict GxP (Good Practice) standards. The detailed documentation which is required by regulatory authorities like FDA can create physical foundations for the project and point out the stability, security and validation compliance from the initial stage with full control of each action. This capability is extremely important for the quality department because it creates a secured environment and supports the regulatory compliance by making easier to receive the relevant approvals.

Additionally, the model applies the principles of Agile model by creating iterative sprints to build up, test and continuous refining the technology sector. This approach provides the opportunity while implementing Pharma 4.0 projects to have fast validated results before proceed to the next stage without disrupted the quality regulation. This helps the engineering department to complete the digital transformation tasks from technology perspective fast, precise and in parallel with the traditional model by mitigating "bottleneck".

The Hybrid model provides the ability to combine the complementary assets from both models by creating a compatibility stream flow and protecting the principles of each model. This combination creates a powerful adaptive model that minimizing the delivery time but maintain the required quality at the same time by using the following major principles.

1. **Structured Governance**: The important milestones which require regulation are tracked via Waterfall model by satisfying the stakeholders and regulatory reporting.
2. **Iterative Execution:** The development teams have the ability to run Agile method for specific tasks via short sprint cycles which allows the continuous integration and feedback.

3. **Compliance Integration**: The automated and continuous Agile validation techniques are used to create documentation incrementally at each step of the project rather than at the end by minimizing deviations.
4. **Risk-Based Allocation:** Managing the heavy regulation documentation via Waterfall model because is reserved as high-risk tasks and technology installation reserves as low-risk being managed via Agile model. This adaptability creates a dynamic management process by choosing the proper method depending on risk task evaluation.

Table 2-2: Comparison Table of traditional vs. agile vs. hybrid project management (Source: S. Kashyap ProofHub 2026)

Feature	Traditional	Agile	Hybrid
Planning	Upfront	Ongoing	Initial planning but not strictly fixed. Room for changes
Flow	Linear and sequential	Incremental and iterative	Blend of sequential, overlapping, iterative
Deliverables	Fixed	Changing	Fixed with space for improvement
Timelines and costs	Upfront fixed	Ongoing calculations	Some upfront idea with space for changes
Change management	Difficult, disrupts the flow	Quite easy as you are working in short cycles	Better than waterfall
End-user feedback	After the big launch	Throughout the development process	Throughout the development process
Client collaboration	Heavily during the planning phase and launch	Throughout the project	Blend of both
Project types	Well-defined fixed requirements, stable market environment	Evolving requirements, fast-paced market environment	Projects with some defined elements and room for change
Testing	After the development phase	After every sprint	After every sprint
Team collaboration	Within the department	Cross department collaboration	Both

2.3 Success Factors in Digital Transformation Projects

The digital transformation I can be considered that is has to do “less” with the digital fixed technologies but it has to do “more” with the transformation process and its principles. While the technology itself act like a major core catalyst by providing the fundamental milestones the real success of these kind of projects is strictly rely on a holistic blended alignment between strategy, culture and people. Organizations which handle the digital transformation as single-dimensional project of IT upgrade often fail instead of handle it as a multi-dimensional project with continuous evolution for their business by focusing on agility, data-driven decision-making, customer-centricity in order to realize long-term value. The digital advantage could be found when the strong digital capabilities meet the stronger leadership capabilities in order to create the Success Factors to steer the transition through organizational structure-culture, leaderships and technical infrastructure Westerman et al. (2014).

2.3.1 Organizational Structure

The traditional management method from the top hierarchy level is usually the most common and the greatest bottleneck regarding the digital transformation projects. If the top management levels refuse to committee and support the project management teams then multiple obstacles will be emerged within the organization structure by discouraging and creating a defensive environment. The success requires the transition toward through cross-functional teams and structures by allowing the creative and rapid information flow steam. When departments operate in isolation or independently at-will instead of been under an synchronized agile and adaptive structure the data could become fragmented which is a dangerous condition for the project’s clarity.

2.3.2 Organizational Culture

The culture in an organization could be characterized as the "innovation Fuel" or the "Operating System" which is responsible for a big portion of the organization's success. Especially in case of digital transformation the criticality is higher due to the high demanded environment and a digital-ready culture which prioritized the innovation, risk tolerance, and continuous learning is a mandatory section. The resistant to change from the existing working pattern to the new one the digitalized is the primary cause of the project failure even if the support from the top management is in place. The key point is to fostering a mindset for all levels by empowering the employees to proceed with the digital transformation project even if the possibility of failure is vital. The biggest barrier that could be emerged is the lack of digital maturity due to the lack of an organizational culture that supports the digital initiatives Kane et al. (2015).

2.3.3 Leadership

The digital transformation transition should be supported from the top to the bottom in terms of leadership. All leaders have to act and behave as passionate visionaries who must make clear out "why" it is so important to transition to digital era and explain with clarity what is behind this change by securing the support/trust from the workforce. The leadership role is very important because can motivate and create a culture that the workforce is willing to handle the digital transformation as a personal goal instead of feel that they are forced by top management to proceed. Moreover, the leaders beyond that just funding and presenting the project they must provide guidance and demonstrate a "digital agility" by showing their personal willingness to move away from legacy business models and bridging the gap between technical execution and strategic business goals.

2.3.4 Technical Infrastructure

While the structure, culture and leadership are the "soul" of digital transformation projects the technical infrastructure is the skeleton "body" and the combination of both provide all required assess for an organization to proceed with digital transformation projects. A robust and well structures infrastructure which could include technologies such as cloud computing, scalable data architectures, and cyber security protocols gives the opportunity to the organizations to move away from the old and inflexible systems toward to modular and API-drive ecosystems by integrating the new technologies/tools in their existing system without rebuilding it which is a catastrophic approach.

3. Chapter 03: Research Methodology

This study adopts the Systematic Literature Review (SLR) method in order to evaluate, identify, compare and synthesize the existing research and reported results regarding the implementation of Agile and Hybrid Project management models within the digital transformation framework of Pharma 4.0 and identify the Critical Successful Sectors (CSFs). This method was chosen due to the Pharma 4.0 complexity project management, the strict pharmaceutical regulatory framework and confined implemented projects because Pharmaceutical Industries generally are not early adopters of innovation but followers.

3.1 Research questions (RQs)

The review was structured and based on the following research questions (RQs) in order to guide the research process.

1. Which is the current project management model being used by the pharmaceutical industries regarding digital transformation projects?
2. Do Pharmaceutical industries aim to implement Pharma 4.0 projects via internal teams, external vendors or a combination of both?
3. What are the current Agile or Hybrid project management models that are used by the pharmaceutical industries regarding digital transformation projects?
4. What are the Success Factors (SFs) which was identified regarding the successful and uninterrupted digital transformation transition to Pharma 4.0?
5. How the Hybrid projects management models and its activities can bridge the gap between Traditional “Waterfall” and Agile “dynamic iterative” project management by respecting the regulatory requirements to lead in digital agility?

3.2 Search Method

The study will be conducted via major international official databases in order to ensure that multifunctional perspective (last 5 years) to capture the most recent advancements in Pharma 4.0 & digital maturity by covering both project management and digital transformation technology by focusing on pharmaceutical sector. It will adopt the framework of a systematic review of international literature by mapping, analyzing and evaluating the findings regarding the existing project management framework in the pharmaceutical industry regarding the Pharma 4.0 projects implementation. In order to ensure the transparency and reproducibility the research will be conducted following the

PRISMA 2020 guidelines in combination with search design strategy by identifying the literature of digital transformation of pharmaceutical industry (Pharma 4.0) and the agile/hybrid project management.

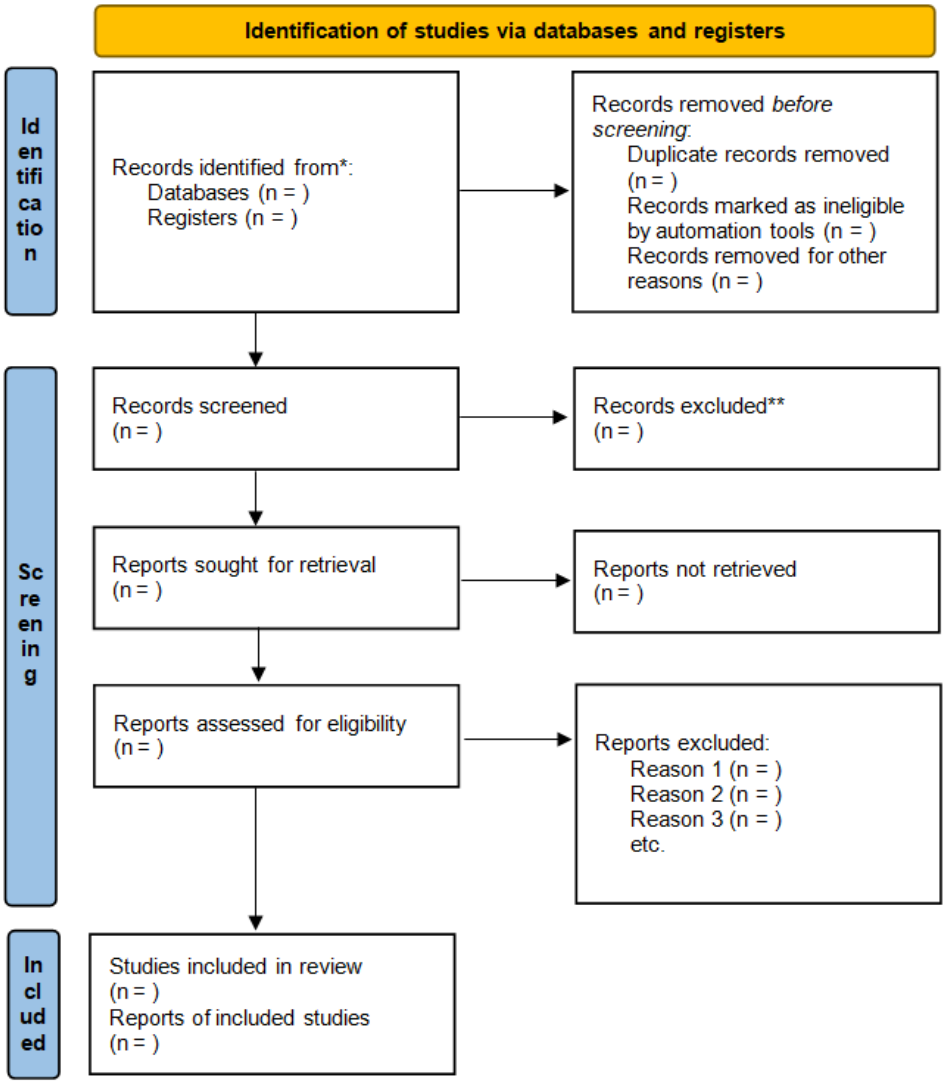

Figure 3.1: Template of PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only (Source: PRISMA Statement 2020)

3.2.1 Database Sources

To achieve a focused perspective regarding the pharmaceutical industries the search will be performed across the NIH (National Library of Medicine) “PubMed” (for Pharma specific context) database regarding technology and project management and will be visualized via VosViewer mapping process (for the last 5 years and free access papers). The alternative databases such as Scopus and Web of Science will be used in case of needed complementary sources.

3.2.2 Search Query to retrieve the documents and keywords

The search will be utilized Boolean operations (AND, OR) in order to provide a combination of the three major clusters Industry (Pharma 4.0), Digital Transformation and project management. The applied search string will be a used is ("Agile" OR "Hybrid" OR "Success Factors") AND ("Project Management" OR "Process Model" OR "Pharmaceutical Industry" OR "Pharma 4.0" OR "Digital Transformation").

3.3 Inclusion and Exclusion Criteria

The fundamental structure of the research is based on PICOSs framework (Population, Intervention, Comparison, Outcome and Study Design) which is often used for systematic review and meta-analysis. This framework has the ability to provide adaptive analysis method for project management models and digital transformation processes in order to establish the inclusion and exclusion criteria.

The search was based on the following inclusion and exclusion criteria.

1. **Inclusion criteria:**
   1.1. Papers, books, journal articles and articles and conference proceedings published between 2021 and 2026.
   1.2. Studies which focusing on Agile, Hybrid and its implemented principles in pharmaceutical industries regarding Pharma 4.0 projects.
   1.3. The research identifies the Critical Success Factors (CSFs) in digital transformation context for Pharma 4.0 projects.

2. **Exclusion criteria:**
   2.1. The source context which is not related to the pharmaceutical sector.
   2.2. Articles which focusing only in traditional project management "Waterfall" without any reference in Agile or Hybrid project management.
   2.3. The source context which lacking empirical or theoretical rigor.

3.4 Systematic Review Protocol

3.4.1 Prisma Chart flow

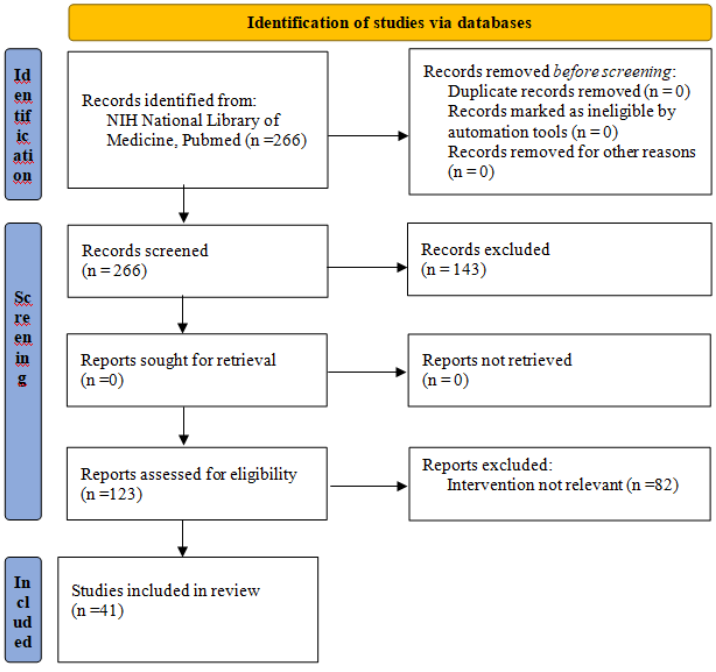

Figure 3.2: PRISMA 2020 flow diagram for new systematic reviews which included searches of Pubmed database.

3.4.2 VosViewer Map

The VOSViewer map is created via the related software by using the data source results from PubMed for each stage of the Prisma Chart Flow diagram. In the visualization of the map paper's key words was used in order to create the map of the findings. The created clusters provide the relationship and the connectivity between the findings by making easies the Prisma flow analysis regarding the included and excluding papers. This roadmap is also useful to identify the connections between the clusters and how the findings could be combined and used in order to support the study.

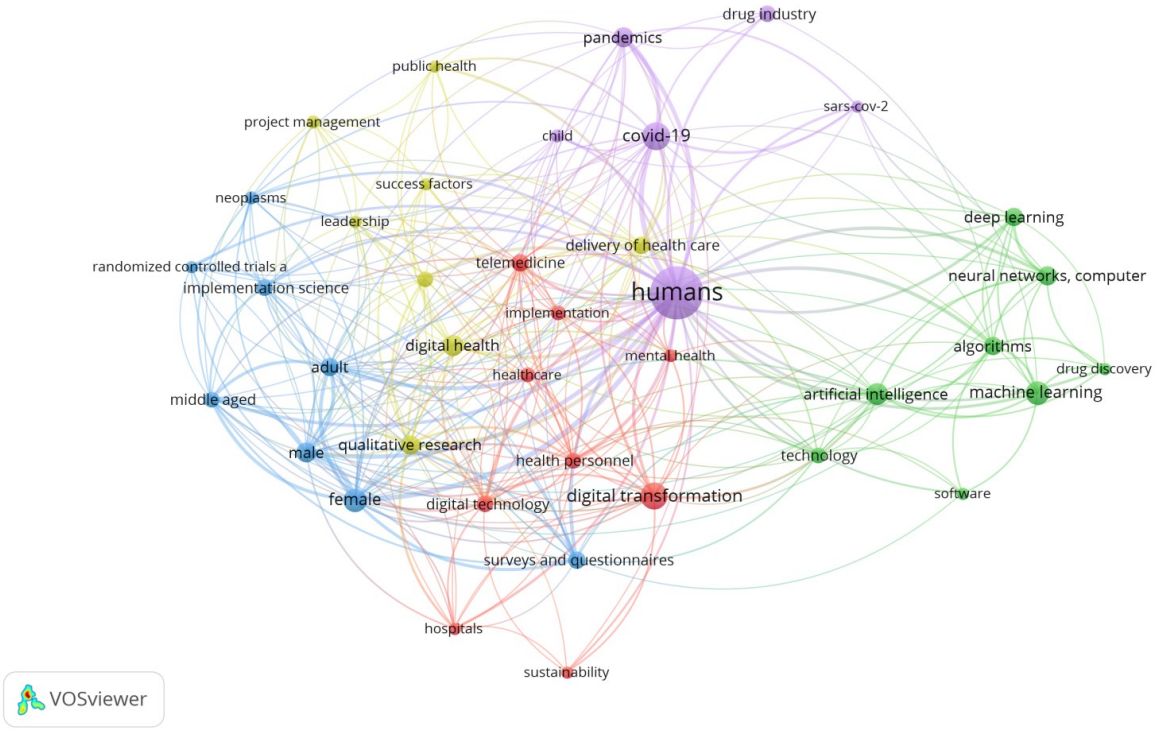

Figure 3.3: VOSViewer Map: The identification Prisma flow level.

Keywords Clustering Layout of 266 papers.

Cluster 1: Red color.

Cluster 2: Green color.

Cluster 3: Blue color.

Cluster 4: Yellow color.

Cluster 5: Purple color.

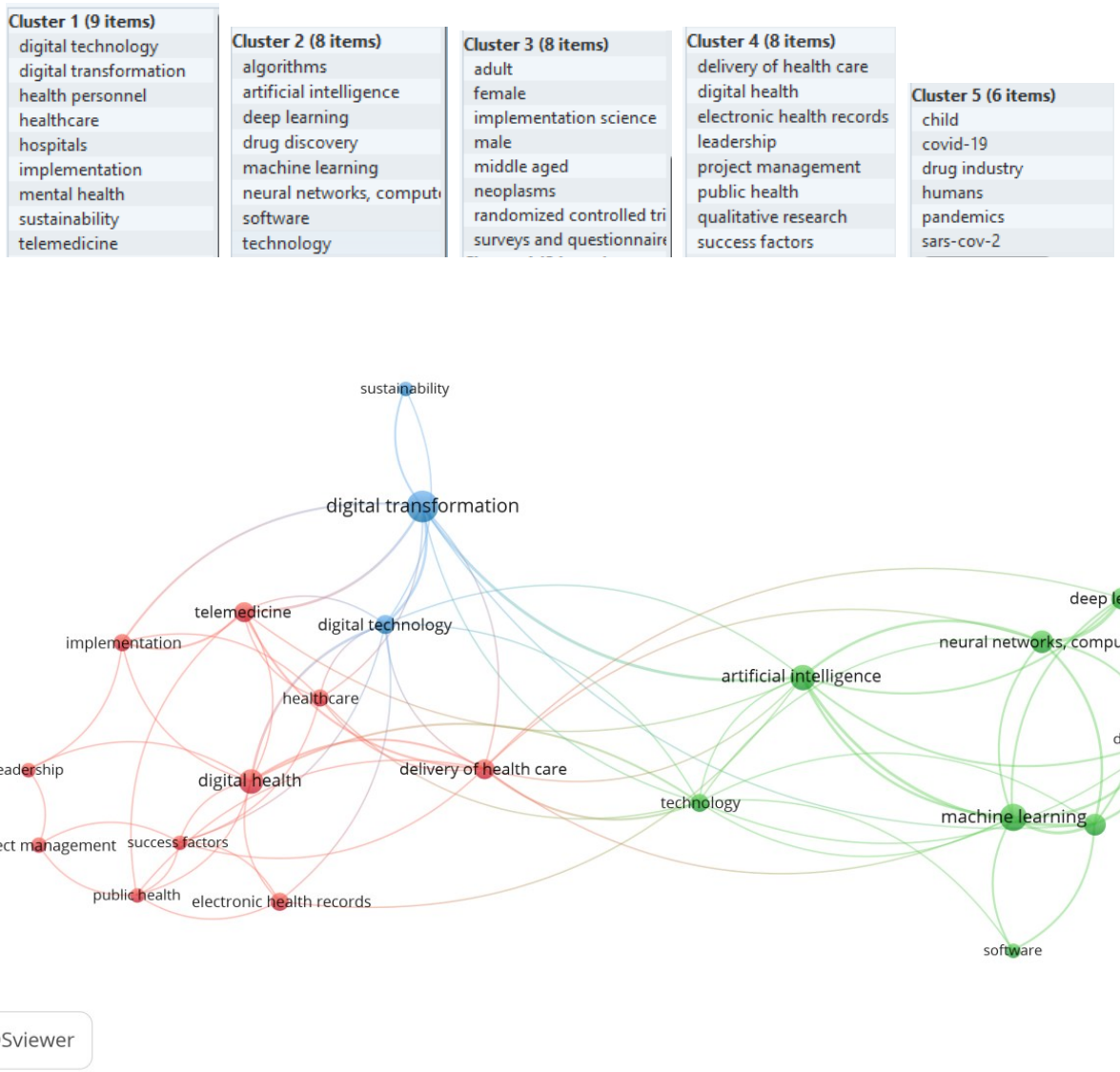

Figure 3.4: VOSViewer Map: The Screening Prisma flow level.

Keywords Clustering Layout of 123 papers.

Cluster 1: Red color.

Cluster 2: Green color.

Cluster 3: Blue Color.

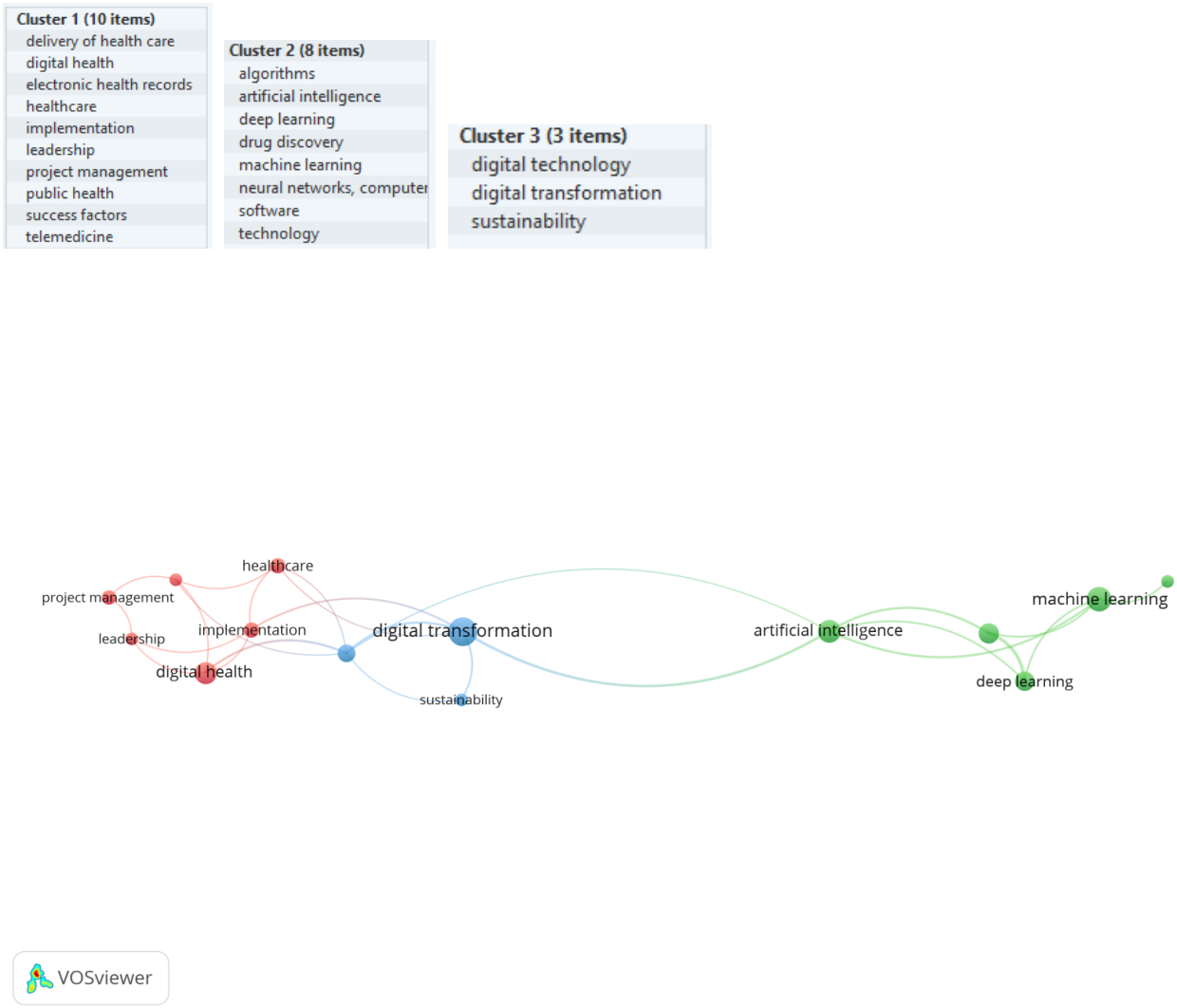

Figure 3.5 : VOSViewer Map: The including Prisma flow level.

Keywords Clustering Layout of 41 papers.

Cluster 1: Red color.

Cluster 2: Green color.

Cluster 3: Blue Color.

Cluster 1 (6 items)
digital health
healthcare
implementation
leadership
project management
success factors

Cluster 2 (5 items)
artificial intelligence
deep learning
machine learning
neural networks, computer
software

Cluster 3 (3 items)
digital technology
digital transformation
sustainability

The following extra keywords have been used which are not included in the database map.

-Agile

-Hybrid

-Pharma

3.4.3 Review method of rejected papers

From the overall 266 papers were found in Pubmed database by using the search string ("Agile" OR "Hybrid" OR "Success Factors") AND ("Project Management" OR "Process Model" OR "Pharmaceutical Industry" OR "Pharma 4.0" OR "Digital Transformation") the number of the final chosen paper which were included in the study are 41.

1. **Step 1:** To review the papers I have used the VosViewer application in order to create a keyword clustering map and identify the relationship between papers by including all keywords (Figure 3.3).
2. **Step 2:** I created again the map by excluding all the non relevant keywords regarding the study by creating a specific relevant keyword clustering (Figure 3.4).
3. **Step 3:** I extracted the master list of 266 papers from PubMed as CSV file which including all relevant useful data for the papers such as the keywords which were used in the VosViewer maps.
4. **Step 4:** I used advanced filtering in order to identify and exclude 143 non relevant keywords-papers from the 266 initial papers (Step 2) by creating a valid paper list of 123 papers for further evaluation.
5. **Step 5:** I searched for the chosen keywords (step 2) by evaluating all 123 papers based on their keywords and I excluded in total 82 non relevant papers for the study.
6. **Step 6:** The final evaluated and chosen papers are 41 and their keywords have created the final VosViewer map (Figure 3.5).

By having the list of the chosen papers with all relevant search data, the papers could be identified and accessed via PubMed database in order to be used in the study.

4. Chapter 04: Findings and Results

4.1 Descriptive Analysis

Table 4-1: Table of literature (Studies included in review) per Keyword Category and Publication Year.

Keywords Category	Publication Years						
	2021	2022	2023	2024	2025	2026	Total Papers
Agile			1	1			**2**
Artificial intelligence			1		1		**2**
Deep learning/hybrid					1		**1**
Digital health					1		**1**
Digital transformation			1	1	2	1	**5**
Hybrid		1	2				**3**
Implementation		1	3		1		**5**
Leadership						1	**1**
Neural networks	1			1	1		**3**
Pharma		2	2	1	3		**8**
Project management		1	1	2		1	**5**
Software			1	1			**2**
Success Factors			1	1			**2**
Sustainability					1		**1**
Total Papers	**1**	**5**	**13**	**8**	**11**	**3**	**41**

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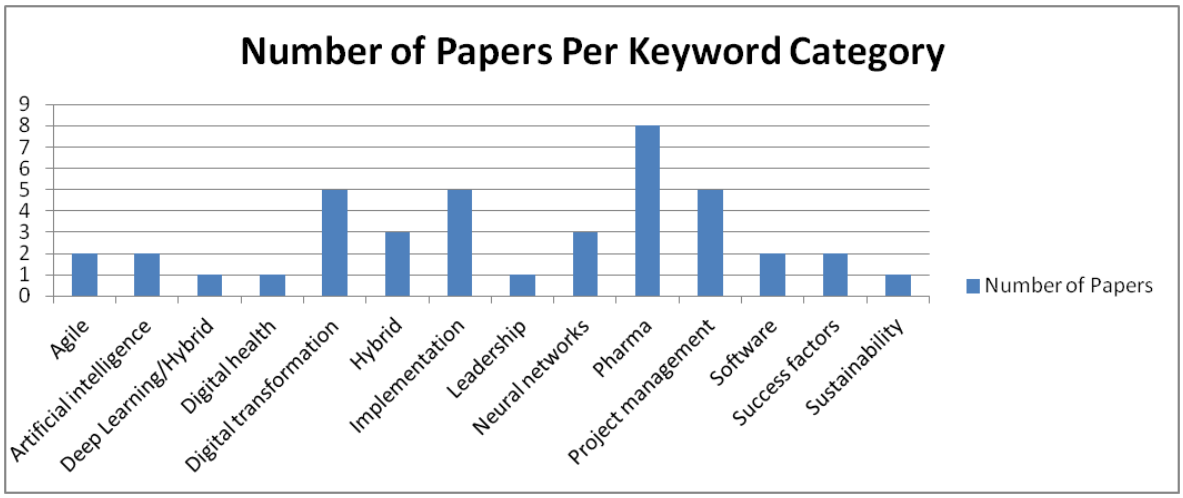

Figure 4.1: Number of Papers per Keyword Category

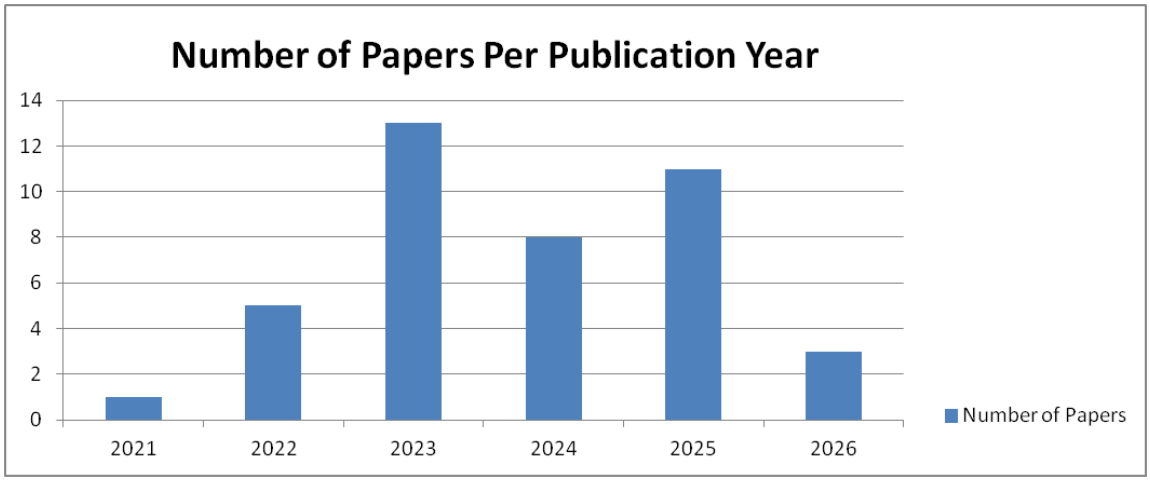

Figure 4.2: Number of Papers per Publication Years (Keyword Categories)

Table 4-2: Table of literature (Studies included in review) per Representative Title Sector and Publication Year.

Representative Title Sector	Publication Years						Total papers
	2021	2022	2023	2024	2025	2026	
Digital Applications				1			**1**
Digital Transformation		1	4	3	5	2	**15**
Informational Systems			1				**1**
Management			1				**1**
Pharmaceutical Manufacturing		1	1	1	1		**4**
Production Process			1		1		**2**
Project Management	1	2	2	3	4	1	**13**
Quality System			1				**1**
Research & Development			2				**2**
Supply Chain		1					**1**
Total papers	**1**	**5**	**13**	**8**	**11**	**3**	**41**

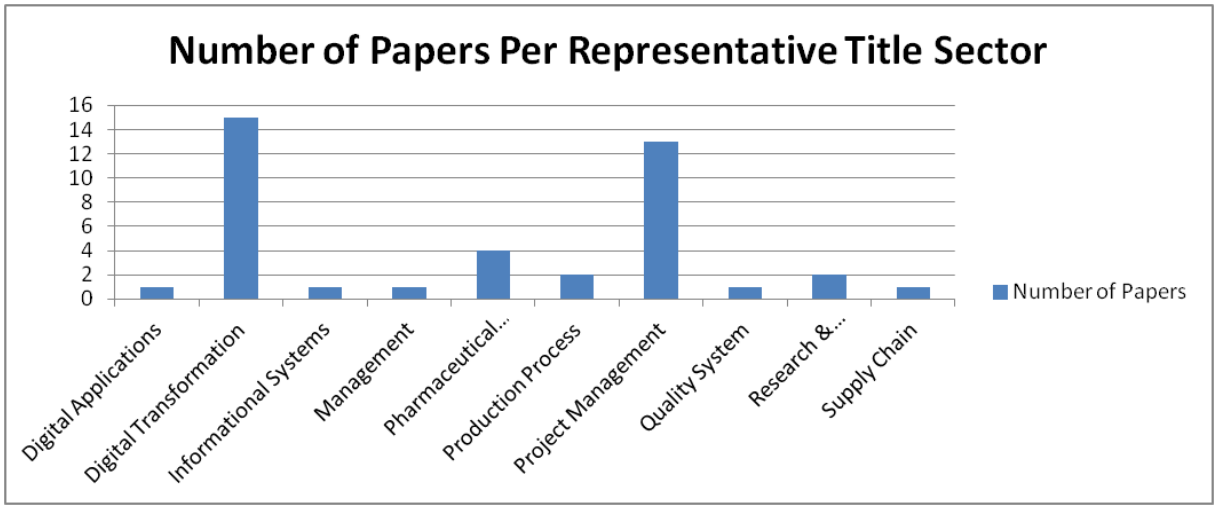

Figure 4.3: : Number of Papers per Representative Title Sector

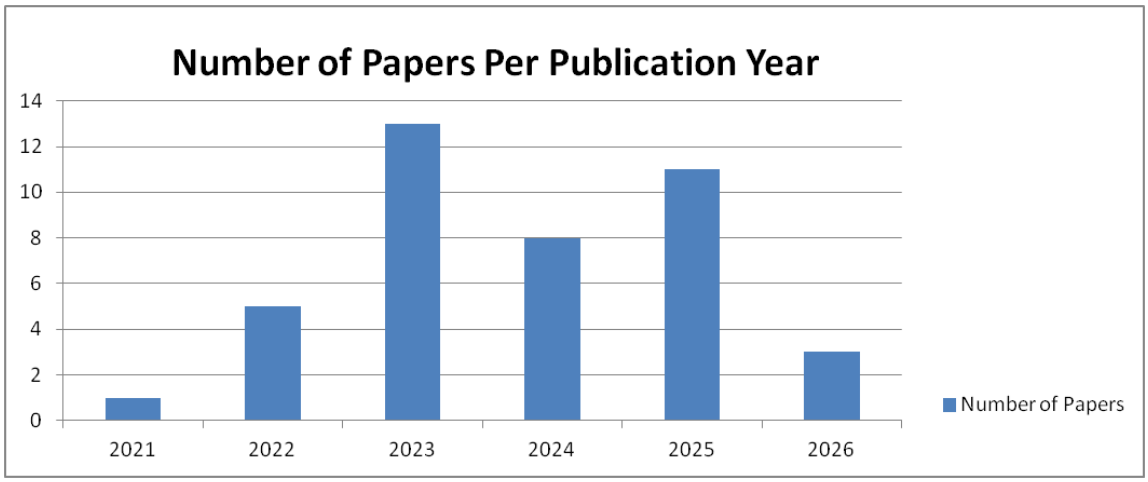

Figure 4.4: Number of Papers per Publication Years (Representative Title Sector)

4.2 Analysis of Agile/Hybrid Models and Value Creation in Pharma

The Pharmaceutical Industry is currently under the process of a paradigm shift from the traditional management towards to the new are of digitalized management which is driven under the umbrella of "Pharma 4.0" initiatives. These initiatives include edge technologies such as Internet of Things (IOT), Big Data Analysis and automated manufacturing processes which are strategically blended and integrated in the into the life sciences sector.

This transformation process is not only a technological achievement for each industry in order to enhance their operation but is also a methodological decision with a complex background strategy by investing in long term sustainability and continues value creation via completing routine and not projects in the most efficient way. Traditionally, the pharmaceutical industry is relied on the Traditional "Waterfall" or "V-Model" project management frameworks due to the he stringent requirements of drug authorities regulatory (Khan et al., 2024) by being fully compliant but characterized from rigid and non flexible initiatives with negative impact in the modern Pharmaceutical Industry. This approach changed radically when the need for or rapid response to global health crises emerges like the COVID-19 pandemic in which the complexity of personalized medicine necessitated more flexible approaches Agile or Hybrid project management models (Shayannia, 2023) such as the rapid development, production and distribution of vaccines in huge amounts worldwide.

The Agile and the Hybrid project management model have emerged via this kind of critical situations as fundamental critical enablers in this strict landscape with the ability to undertake the obstacles and deliver each project's task in time. The Agile models respects and prioritize the iterative development and the rapid feedback while the Hybrid models aim to combine the strong initiatives of Traditional and Agile model, for Agile model the flexibility and for Traditional model the rigorous documentation and safety-critical compliance (Khan et al., 2024). The following analysis explores both Agile and Hybrid models are mapped onto pharmaceutical industries by enhancing and solving emerged obstacles for multiple departments while ultimately creating value through enhanced sustainability, resilience, and regulatory alignment.

4.2.1 Analysis of Agile Model in Pharma

The mapping and the application of Agile method in pharmaceutical industry has great compatibility onto supply chain and rapid manufacturing systems which are very crucial

sectors for the product development-production life cycle. Shayannia (2023) discusses and points out the importance of the implementation of an Agile Supply Chain (ASC) in the pharmaceutical industries and the provided benefits specifically for COVID-19 drugs by characterizing this model as a rapid salvation respond to volatile demand and supply shocks during the pandemic period which was very crucial. The "Agile" aspect here was distinguished in four main pillars economic, social, environmental, and political sustainability (Shayannia, 2023) by utilizing the new developed algorithms during implementation to optimize this network. Therefore the industry can achieve the required strategic agility which allowing for the rapid reallocation of resources during health emergencies.

Furthermore, the agility has been integrated into machinery and drug process production by creating a modular manufacturing process which provides fast changes and adaptiveness and evolves the existing production processes in order to suit new conditions or environments. Sundarkumar et al. (2024) analyzes a modular and continuous drug manufacturing ecosystem which utilizing the "agile and flexible" manufacturing process by allowing the rapid production of personalized medicine and mini-tablets. This way of production provides fast reaction of the pharmaceutical industries in cases of high emerged demand, lowering the costs due to the production of specific needed quantity and can support specific patient clusters more efficient. This modularity is representative of Agile principles by distinguishing the complex and large process flow into smaller tasks which are independent and configurable by combining speed and quality output as perfect blending in cases o pandemics or extended disasters.

4.2.2 Analysis of Hybrid Model in Pharma

The mapping and the application of Hybrid method in pharmaceutical industry is increasingly utilized and applied into the development of Medical Device Software (MDS) and Digital Health Applications (DiGAs) by bridging the conflict between Agile's non

efficient planning and the required strict authorities regulatory. A high valued development in this sector is the Enhanced Agile V-Model (EAV-Model) by creating agile mapping with continuous testing (iterative cycles) onto the traditional V-Model used in systems engineering (Khan et al., 2024). The companies who adopt and apply this model can maintain regulatory compliance while exploiting the speed of Agile process. This hybrid system is also observed in Hybrid Care Services in which the digital health application technology is combined with the physical clinical process. Pilosof et al. (2023) points out that the design of a flexible hybrid health care system requires a strong balance between the clinical standardization and the dynamic nature of remote monitoring.

In terms of organizational sector, Smith-Sreen et al. (2022) has identified that the organizations that are hybrid driven within the pharmaceutical sectors aim and seek to balance the commercial value with the social value that could be created through specific programs. These programs usually use hybrid management frameworks in order to create a clear roadmap and navigate their success path when the social targets are fully aligned with the profit-driven pharmaceutical operations.

4.2.3 Value creation

The value creation is critical sector in Agile and Hybrid models by providing resilience and sustainability to the organization that adopt them by giving the ability to reinvest profits to further evolution such as reducing the financial-environmental impact via Agile supply chain through distribution optimization and waste reduction (Shayannia, 2023). In the pharmaceutical manufacturing sector the pure value lies in Quality Assurance (QA) which ensures that the products were produced in accordance with the specific regulatory by avoiding destroying malfunctioned batches or recall it from the market with financial and commercial impact. A representative example is the use digital twin technology for continuous twin-screw wet granulation production process by exploiting the value of real-

time process feedback and live adaptive advanced process control optimization by reducing the "trial and error" during production (Zhao et al., 2023).

Additionally, the data reliability is also linked with the value creation which is usually applied in cloud-based Pharma management via Hybrid framework by increasing reliability and performance of the organizations via storing data and using sophisticated AI algorithms is required of Pharma 4.0 data analytics and decision making process.

4.2.4 Agile and Hybrid Model link with Pharma 4.0

The Agile and Hybrid model frameworks are strongly linked with Pharma 4.0 which can be considered metaphorically as the “core operational engine” for the digital transition in accordance with Debnath et al. (2023) who has identified that all industry 4.0 technologies are critical Success Factors for the new era of pharmaceutical sustainability by using the fundamental milestones of Real-Time Monitoring (auto created data which are collected and evaluated in real time in order to adapt the operation), Advanced Process control (APC) (use of iterative (Agile) improvements in continuous manufacturing technologies like digital twins) and Interolability (the Hybrid models facilitate the big data storage and analysis via cloud computing systems).

In summary, the Agile and Hybrid models framework are mapped across the pharmaceutical value chain by providing speed while are oriented to the necessity of safety. The Agile models mainly can support the modular manufacturing structures while the Hybrid models are more specified to support the development of complex project with high regulatory restrictions. Both models are necessary for the Pharma 4.0 transformation process in order to exploit the new digital real world via a sustainable road map.

4.3 Identification of Success Factors (CSFs)

4.3.1 Technological factors

The technological factors are representing the fundamental category of Critical Success Factors (CSFs) for the digital transformation and the modern pharmaceutical industries. This kind of shift is called Pharma 4.0 and leverages technologies such as the Internet of Things (IoT), big data analytics, and artificial intelligence (AI) to create smart, data-driven manufacturing systems (Debnath et al., 2023). The technological Success Factors are vital for the organizations while trying to explore outdated structures which need to be upgraded but under string regulatory rules. The following technological factors have been identified as critical for success in the pharmaceutical and digital health sectors in terms of digitalization.

1. **Sufficient Investment in technological Advancement:** The high end technologies of Pharma 4.0 are quite expensive and these type of projects often canceled before even have started due to financial restriction. Therefore, the financial commitment that will provide all necessary funds is a significant success factor by allowing and supporting the purchase of hardware and software equipment (Debnath et al., 2023).
2. **Digitalized Product Monitoring and Traceability:** The utilization of industry 4.0 technologies regarding the real-time data visibility vertically into the organization's structure providing the capability for improving resilience and performance (Debnath et al., 2023).
3. **Data Protection and Information Security:** The data and information security is a crucial requirement in order to avoid manufacturing failures. Due to the fact that the digital transformation is data driven ecosystem especially in pharmaceutical industry the data integrity is crucial successful factor because it affects directly the real-time adaptability decision making and big data analysis in terms of historical data (Schramm and Carbon, 2024).

4. **Computer-Integrated Cloud Manufacturing Systems:** The implementations of a structured cloud based computing infrastructure can support the bridging of of diverse manufacturing processes and data management in one common but dynamic base (Debnath et al., 2023). This is a useful factor in order to produce from the decentralized to the centralized data driven ecosystems with specific norms and process methods which can provide structure, speed quality and enhance efficiency.
5. **Interoperability and Standardized Data Processing:** The way that the data are collected, stored and analyzed should be a standardized approach vertical in the organization's system because are vital for the success transformation process as is fully data driven environment with strict regulation (Kraft et al., 2026; Schramm and Carbon, 2024).
6. **User-Friendly technological solutions design:** The technological solutions must have a user-friendly design by prioritizing the easy usability and user's engagement in order to ensure the high acceptance and effectiveness outcomes (Schramm and Carbon, 2024). Due to the fact that the digital transformation projects in Pharma have direct impact in the daily routine of multiple employees with different digital literature levels and the key point is to offer an adaptive solution which will be suitable for every user.
7. **Integration of Artificial intelligence (AI):** The AI technology is a complementary asset for the Pharma 4.0 technologies which can enhance the efficiency, speed, quality and provide high value with minimum resources but should be integrated in the Hybrid model by expoiting the humans expertise rather than replacing it, to avoid stifling creativity (Nikolić and Bjelica, 2025).

4.3.2 Organizational Factors

The organizational factors are representing the structure and the rational of the chosen strategy of each pharmaceutical industry which aims to precede with digital transformation projects. Due to the strict regulations in pharmaceutical industries the organizational factors are key elements to successfully support and deploy the required initiatives by

serving a strategic roadmap for decision-makers to optimize resources and navigate structural transitions efficiently while facing complex operational and structural challenges. Therefore, the organizational factors are critical elements by addressing the strategy, culture and managerial alignment which are mandatory for an enterprise to sustain technological and infrastructural shifts. The following organizational factors have been identified as critical for success in the pharmaceutical and digital health sectors in terms of digitalization.

1. **The proper Support from Top Management:** The successful organizational transformation projects require an active, visible, visionary and high enduring committee from the leadership hierarchy level which should act as activators who provide support and guidance. The top management is responsible for creating the required digital culture and establishing the core vision for the organization by mitigating any emerged risks, providing the required funds and stop possible resistance to change within the organization (Debnath et al., 2023).
2. **Dedicated and structured Research and Development (R&D) Team:** The presence of an expert, innovative, active, pioneer and focused R&D department in the internal core structure infrastructure of the pharmaceutical industry is considered as a top-tier success requirement with high level advantages. Due to the fact that, generally in the pharmaceutical market the drug manufacturing process is heavily rely on scientific experimentation and rapid prototyping a robust R&D department can enable mass customization while minimizing the product's lifecycle impact and build a sustained/advanced operating environment (Debnath et al., 2023).
3. **Sustainable organizational Strategies:** The organizations have to create a pre-established strategic framework which should include core corporate long term values such as sustainability, profitability, lean operations and environmental sustainability by being aligned with the existing corporate goals rather than conflicting with business KPIs (Debnath et al., 2023). This framework allows the organizations and especially the pharmaceutical industries to create the initial clear road map which should be respected in order to create strategically the forecasted value by maintaining

sustainability/profitability which is crucial for funding the digital transformation projects.

4. **Structured Technical Team:** The correct organizational allocation of human resources is a crucial factor because it creates cross-functional department linkages and a highly specialized support team which can contribute actively to the digital integrated technologies. In the Pharmaceutical industries the supply chain can be integrated with technical services via specific predictive maintenance algorithms by creating real-time machinery smart tracking systems while minimizing the operational downtime by ensuring continuous system resilience/rapid troubleshooting and enhancing the profits-drugs availability (Debnath et al., 2023).
5. **Organizational link with governmental policy and technological investments:** The organizational elements in the pharmaceutical industry do not operate isolated instead they are strongly connected with the governmental policy and technological investments. The combination of organizational culture and technical capabilities which are fully aligned with regulatory regarding acceptant and failure mitigations usually leads in higher success rates during digital transformation (Debnath et al., 2023).

4.3.3 Regulatory/Process Factors

The Regulatory/Process factors in pharmaceutical industry are representing the structure of a highly complex environment which is controlled by strict compliance frameworks, complex process protocols and different regulatory standardizations per market area globally. These factors are crucial for the operations in order to ensure the product's quality and regulatory compliance in order to allow companies to successfully manage technology integration, meet stringent conformity assessments, and mitigate manufacturing disruptions. It is also important to point out that, in pharmaceutical industries the regulatory sector which is driven internally via Quality department and externally via regulatory authorities is critically linked with operation process and has the

authority to stop/reject product batches if are not aligned with regulation. The following Regulatory/Process factors have been identified as critical for success in the pharmaceutical and digital health sectors in terms of digitalization.

1. **Transition from traditional paper-based documents to digital data-driven standardization:** This factor is a crucial and fundamental process which aims to change radically the way the process documentation is managed by quality and regulatory departments. This change has a direct impact to regulatory affairs and is a major challenge by turning the instructed information into digital standardized data models were the documents are totally controlled via granted access level. The adoption of data-exchange standards can successfully implement the international structured guidelines such as the Identification of Medicinal Products (IDMP) by promoting the interoperability, data consistency, and transparent regulatory tracking. Additionally, the adoption of automated data process stream flows by integrating the advanced technologies such as Large Language Models (LLMs) and Retrieval-Augmented Generation (RAG) can act as an operative process mechanism which enables the product submissions and bolster overall regulatory adherence (Kadi, Abdellatif, Kemajou Njamen, and Pereme, 2025).
2. **Digital Product Monitoring, Traceability and Agile in Supply chain:** The real-time operational transparency is a pre-requisite for the pharmaceutical industries in order to mitigate the supply chain deviations and maintain the continuous improvement (CI) quality control. This factor applies the quality principles on to the complex supply chain flow by ensuring that the core of the product which is the raw materials are controlled and distributed as it should be. The adoption of digitalized systems can provide a structured product monitoring and end-to-end traceability framework by enhancing the supply chain efficiency, capacity resilience, and long-term ecosystem viability. Additionally the technological infrastructure investments, act as fundamental process enablers by controlling vertically the whole product life cycle and supporting the digitization initiatives across manufacturing pipelines (Debnath, Shakur, Bari, Saha, Porna, Mishu, et al., 2023).

3. **Real-Time Process Monitoring and Quality Assurance:** The modular small-scaled drug production process and traditional testing in the pharmaceutical industries are replaced with proactive/continuous regulatory framework. The adoption of real-time track-and-trace framework provide all necessary digital tools to continuously track critical process parameters (CPPs) and critical quality attributes (CQAs) during drug production as a proactive action in order to identify in an early stage a possible product's quality deviation by allowing the organization to act immediately. Moreover, the use of these integrated analytical tools allows the agile drug batch production/release while maintaining the strict regulatory conformity (Sundarkumar, Wang, Mills, Oh, Nagy, and Reklaitis, 2024).
4. **Compliance Mapping of Hybrid Engineering Systems:** The proper Software integration onto the pharmaceutical products and machinery is a crucial process which must be compliant with the regulation rules because it harmonize the required fast-paced production cycles by applying a plan-driven regulatory checks while mitigating the potential severe operational risks. The implementation of enhanced Agile V-Model (EAV) and Computerized Validation System (CSV) frameworks provide crucial Success Factors in terms of operational process by bridging the gap between flexible agile workflows and documentation-heavy waterfall structures. Additionally, the implementation of Conformity Verification frameworks (such as MDEVSPICE and standard IEC62304) provides a systematic process-to-standard alignment mapping by ensuring a seamless verification across software and hardware integration loops. This verification is crucial because it ensures the software compliance via a safe side way while continuously updating the documentation to be ready for immediate regional regulatory audits (Khan, Akram, Butt, and Sirshar, 2024).
5. **Standardized Data Protection Laws:** The digital transformation projects requires a standardized security conformity in terms of data by maintaining regulatory restrictions which are depend heavily on protection and information security requirements. The utilization of data security systems is a mandatory defensive success factor for Pharma 4.0 ecosystems which are data driven and have direct impact in

product's quality by preventing the retroactive legal removal of digital healthcare assets from institutional frameworks (Schramm and Carbon, 2024).

6. **Balanced Structured Automation and Human Creativity:** The hybrid operational framework provides the appropriate balance between the Artificial intelligence (AI) and the human flexibility is an important procedural success factor. A hybrid system should be designed in a specific way in order to provide upfront the collaborative innovation process instead of the completely overriding human contextual judgment which ensures that exploratory and regulatory components remain strategically aligned during product development cycles (Nikolić and Bjelica, 2025).

4.3.4 Barriers and Challenges

The Critical Success Factors (CSFs) represents the specific areas of activities which must be managed efficiently in order to ensure the competitive advantage and sustainability by allowing the value creation without deviations. In the pharmaceutical industries in case of Pharma 4.0 (digital transformation) these Success Factors are heavily rely on the adoption of advanced technological frameworks such as Internet of Things (IoT), big data, digital twins, cloud computing and adaptive automations by optimizing the production process while reducing the environmental degradation and waste. In contrast, there are multiple constraints and barriers that can emerge while aiming to achieving these Success Factors in the pharmaceutical industry due to the operational challenging environment characterized by regulatory compliance and production complexity. The following barriers and challenges have been identified as critical for success in the pharmaceutical and digital health sectors in terms of digitalization.

1. **Financial and Cost Constrains:** The financial investment stability is vital for the CSF implementation and the funding cut down meters is one of the most important obstacles. The need of high initial investment costs for the digital transformation projects in order to provide a sustainable transition requires the purchase of specialized

equipment, modifying the existing facilities, software modification and integration of automated technologies in a new customized ecosystem. These high upfront expenses acting as a major roadblock for emerging economies and smaller firms (Debnath et al., 2023; Khan and Ali, 2022). Additionally, the high costs of Green/Sustainable operations which requires continuously to maintaining the circular mechanisms in order to applying an eco-friendly footprint character, over-pressuring the financial department which jas to manage a specific approved annual budget and ensure the undisrupted operations (Khan and Ali, 2022).

2. **Regulatory, Legal and Policy bottlenecks:** The lack of government support, strict policies and unsupportive national policies regarding pharmaceutical industries usually create serious barriers during digital transformation. Without standardized regulations, structural support systems for state authorities the companies lack the external push to start investing within an unstable environment in the digital transformation Pharma 4.0 (Debnath et al., 2023; Khan and Ali, 2022). Additionally, the compliance complexity and the strict/non flexible pharmaceutical regulations could be characterized as non user-friendly processes during digital transformation projects when changing the existing validated production processes (Schramm and Carbon, 2024; Debnath et al., 2023).
3. **Organizational and Cultural remissness:** The lack of top management commitment regarding the strategic prioritization, risk aversion and focus on profitability creates obstacles with direct impact in sustainability, strategic alignments by reducing employee morale and organizational resilience and creating resistance to change barriers (Debnath et al., 2023; Khan and Ali, 2022). The employee resistance to change regarding leaving back the traditional manufacturing methodologies toward to the automated or agile circular process, due to the fact that the organizational benefits of these shifts where not communicated correctly by top management, have an important barrier because it has direct impact in organization’s core profitability strategy.

4. **Technological and Infrastructure Gaps:** The lack of the proper and mandatory technological prerequisites creates critical obstacle which eliminates the success of the digital transformation projects. The Pharma 4.0 technologies required advanced digital infrastructure and technology maturity which is non-negotiable. The poor Internet of things (IOT), outdated software with low process , connectivity & compatibility capabilities and the lack of real-time monitoring / data archive undermine the initiatives of digital transformation projects (Debnath et al., 2023; Tun and Madanian, 2023). Additionally, the application of Poor Interoperability and Standard Information Systems in pharmaceutical industries especially for the supply chain department creates lack of cross-functional information systems between all functional departments. This affect the organization by generating wastes, inventory over/low management and the raw materials can't be supplied accordingly and smoothly across different sectors by supply chain (Khan and Ali, 2022).
5. **Workforce Skills and Expertise Deficits:** The lack of skilled and the inefficient training employees regarding the transitioning to high-tech technologies such as data analytics, automated robotics management and sustainable chemical processing expertise in pharmaceutical industries creates a critical barrier with direct impact in core business. The non-qualified personnel which are not capable to support and operate these advanced ecosystems but at the same time is the power and the heart of the organization creates an unsafe and risky environment for the venture of Pharma 4.0 projects which will not been supported by top management (Debnath et al., 2023; Khan and Ali, 2022).
6. **Market Challenges:** The lack of integration and low customer awareness concerning sustainable pharmaceutical disposal which is combined with weak collaboration between pharmaceutical suppliers and distributors create barriers in terms of smooth operation/coordination which is severely weakens reverse supply chains (Khan and Ali, 2022).

4.3.5 Frameworks used in Agile/Hybrid models

The pharmaceutical sectors operate within highly controlled environments managed by strict regulatory frameworks in order to ensure quality assurance, safety, and operational excellence. These functions are operating under traditional "Waterfall" or conventional "V-Model" frameworks which strongly support extensive documentation and traceability requirements. However, the modern pharmaceutical sectors encounter dynamic shifting criteria which rapidly changing by making the making the linear project methodologies highly restrictive and ineffective to the emerged challenges. These restrictions forced the pharmaceutical industries to proceed with customized Agile and Hybrid methodologies using specialized frameworks for each model by exploiting the speed of these models while safeguarding regulatory compliance. The following Agile and Hybrid model's frameworks have been identified as effective methods in the pharmaceutical and digital health sectors in terms of digitalization.

1. **Agile Model's Frameworks:** The pure Agile models aim to focus on fast adaptation, short-simplified intervals and conterminous feedback loops but in high regulatory environments such as pharmaceutical industries are facing limitations due to strict regulatory compliance.

    1.1. **Scrum Framework:** It's a well known and widely used framework which aims to leverage short sprints (Development Cycles) and is specialized to manage system/software creation, utilize iterative and fast/direct adjustments. However, when is used against strict compliance criteria it has noticeable gaps regarding its native documentation deficits and a historical lack of rigorous requirement tracking (Khan et al., 2024).

    1.2. **Extreme Programming (XP):** It focuses on engineering code quality in digital environments but when is applied directly within strict regulatory environments

creates obstacles due to lack of safety standards, code and document traceability and structured planning in early-stage (Khan et al., 2024).

2. **Hybrid Model's Frameworks:** The Hybrid frameworks have major advantages in case of complex pharmaceutical and medical sector in terms of digital transformation because can achieve regulatory compliance while embedding flexible Agile loops or fast adoption based on current demand**.**

   2.1. **Agile V-Model (AV Model):** This model is integrated in hybrid approaches by establishing a compliance framework while maintaining the Agile characteristics. This framework maintain strong verification and validation process which is tracked by the standard V-Model while emending Agile activities within its process cycles in order to integrate the initiatives of digital transformation shift in operational parameters (Khan et al., 2024).

   2.2. **Enhanced Agile V-Model (EAV Model):** This model is the evolution of Agile V-Model (AV Model) by having advanced optimizations which allows the explicitly break down of massive activities or systems into separated isolated subsystems which are managed faster and more efficient. Additionally, this model provides dual execution paths as it is embedded in hybrid framework by allowing the project managers to decide which path should be chosen based on the current or emerged project's requirements. The first path is the Plan-Driven Windows which is specialized to cover the non-negotiable safety-critical requirements of the project and the second one is the Agile Sprints (Scrum-driven Windows) which is designed to manage the emerged changes or requirements via applying dynamic daily checkpoints-designs with speed-accuracy(Khan et al., 2024).

5. Chapter 05: Discussion

5.1 Research Questions (RQ) Answers based on findings and results.

The modern pharmaceutical sector operations which are currently undergoing a critical transformation shift from traditional “waterfall” operations towards to digitalized management frameworks under the umbrella of Pharma 4.0 framework. The integration of the Pharma 4.0 edge technologies such as the Internet of Things (IoT), Big Data analytics, cloud computing, and automated processes—promises to enhance long-term corporate sustainability, efficiency and real-time process visibility automatically creates a complex environment within a high controlled system supervised by regulatory authorities. Due to the fact that the pharmaceutical industries historically relied on the traditional "Waterfall" or "V-Model" project management frameworks in order to maintain and achieve full compliance with regulatory faced multiple obstacles and gaps while trying to implement the new modern pharmaceutical operation framework in order to enhance their competiveness . This emerged systemic pressure forced the pharmaceutical and health sectors to re-evaluate the value of traditional models by exposing its rigidity which push the system to be shifted toward to Agile and Hybrid methodologies which can bridge the gaps and balancing the speed with mandatory regulation compliance.

The scope of this study focuses specifically on examining how the pharmaceutical industries aim to explore the digital transformation landscape by identifying-evaluating project methodologies, resources allocation, critical Success Factors and operational structures during the venture of digital transformation shift. To create a clear and structured road map analysis for the way these technological shifts are performed without disrupting regulatory compliance, this systemic literature review research present five core research questions. The main scope of the following questions, is to identify the current applied project management models which dominating in digital transformation sector, under which circumstances the organizations utilizes internal or external collaborations

during Pharma 4.0 projects, identify the exact of Agile & Hybrid frameworks (such as the Scrum and Enhanced Agile V-Model), discover the Success Factors (SFs) for an uninterrupted transition and evaluate how Hybrid models bridge the historical gap between "Waterfall" structure and Agile's speed by strategically combining the strong attributes of each one.

Core research questions:

1. Which is the current project management model being used by the pharmaceutical industries regarding digital transformation projects?

    1.1. **Answer**: This question aims to identify and reveal what type of project management is currently adopted and applied in the pharmaceutical industries during digital transformation venture.

    The pharmaceutical industries are actively shifting from traditional linear operational management toward to a new era of digitalized data driven ecosystem driven by Phama 4.0. The traditional "Waterfall" or "V-Model" frameworks despite the fact that is perfect for the regulatory compliance the new operation models requires agility, fast cycles, cost reduction and adaptability which can be provided by Agile project management. Unfortunately, the pure Agile project management has multiple gaps regarding the regulatory compliance which is non-negotiable in the health care sector. The organizations in order to perform successfully the digital transformation project s have accelerated the process by using the Hybrid project management frameworks which combines the strong points of traditional method to maintain regulatory compliance while the Agile method providing the fast, iterative adaptation necessary to deploy digital transformation tools.

    The Hybrid model is the golden ratio for the pharmaceutical industries because it combines strategically all the complementary assets from Traditional and Agile

frameworks which can be used separately at the same time in order to fulfill the project's goals in accordance with the schedule without creating deviations in terms of regulatory compliance.

1.2. **Discussion:** The transition of pharmaceutical industries toward to a new era of Pharma 4.0 reveal an intense fundamental tension between absolute predicatively and the rapid adaptability/speed which is required by digital transformation projects. The findings, indicates that the traditional project management framework is deeply rooted in pharmaceutical industries structure and is totally embedded in their operation methodology within the organization. This has to do with the strict regulatory compliance which must be respected (such as GxP and FDA guidelines) and the traditional framework is a safe side option for Quality Driven environments like these. In case of digitalization these frameworks create significant bottlenecks during digital initiative implementation activities which mainly require rapid iterative, continuous integration and data driven agility. The pure Agile framework despite the fact that it fits perfectly to digital projects is not preferred due to its regulatory gaps and because may cause multiple risks.

Therefore, the need to proceed to Pharma 4.0 projects fast while respecting the regulation forced the pharmaceutical industries to use the Hybrid model framework. This framework combines smoothly totally different "worlds", the speed and the compliance by being characterized as the golden ratio for digital projects in Pharma. The Hybrid model allows pharmaceutical industries to create structured but dynamic project workflows by using these dual speed mechanisms strategically for different purposes at the same time to meet the pre-requisite targets and minimize deviations.

The perspective of this strategy to adopt Hybrid models reveals that the pharmaceutical industries trying to be more flexible, move away from the classic tradition project management framework because nowadays is not effective while

maintaining the regulatory compliance. This is a strong point because in these complex environments the successful bridging gap of speed and compliance creates a long-term value and safety for digital projects by creating fundamental structure as a protective barrier.

2. Do Pharmaceutical industries aim to implement Pharma 4.0 projects via internal teams, external vendors or a combination of both?

2.1. **Answer:** This question aims to identify the project management rationale behind the structure of pharmaceutical industries while implementing Pharma 4.0 projects and how the project teams are set up.

The implementation of Pharma 4.0 projects is mainly driven by an internal-led structure approach which is focused on specialized internal technical department personnel and via strategic cross-functional collaborations within organization's departments in order to achieve the absolute alignment. This process is distinguished in two main internal pillars the Dedicated Internal R&D Teams and the Structured Internal Technical Teams which each one has its unique strong points.

2.1.1. **Dedicated Internal R&D Teams:** The member of these teams belongs to a dedicated, expert, innovative and focused internal Research and Development (R&D) department which is a high value asset requirement. Due to the fact that the pharmaceutical industries in terms of manufacturing operation relies heavily to scientific, experimentation and rapid prototyping process these departments can provide multiple customizations and active operational upgrades. Thus, during Pharma 4.0 projects these teams playing a critical and important role by providing all validated information to project management team by helping them to confirm if the new digital technological requirements are accepted.

2.1.2. **Structured Internal Technical Teams:** The member of these teams belongs to the core organizational structure by establishing crucial cross-functional collaborations internally and externally within organization. Due to the fact that the machinery equipment of the pharmaceutical industries is specialize and extremely sophisticated the role of this specialized team is crucial for the everyday maintenance and continues improvement of production operation. Therefore, during digital transformation project these teams are the valuable technical informational flow streams which can collaborate with specialized external vendors via the project management team and contribute actively by transferring technical knowledge.

2.2. **Discussion:** The pharmaceutical industries support the internally drive team philosophy approach when executing Pharma 4.0 digital transformation projects. Their perspective is that these types of projects are a core complementary asset for their organization than an outsourced service while protecting their trade secrets such as technology, process and product portfolio. The combination of high specialized dedicated R&D teams and the Structured Technical Teams reflects the nature of pharmaceutical data the extreme customization which is required during product's production process. Additionally, by prioritizing the exploitation of internal talents of the organization which are experience and familiar with the Pharma operations methodology they have multiple advantages such as mitigating implementation project risks, ensuring safety of intellectual property, ensuring that the developed digital technology will be aligned with the regulations and the workflows of the organization.

This operational division, which is distinguished into pillars of R&D and Technical Teams, is the proof of the wise strategic approach mapping with is a common characteristic for pharmaceutical industries by combining innovation and continuous improvement. On the one hand, the dedicated R&D teams are serving the scientific experimentation and rapid digital prototyping while acting as critical

protection barrier that aim to validate the technological feasibility of the project and compliance alignment before rapid prototyping. On the other hand, the structured internal technical teams leverage the deep knowledge and experience of the existing equipment in terms of maintenance, improvement, and micro fine-tuning of day-to-day operation sustainability. Even though, these divisions approaching the digital transformation projects in totally different way the merging of these assets creates a strong robust ecosystem that ensures the smooth digital transition process within the organization by applying speed, dedicated technical-regulation knowledge with positive impact and strong risk management methodology.

However, the internal driven approach is not implementing a total isolation from the outsourcing sources regarding the digital transition but is a way of controlling when and why they should collaborate with outsourcing specialized vendors. The digital transformation projects include sophisticated advanced technologies which can't be totally managed by the internal teams due to lack of specialized complementary technology assets. Therefore, the organizations can find these assets in the open market and start working with dedicated companies which can offer vertical Pharma 4.0 solutions. The key point here is that, the organization will exploit only the necessary assets from vendors and engage it’s teams to have the full control of the process and which data will be shared with the vendor. The integration of internal and external vendor teams is a focused pillar which provides to management team to acquire the cutting-edge technologies from digital experts while marinating/securing the strict ownership of the overall project process and underlying the preferred technological architecture.

3. What are the current Agile or Hybrid project management models that are used by the pharmaceutical industries regarding digital transformation projects?

3.1. **Answer:** This question aims to identify the type of the project management models of Agile and Hybrid frameworks that are used in the pharmaceutical industries and how are used in favor of digital transformation projects success.

In case of Agile frameworks the adapted to manage digital transformation projects in the pharmaceutical industries are the Scrum and Extreme Programming (XP) framework. Each one has its own strategic points by contributing actively to management of digital health applications, software integrations, and supply chain operations. The first is the Scrum Framework, is utilized for system and software creations by breaking down the huge solid tasks into small sprints by allowing fast, direct adjustments. The second is the Extreme Programming which is focused on engineering code quality within digital environments.

In case of Hybrid frameworks adapted to manage digital transformation projects in the pharmaceutical industries are the Agile V-Model (AV Model) and Enhanced Agile V-Model (EAV Model) framework. The first, Agile V-Model (AV Model) framework is a flexible and can establish the regulatory compliance while maintain the flexible capabilities of the pure Agile framework via sequential V-Model process verification cycles. The second, Agile V-Model (AV Model) framework is an advanced evolution of AV Model with is designed to break down the project tasks in order to provide fast and efficient management while covering non-negotiable safety-critical and validation requirements .

3.2. **Discussion:** The deployment of specific Agile/Hybrid based on frameworks like Scrum, Extreme Programming (XP), the Agile V-Model (AV), and the Enhanced Agile V-Model (EAV) indicates that the pharmaceutical industries has proceed with customization of a standardized project management methodology regarding the digital transformation projects. This type of framework helps the pharmaceutical industries to speed up iterative project sprint cycles by allowing

the breakdown of massive data silos into smaller manageable deliverables with improved quality and limited digital transition failures.

When digital transformation projects interact with validated manufacturing systems with strict regulatory like pharmaceutical industries, the organizations must heavily rely on the AV and EAV models. On the one hand, the standard Agile V-Model can successfully manage/embed the flexible capabilities of Agile sprints with sequential verification cycles of the traditional V-Model by ensuring that each task will be verified at each of its steps. On the other hand, the enhanced Agile V-Model introduce a more sophisticated approach which is specialized to manage the safety-critical systems by breaking down the tasks to maximize the execution speed while embedding automated continuous validation protocols.

The use of these specialized models from pharmaceutical industries during digital transformation projects indicates the high level of maturity and adaptation in a strict regulation environment which automatically create obstacles each time the organization try to make a radical change by avoiding the pitfalls of methodological dogmatism. However, the challenge for the project management teams is to avoid the operational conflicts which could be generated while applying these models and pre-create in time high sophisticated governance teams which can support these type of project properly.

4. What are the Success Factors (SFs) which were identified regarding the successful and uninterrupted digital transformation transition to Pharma 4.0?

4.1. **Answer:** This question aims to identify the Success Factors (SFs) which are adapted in the pharmaceutical industries during Pharma 4.0 projects and the implementation of these factors helps the organizations to succeed.

The identified critical Success Factors (SFs) in the pharmaceutical industries which helps the organizations to succeed during digital transformation projects are distinguished in three core pillars, the technological factors, the organizational factors and the regulatory/process factors. Each category has specific characteristics which are complementary assets among the categories by focusing on targeted sectors.

4.1.1. **Technological factors** aim to create a technological driven action plan with specific activities in order to enhance the digital projects structure framework and introduced as complementary assets for the organizations as following:

4.1.1.1. **Sufficient Investment:** Sustain and long-term financial commitment in order to fund expensive technology and prevent project cancelation.

4.1.1.2. **Digital monitoring traceability:** Utilize digital technologies of Pharma 4.0 in order to enable real time data visibility.

4.1.1.3. **Data Protection & Information Security:** Maintain strict rules for data protection in order to secure real-time data adaptability which supports the decision making process and minimize failure.

4.1.1.4. **Cloud Manufacturing Infrastructure:** Implementing cloud based ecosystem by creating data flow pipelines within the organization with centralized and controlled data.

4.1.1.5. **Interoperability & Standardized Data Processing:** Creating vertical standardized protocols which should be implemented within the organization in order to achieve a solid structure data analysis across the system.

4.1.1.6. **User-Friendly Designs**: Prioritize the creation of easy use tools in order to be suitable for employees with varying levels of digital literacy and make more convinced the engage process.

4.1.1.7. **Human-Centric AI Integration:** Use the technology in favor of employees in order to create tools that enhance human expertise and operational efficiency rather than replacing them.

4.1.2. **Organizational factors** aim to create a robust management structure that will be prepared to support the strategic digital projects by solving all the merged problems and ensuring that all required resources will be provided to project management teams via the following factors:

4.1.2.1. **Top management support:** Require an active, visible and visionary leadership team which major role is to create a digital culture, allocate funds and mitigate employee resistance to change.

4.1.2.2. **Dedicated internal R&D Team:** A team of focused experts in R&D process that aim drive scientific experimentation while maintaining /integrating digital technology into mass production.

4.1.2.3. **Sustainable Corporate Strategies:** The alignment of digital roadmap flows with specific corporate goals such as profitability, lean operations and sustainability while establishing business KPIs in order to protect project funding.

4.1.2.4. **Structured Technical Teams:** The importance of internal aligned resources by creating cross-functional linkages along with operational departments.

4.1.2.5. **External/Policy Alignment:** The structural linkage of organizational internal structure with internal/external technical departments by ensuring the vertical policy alignment.

4.1.3. **Regulatory/Process Factors** aim to create a controlled driven quality framework that will provide all mandatory prerequisite requirements that should be taken into account from the project management teams in case of digital teams by integrating the quality rules in the core of the project and achieving the vertical regulatory complaisance via the following factors:

4.1.3.1. **Paper to Design Standardization:** The change management from traditional documentation towards to new digitized models by using automated streams.

4.1.3.2. **Agile supply chain Auditing:** The integration of real-time traceability and end to end cross checks by mitigating the deviations at raw material supply stream flows.

4.1.3.3. **Real Time Process Monitoring:** The continuous tracking of critical parameters regarding Quality and Production sectors to identify quality deviations proactively.

4.1.3.4. **Compliance Mapping of Hybrid Systems:** Implementing and maintaining advanced frameworks like he Enhanced Agile V-Model (EAV) and Computerized Validation Systems (CSV) in order to bridge the speed with documentation-heavy structures.

4.1.3.5. **Conformity Verification Mapping:** Applying systematic process control frameworks in order to maintain the continuous documentation and maintain the regulatory audit readiness.

4.1.3.6. **Standardized Security Law compliance:** Create and maintain strict data security systems that will be protected by legal frameworks in order to protect the digitalized assets.

4.1.3.7. **Balanced Human-Automation Procedures:** Design operation frameworks based in Hybrid mode while balancing the automated procedures with human's context in order to secure and ensure the collaborative innovation.

4.2. **Discussion:** The identification of critical Success Factors (SFs) across technological, organizational and regulatory pillars indicates the high success ratio during digital transition of Pharma 4.0 projects via a holistic socio-technical aspect rather than simply the technological upgrade itself.

In terms of technology, the factors such as cloud infrastructure, interoperability, and data security are not only operation tools that will be used by the teams but are also important tools for the core preparation of the data driven structure which is required from Pharma 4.0. The tools must be user-friendly designed to be easy for employees to use them without creating obstacles while ensuring real-time data visibility and traceability. Additionally, technology must enhance human skills rather than replacing them by creating an unsafe working environment.

In terms of organizational, top management has a key role in the whole process by supporting and sustaining corporate strategies by improving core project's viability. The digital transformation projects require long term commitment, funding capabilities, and visionary leadership which must protect the core needs of the project while providing corporate profitability. Additionally, the leadership role is to enhance and drive cultural change by preparing the organization for the upcoming digital change and mitigate the employees resistant to change. Without this supportive organizational structure, even the most advanced technological infrastructures will fail to achieve full operational integration and will not create the expected value for the organization.

In terms of regulatory, the Success Factors could be considered as the ultimate gatekeeper for the Pharma 4.0 success. The transition from traditional way to the new digital approach of automated documentation, digitalized stem flows requires a specific and precise reset of the existing quality management system. The Success Factors such as real-time process monitoring and regulatory compliance mapping via hybrid models (via CSV and EAV frameworks can ensure the audit trail readiness which is continuously maintained. The organizations can embed the conformity verification mapping and strict data protection frameworks in the digital transformation projects to achieve the required agility while fully protecting the regulated assets.

5. How the Hybrid projects management models and its activities can bridge the gap between Traditional "Waterfall" and Agile "dynamic iterative" project management by respecting the regulatory requirements to lead in digital agility?

5.1. **Answer:** This question aims to identify and evaluate the Hybrid projects capabilities on how bridging the gap between Traditional "Waterfall" and Agile "dynamic iterative" project management without violating the regulatory requirements in order to lead in digital agility.

The hybrid project management models have the ability to eliminate the historical conflict between Traditional and Agile frameworks and are very valuable in the strict environment of Pharmaceutical industries. These models combine the Agility speed with the regulatory compliance commitment by breaking down the tasks in multiple clusters which can be performed at the same time with different principles. The structures of the Hybrid models are structured through a dual execution path into a single final project lifecycle via following foundations. Additionally, the isolation of safety critical validation enables the Hybrid model to exploit the execution speed and competitive advantages of digital transformation and create value for the organization.

5.1.1. **Plan driven Waterfall/V-Model Foundations:** This pathway's specialization is to handle with safety the critical processed which are plan-driven and ensuring the regulatory compliance via CSV framework. Moreover, it has the ability to manage effectively the extensive documentation which is required by global drug authorities.

5.1.2. **Agile sprints Scrum-driven foundations:** This Pathway allows the project management of break down complex massive tasks silos into smaller independent ecosystems by providing the opportunity of isolated agile loops and fast iterative cycles. This is very useful on daily checkpoints in order to respond instantly to emerged changes or digital requirements.

5.2. **Discussion:** The capability of Hybrid project management framework to bridge the deep gap between plan-driven Waterfall foundations and dynamic, iterative Agile sprints resolves a historical paradox in the pharmaceutical industry because all their process is based on traditional project management. The approach of pharmaceutical industries regarding digital transformation projects was viewed as a project which was incompliant with regulations and couldn't manage via the traditional project management framework. This approach automatically creates a major obstacle that cancels the project before it starts because pharmaceutical organizations couldn't manage it with the existing tools. Despite that fact, the pharmaceutical industries had to proceed with Pharma 4.0 to be more competitive and increase product quality and they did it by applying the Hybrid project management framework. The Hybrid model by isolating the safety-critical validation activities from tasks via rapid cycles provide the opportunity to the organizations to exploit the competitive advantages of digital transformation such as speed, cost reduction while mitigating compliance failures or regulatory deviations.

This bridging mechanism acts as a fundamental merging process by using the most valuable foundations from both Traditional and Agile models which will contribute positively to the whole process. On the one hand, the traditional "waterfall" model (V-Model) can provide stability, extensive documentation management and Computerized Systems Validation (CSV) which are required by the global health authorities like FDA or GXP. On the other hand, the agile model can provide the sprint foundations via daily dynamic iterative checkpoints, rapid prototyping pipelines and readiness to manage any emerged needs regarding digital transformation projects. Taking into account the above representative value from both models this bridging mechanism is a crucial function of the Hybrid model which creates a unique and adaptive system tailor-made for each organization's needs.

Significantly, the success of this bridging method is depends on the strategic integration of both models by using wisely each required core foundation which meets the needs of the project. The project activities must be designed so the output of the iterative agile sprints to fit perfectly into the verification strict stage-gates of the traditional model. This is not a simple blending of two different frameworks but it requires experienced project management team by taking into account the creation of a mapping on how the agile actions will have interaction and intervention in Traditional model's actions with full aliment with regulations while acting as an intermediate "translator" for both models. Ultimately, transforming the relationship between compliance and innovation from a non compatible status with strong conflicts into a united ecosystem is a high value asset that can be exploited by pharmaceutical industries via the Hybrid models which can provide the tools and the methodology for a sustainable blueprint framework.

5.2 Strategic Suggestions for Project Managers per Research Question (RQ).

1. Which is the current project management model being used by the pharmaceutical industries regarding digital transformation projects?

    1.1. **Strategic Suggestion for Project Managers (PM):** The project managers must reject the pure Traditional methodologies and actively adopt the Hybrid models as standardized framework regarding Pharma 4.0 projects. The modern pharmaceutical industries and its market have multiple dynamic characteristics and needs that can't be performed via traditional project management. Even the everyday operation nowadays is a fast sprint with dynamic adoption based on the

requirements and high demand tasks while requiring the regulatory compliance. The pure Traditional or Agile model can't stand effectively against these requirements and the only way for the project managers to create value via digital transformation projects is the Hybrid approach. The project managers can create and exploit value by utilizing the dual-speed of Hybrid model that deploys the Traditional model to ensure the regulation compliance and the agile model in order to minimize time execution and project costs. Additionally, PM Managers can exploit this "golden ratio" by strategically creating specific mapping regarding documentation workflows via safety gates which acting as structured pathway for for rapid, low-risk digital sprints.

2. Do Pharmaceutical industries aim to implement Pharma 4.0 projects via internal teams, external vendors or a combination of both?

2.1. **Strategic Suggestion for Project Managers (PM):** The PM Managers can maximize the value of the internal teams by adopting an internal led and creating cross functional robust structured stream flow. They can use wisely the two pillars of internal teams the R&D and technical teams by providing cross functional knowledge streams and use it a complementary assets for each other team. This method can bridge gaps and decode emerged problems which could be solved via the other team by providing deep knowledge to this specific ecosystem from each team's expertise internally and securing the core intellectual property-trade secrets. The external value which can be exploited by the PM Managers by engaging specialized vendors regarding Pharma 4.0 projects can ensure that the internal teams have the ability to enhance their knowledge range through these external complementary assets and maintain the project architecture, governance and strategic direction.

3. What are the current Agile or Hybrid project management models that are used by the pharmaceutical industries regarding digital transformation projects?

    3.1. **Strategic Suggestion for Project Managers (PM):** The PM Managers must actively customize a tailor made Agile and Hybrid framework which will meet all requirements of the digital transition projects for their organizations. This is an important pillar because there are major differences among pharmaceutical industries based on their operational business model. For digital transformation projects the PM Managers should apply agile frameworks such as Scrum in order to breakdown data silos into focused targeted short sprints by emphasizing to quality. In case of more complex physical integration projects, the PM Managers should utilize Hybrid models such as AV and EAV in order to integrate automated actions, continuous validation process with within sequential verification cycles. Therefore, the PM Managers can exploit the value of these frameworks by creating a robust team in an early stage in project's lifecycle by mitigating conflicts with a quality driven organization and avoid digital transformation failure.

4. What are the Success Factors (SFs) which was identified regarding the successful and uninterrupted digital transformation transition to Pharma 4.0?

    4.1. **Strategic Suggestion for Project Managers (PM):** To ensure the uninterrupted digital transition the PM Managers must be visionaries and have critical thinking approach by looking beyond the massive technical upgrade but managing the projects through a holistic socio-technical lens by taking into account the technological, organizational and regulatory pillars via using wisely the related Success Factors. Regarding the technological aspect, they have to create user-friendly tools, cloud based infrastructures that enhance human's capabilities while creating a knowledge exchange stream flow by exploiting the maximum value from each aspect. Regarding the organizational aspect, the PM Managers must

request from the top management the maximum support in order to secure the long-term undisrupted funding and proactively manage the employees' resistance before engaging them into the project by creating a digital culture. Finally, regarding the regulatory aspect the PM Managers must embed the Quality Regulatory Design process from the day one in their projects by preparing the appropriate pathway to avoid deviations due to regulatory non-conformity.

5. How the Hybrid projects management models and its activities can bridge the gap between Traditional "Waterfall" and Agile "dynamic iterative" project management by respecting the regulatory requirements to lead in digital agility?

5.1. **Strategic Suggestion for Project Managers (PM):** The PM Managers must act like dynamic translators between different project management approaches and especially from Traditional to Agile method and vice versa. To achieve this, they have to create a bridging mechanism which can exploit the maximum the valuable assets of each model by finding the "opened window" which allows the bridging mechanism to create a stream flow pipeline. Through this pipeline the project team can coordinate more efficiently the tasks by allocating them wisely into the correct model cluster (Traditional: Compliance and Agile: Innovation) by achieving the maximum implementation performance value. Additionally, extra value is created due to the fact that via this bridging mechanism the PM Managers have the ability to convert the conflict between innovation and compliance into a high-performed ecosystem by mitigating costs, deviations and achieving digital agility.

6. Chapter 06: Conclusion and Recommendations

6.1 Summary of Findings

The thematic and keywords analysis of the specific literature from 2021 to 2026 reveals that the Pharmaceutical sector which accounts the biggest part of the evaluated publications is followed by digital transformation projects with multiple combinations of project management methodologies. More specifically, the study explores the way the project management methodologies of Traditional and Agile frameworks within pharmaceutical industries can contribute to the digital transition projects of Pharma 4.0 success and evaluates how the Hybrid project model can bridge the approach gap of the above mentioned frameworks while driving the required digital agility within a strict regulatory environment along with the Success Factors. Additionally, the Pharma 4.0 technologies such as artificial intelligence, neural networks and deep learning are already adopted from multiple healthcare organizations which indicate that these core technologies are widely known and push the organizations toward to adopt those regarding digital medical solutions.

A main crucial tension which was identified is the operational dilemma between compliance and innovation regarding the digital transformation projects in Pharmaceutical industries. The Pharmaceutical industries use the Traditional project management method because they rely on the strict regulatory rules and are the only model that fits perfectly in order to satisfy stringent regulatory mandates via a linear project management framework. These traditional project management methods usually create conflicts with the iterative cycles that are required for digital transformation projects and innovation projects in Pharma sector. The findings indicate that the golden ratio is the Hybrid project management methodologies which can serve efficiently as a critical bridge to resolve this conflict. Via this method the tasks are divided in multiple different clusters by utilizing the

traditional method to secure regulatory compliance and the agile iterative methods to drive innovation and leverage the advantages of both frameworks.

This project management synthesis reveals that the PM Managers have a strategic role in the Phamra 4.0 projects by evolving dynamic team members who will act as expertise translators capable to understand & communicate correct the pros and cons of each method. This approach is extremely crucial because it merging smoothly multiple frameworks and operational models under one unique ecosystem which will act as structured mechanism that creates common communication pipeline between different systems. Through this pipeline the organizations can ensure that, will be in place effective task coordination and allocation in specific clusters by achieving high performance and low conflicts during project implementation.

In summary, the standardization of the Hybrid model pathway allow the organizations to actively managing the projects in a more efficient way in terms of mitigation cost, minimization of procedural deviations, creating a digital driven culture while embedding the quality regulatory design process from the earliest stages of the project. This has a significant positive impact for the digital projects by establishing a proactive pathway that can avoid regulatory deviations and in combination with the implementation of success critical factors the maximum value of the digital transition can be exploited on favor of the organizations.

6.2 Limitations of the Study

The findings of this systematic literature review highlight the rapid evolution, the importance of the critical Success Factors and the challenges during toward "Pharma 4.0" through Agile and Hybrid project management frameworks in pharmaceutical industries. While the study provides a valuable insights regarding the integration of Agile and Hybrid

methodology within the regulated environment of Pharma 4.0 there are some limitations which should be taken into account in accordance with the following categories.

1. **Methodology:** The study is designed as a systematic literature review and is based on the secondary literature of the last 5 years without taking into account quantitative surveys, interviews with focused groups or with active pharmaceutical project managers.
2. **Sample variety:** The study used 41 peer-reviewed papers that met the strict inclusion and exclusion criteria for a more focused analysis while losing the extent informative analysis. Additionally, the Pharma 4.0 is introduced as a new concept for the Pharmaceutical-Health Care organizations since 2017 and the available studies are limited.
3. **Temporary constrains:** The literature matrix spans from 2021 to 2026 due to the fact that the Pharma 4.0 is an new framework for pharmaceutical industries and the applied project methods of Agile and Hybrid frameworks are not applied/tested for multiple years in strict regulatory environments such as pharmaceutical industries.
4. **Database and Publication:** The source of literature review papers was focused on pharmaceutical and health care organizations via a dedicated search portal “PubMed” and via using a specific keyword query regarding the outcome results without taking into account internal corporate validation playbooks, whitepapers from regulatory bodies (e.g., FDA, EMA), and confidential case studies from major pharmaceutical firms.

6.3 Suggestion for Future Research

This study has explored how the pharmaceutical industries can use the Agile and Hybrid project management framework to successfully balance the strict regulatory rules and the digital innovation within the Pharma 4.0 projects while identifying the key successfully factors. Despite the fact that the study offer a valuable guidance and evaluated results there are several areas which are suggested for future research as following.

Firstly, the technology of industry 4.0 (Pharma 4.0) is changing radically each year and the current technology in the next 5 years may be considered as obsolete technology of low value for advances pharmaceutical industries. Therefore, the study should be performed again in the next 5 years.

Secondly, this study is based on literature review which is theoretical and semi practical source of data regarding a non mature digital transformation framework in the pharmaceutical industries the Pharma 4.0. Therefore, in the re-evaluation of the study as source of data should be included real performance results within pharmaceutical industries worldwide by measuring the real value of profit and reduce of regulatory errors.

Thirdly, future research should focus on AI (Artificial Intelligence) and automated tools performance-integration and how contributed – created value during the digital transformation projects and how managed to be fully compliant with regulation without losing the humans expertise need to double-check for safety. This is important due to the radical evolution of AI within a strict regulatory environment of pharmaceutical sector which operates with total opposite way.

Fourthly, because many employees may resist leaving behind the old traditional operation paper based method the future research should evaluate and indentify training methods for organizations on how they have to train their teams and change company's culture to embrace a digital and agile mindset.

Fifthly, due to the fact that current high costs of Pharma 4.0 projects are too expensive for the pharmaceutical industries to invest in projects called nice to have and not mandatory for their operation, the future studies should focus on identifying low cost – budget friendly solutions to attract their interest.

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