Pharma 4.0 Quality Management Challenge: A Literature Review

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Abstract

This paper aims to review several related papers on Quality Management and Industry 4.0 in the pharmaceutical industry environment to achieve the benefits required future and give a better vision of the extant regulatory and technical barriers for realizing it. Quality Management and industry 4.0 require efforts to better understand a GMP (Good Manufacturing Practices) pharmaceutical industry situation. Product quality in the pharmaceutical industry is a fundamental thing that must be achieved as a fulfillment of regulatory requirements. GMP for the Pharmaceutical Industry is a minimum standard of compliance for the pharmaceutical quality system requirement that must be designed, applied, managed, and maintained properly so that the main objective is achieved where the production process so that medicinal products always have robust quality in fulfilling efficacy and patient safety. Industry 4.0 in the pharmaceutical industry (which is popular with the term Pharma 4.0) is challenging to implement within the GMP 'high-regulated industry' environment. It will have consequences to moving transition into it step by step in a delicate careful slide. The internet of things (IoT), artificial intelligence (AI), robotics, machine learning, cyber-physical system, and advanced computing as a character of industry 4.0 will dramatically change the landscape of manufacturing including the quality system inside. The research results presented in this paper show an increasing trend towards research that focuses on the slices of 'quality management', 'pharmaceutical quality system' and 'industry 4.0'. Further research needs to be done to create a pharma 4.0 quality system implementation model.

Keywords
Quality management, Pharmaceutical industry, Industry 4.0, GMP, Pharma 4.0

1. Introduction
In the past several decades, the pharmaceutical industry, including the traditional medicine and biopharmaceutical industries, is always under strict supervision by regulators in each country within its jurisdiction. The regulator must protect patients as drug consumers by always ensuring that medicinal products always meet their quality by controlling the raw materials used and assessing the final product's production processes (Rantanen et al. 2015). For a better understanding among regulators, several countries have legalized a world organization forum in the form of The Pharmaceutical Inspection Co-operation Scheme (PIC/S). They harmonized guidelines which can then be adopted by each member country to become a regulation in their jurisdiction that binds on how the pharmaceutical industry should be operated.

PIC/S published a Guide to Good Manufacturing Practice (GMP) for Medicinal Product. The guide emphasizes the baseline of the Pharmaceutical Quality System (PQS) with the assurance of the medicinal products to always fit for their intended use as the key principle. PIC/S (2021) requires that medicinal products comply with the requirements and not place patients as drug consumers at risk due to inadequate safety, quality, or efficacy. It is a Quality Management with a large scope concept, which covers a wide range of matters that individually or collectively influence the quality of a product. It is put side by side with the understanding of a GMP (Good Manufacturing Practices) concept. It applies to the lifecycle stages from the process design, technology transfer, commercial manufacturing through to product discontinuation, and can extend to the pharmaceutical development lifecycle stage (PIC/S 2021).

PQS initially published in ICH Q10 (ICH 2009) as a guideline to assist pharmaceutical manufacturers by describing a model for an effective quality management system for the pharmaceutical industry (ICH 2009). This guideline is

supposed to be understood side by side with the ICH Q8 Pharmaceutical Development and ICH Q9 Quality Risk Management, which recommend building a product quality through the whole product life cycle and adopting the principle of QbD (Quality by Design) concept. Built Quality since the product design and development (ICH 2009) and apply a risk-based thinking concept approach to maintain a high-quality medicine product and keep assured of patient safety.

While the past decade introduce the term industry 4.0 define as an industry adoption for digitalization, cloud computing, the internet of things (IoT), and big data to gain competitive advantages on their products (Reinhardt et al. 2020), the PQS which is developed in pharmaceutical industry must face a challenging strategy that effectively fulfills the objective and gain as much as possible the industry 4.0 adoption to maximize its benefit. This unique concept is adopted with the terminology Pharma 4.0 (Barenjia et al. 2019), and industry 4.0 application concerning the PQS.

Even if the quality management resource for industry 4.0 becomes a challenging situation, the pharmaceutical industry will deal 'the double impact' for achieving the PQS baseline and taking the advantage of industry 4.0 applied system and technology. It will become a pharma 4.0 quality management challenge.

1.1 Objectives

This paper will give an overview of several papers that study quality management systems in the pharmaceutical industry and make a connection with the industry 4.0 quality management and industry 4.0 application in the pharmaceutical industry (Pharma 4.0). The papers reviewed will be collected starting from 2009 as it is justified for having an implementation study in the pharmaceutical industry since the ICH Q10 Pharmaceutical Quality System final approved guideline published in 2009. Three aspects for keywords used are: 'pharmaceutical industry'; 'quality management' and 'industry 4.0'. Filtered into only at least the two keywords included and only papers with more than 2 citations chosen for review.

The objective is to make a summary on paper reviewed to define hypothetically what quality management resource challenge on the pharmaceutical industry when adopting the industry 4.0 strategy to gain its competitive advantage.

2. Literature Review

For several decades before millennia, pharmaceutical industries have been using a traditional paradigm for maintaining the quality of their products in a quality management system. Product quality assurance is performed based on sampling inspection of the final product. There is a simple statistical approach to final product inspection. Any discrepancy in the sample taken may mean that the entire production batch must be rejected. Meanwhile, samples that meet product quality requirements also cannot provide certainty of product quality behavior in the batch as a whole. Quality only is assured on final product testing and the raw material used (Rantanen and Khinast 2015).

Since the ICH Q10 Pharmaceutical Quality System has been set as a standard that must be fulfilled, all pharmaceutical industries try to find a strategy of how the standard can be applied properly. The QbD based thinking approach as an elaboration of the concept of robust design (Phadke 1989; Belavendram 1995) is a new concept that later became the foundation of the industry so that it can implement its manufacturing activities with its design and operations using scientific studies to ensure the quality of its products. QbD which was then applied consisted of steps to determine Quality Target Product Profile (QTPP), Critical Quality Attribute (CQA), and Critical Process Parameter (CPP) (Rantanen and Khinast 2015) with scientific steps Design of Experiment (DoE) to determine design space and identify control strategy (Gandhi and Roy 2016). The product quality should be scientifically built from the product design stage.

When CQA, CPP, design space, and control strategy are scientifically developed using quality risk management tools, it can be formulated into a robust design criterion for the product, the scale-up in commercial production will follow the validation activity stage as an effort to ensure product quality throughout its life-cycle. There is a measurable monitoring effort on product quality attributes throughout the production process. Understand the process variability during its production in maintaining the quality of this product then, scientists introduced a technology called PAT (Process Analytical Technology) with the concept of quality control in real-time based on the design-space boundaries that have been defined in the early stage of QbD Process Design (Murphy et al. 2016). The terminology for the whole is the Design Process as stage 1, then stage 2 when the implementation of the production process on a commercial scale is called the Performance Process Qualification (PPQ) and stage 3 as monitoring throughout the product life-

cycle is called Continued Process Verification (Kim et al. 2021). Quality is no longer recognized by the reject rate of the product at the final inspection, but by constantly monitoring the behavior of critical quality attributes by observing their variations throughout the production process with design-space constraints that are always within the safety limits of the specifications.

Technology in the pharmaceutical manufacturing industry is currently continuously evolving as it appears to be disrupted by the digital transformation of industry 4.0 which challenges traditional approaches, practices, and business models for the manufacture of medicinal products (Arden et al. 2021). This advanced technology is utilized in the industry so that it will transition into what is called Industry 4.0 which in the Pharmaceutical Industry is known as Pharma 4.0. (Barenjia et al. 2019). It is logical for the industry that the use of advanced technology in the Pharma 4.0 application will always start with business needs and quality requirement fulfillment. Business needs can be related to efficiency, productivity, or creating a competitive advantage. While quality requirements, industry 4.0 provided support for a successful implementation of Total Quality Management (TQM) principles. As Sader et al. (2016) stated TQM is a managerial approach that leads an organization to achieve a so-called world-class manufacturing achievement by ensuring that its products and services are met its requirements and expectations to satisfy customers.

Quality by Design (QbD) is a part of the quality engineering and management concept and was formalized in specific terms to assist the pharmaceutical industry towards the market and operational excellence (Grangeia et al. 2019). Achieving industry 4.0 will require adopting advanced manufacturing technologies and overcoming regulatory, technical, and logistical challenges to control the variability across lots and produce consistently available products. Arden et al. (2021) suggest that readily used PAT and QbD as tools in many pharmaceutical manufacturers, still it is only a few of them are prepared to take the next steps to adopt advanced technologies in support of smart manufacturing. The demand for Process Analytical Technology (PAT) will also be more effective if advanced technology is used effectively. Key components of QbD are discussed and their potential impact on current manufacturing processes along with the technological capabilities of PAT and the benefits associated with real-time process monitoring and control (Murphy et al. 2016). Moreover, advanced technology such as the Cyber-Physical-based PAT framework for the adoption of Smart Pharmaceutical Manufacturing Systems has been developed. The framework is based on multi-smart agents at multiple levels (Barenji et al. 2019).

Not only on the manufacturing side, but the scope also concerns the logistics and supply chain more broadly (Abbas et al. 2020; Mostofi and Jain 2021). And regarding things that must be anticipated, especially on the scope of human resources involved in it (Santos et al. 2021; Pereira et al. 2020).

3. Methods

The method used is to analyze and evaluate papers and draw conclusions at regulatory demands on the PQS in the pharmaceutical industry which focuses on the QbD base-thinking approach, in realizing Quality Management in the pharmaceutical industry and the challenges to technological developments applied in the industry so that they enter the industry 4.0 era.

The initial stage was searching for papers with three main keyword groups (see Figure 1), those are:

1. Pharmaceutical Industry, which was later more specific on matters related to quality assurance, PQS, pharmaceutical QbD.

2. Quality Management, which can be developed in the literature on TQM topics area.

3. Industry 4.0, which can also be linked to the Society 5.0 approach as a concept that also focuses on the role of humans and how industry 4.0 with the benefits of new technology can provide welfare to humans.

So that the search can be narrowed down to the research objective, the search is carried out by pairing at least two of the above among the three.

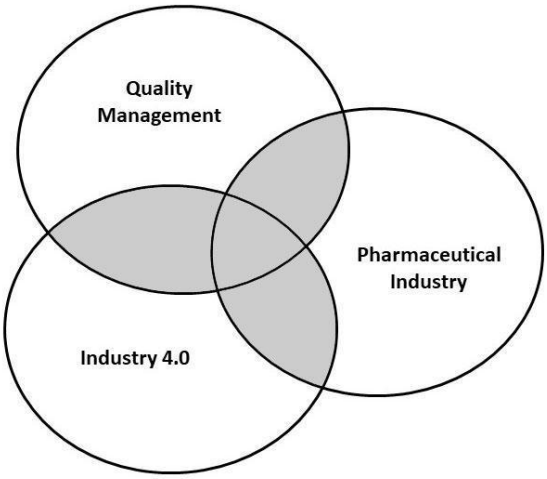

Figure 1. Keywords grouping for literature search

The search was conducted on indexing and filtering papers published in 2009 and thereafter, as justification for having a reasonable study in the pharmaceutical industry since the ICH Q10 Pharmaceutical Quality System guideline was published in 2009. The search was conducted at Scopus and Google Scholar. The search was also carried out on journal publications related to pharmaceutical disciplines (Pubmed, MDPI, ISPE) with keywords and containing title words combining 'pharmaceutical industry' with 'quality management'; 'pharmaceutical industry' with 'industry 4.0' and 'quality management' with 'industry 4.0'. The results are then sorted only on papers that support the research objectives: -as mentioned above- quality management resource challenge on the pharmaceutical industry when adopting the industry 4.0 strategy to gain its competitive advantage.

The results of the selection are then selected only on papers that have been at least cited twice and have a minimum of 20 literature references in their research.

4. Data Collection

Data collection results on keywords 'pharmaceutical industry' and 'quality management', in the initial search for papers published from 2009 to 2021 on Scopus shows 223 papers, for keywords containing 'pharmaceutical industry' with 'quality management', 122 papers containing 'pharmaceutical industry' with 'industry 4.0', and 164 papers containing 'quality management' with 'industry 4.0'. Searching in Google Scholar produced 349 papers with the keywords 'pharmaceutical industry' with 'quality management', 291 papers containing 'pharmaceutical industry' with 'industry 4.0', and 180 papers containing 'quality management' with 'industry 4.0'. And in Pubmed, MDPI and ISPE produced a total of 306 papers for the keywords containing 'pharmaceutical industry' with 'quality management', 87 papers containing 'pharmaceutical industry' with 'industry 4.0', and 77 papers containing 'quality management' with 'industry 4.0'. From those initial search results, The papers were then carefully selected for generally can be included on the topics that relevant to the Pharmaceutical Quality Management, Quality Management Challenges in Industry 4.0 and Pharma 4.0, and came up with 325 Scopus papers, 185 Google Scholar papers and 280 papers from Pubmed, MDPI and ISPE. Further analysis of the papers was carried out by including the study criteria in more specific research regarding matters relating to pharmaceutical quality systems, quality assurance, pharmaceutical QbD refers to the ICH Q8, Q9, Q10 guideline references; quality management in general related to the TQM concept; and industry 4.0 implementation studies which can also be related to the Society 5.0 approach as a concept that also focuses on the role of humans and how industry 4.0 with the benefits of new technologies can provide welfare for humans, by filtering them with a minimum of 2 cited and at least have 20 references.

5. Results and Discussion

The final results of selected papers based on the above method can be shown as follows:

5.1 Numerical Results

26 papers can be categorized as papers that study the implementation of the PQS concept since the publication of ICH Q8, Q9, Q10 in 2009 which then also considers the TQM concept that supports those implementations, which then involves advanced technology as things that can be utilized to achieve the industry 4.0 environment with its implications for human welfare (see Table 1)

Table 1. A final summary of Pharma 4.0 Quality Management Challenge topic papers

Author	Title	Pharma Industry	Quality Management	Industry 4.0
Mazumder et al. 2011	Total quality management in pharmaceuticals: A review	✓	✓	
Trivedi 2012	Quality by design (QbD) in pharmaceuticals	✓	✓	
Jain 2014	Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development	✓	✓	
Yu et al. 2014	Understanding Pharmaceutical Quality by Design.	✓	✓	
Haleem et al. 2015	Quality in the pharmaceutical industry – A literature review.	✓	✓	
Rantanen and Khinast 2015	The Future of Pharmaceutical Manufacturing Sciences	✓		✓
Sader et al. 2016	Industry 4.0 as a Key Enabler toward Successful Implementation of Total Quality Management Practices		✓	✓
Gandhi and Roy 2016	Quality by Design (QbD) in Pharmaceutical Industry: Tools, Perspectives and Challenges	✓	✓	
Murphy et al. 2016	Pharmaceutical manufacturing and the quality by design (QBD), process analytical technology (PAT) approach	✓	✓	
Ding 2018	Pharma Industry 4.0: Literature review and research opportunities in sustainable pharmaceutical supply chains	✓		✓
Singh et al. 2018	Computer system validation in the perspective of the pharmaceutical industry	✓		✓
Grangeia et al. 2019	Quality by Design in Pharmaceutical Manufacturing: a systematic review of current status, challenges, and future perspectives	✓	✓	
Barenji et al. 2019	Cyber-physical-based PAT (CPbPAT) framework for Pharma 4.0	✓		✓
Steinwandter and Herwig 2019	Provable Data Integrity in the Pharmaceutical Industry based on Version Control Systems and the Blockchain	✓		✓
Goecksa et al. 2020	Decision-making trends in quality management: a literature review about Industry 4.0		✓	✓
Pereira et al. 2020	Industry 4.0 and Society 5.0: Opportunities and Threats		✓	✓
Reinhardt et al. 2020	Current Perspectives on the Development of Industry 4.0 in the Pharmaceutical Sector	✓		✓
Abbas et al. 2020	A Blockchain and Machine Learning-Based Drug Supply Chain Management and Recommendation System for Smart Pharmaceutical Industry	✓		✓

Author	Title	Pharma Industry	Quality Management	Industry 4.0
Chiarini 2020	Industry 4.0, quality management, and TQM world. A systematic literature review and a proposed agenda for further research		✓	✓
Lipa et al. 2020	Introducing a Model and a Framework to Unify the Pharmaceutical Quality System Enablers Quality Risk Management & Knowledge Management	✓	✓	
Arden et al. 2021	Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future	✓		✓
Santos et al. 2021	New Needed Quality Management Skills for Quality Managers 4.0		✓	✓
Antony et al. 2021	Quality 4.0 conceptualization and theoretical understanding: a global exploratory qualitative study		✓	✓
Mostofi and Jain 2021	Inventory Management and Control Of Deteriorating Pharmaceutical Products Using Industry 4.0	✓		✓
Kim et al. 2021	Process Analytical Technology Tools for Monitoring Pharmaceutical Unit Operations: A Control Strategy for Continuous Process Verification	✓		✓
Morgane et al. 2021	Model predictive control in pharmaceutical continuous manufacturing: A review from a user's perspective	✓		✓

5.2 Graphical Results

There is an increasing trend year to year since 2009, both in general selection which is also similar to the trend in the final specific result Figure 2 and Figure 3 represent the trend of final selected papers.

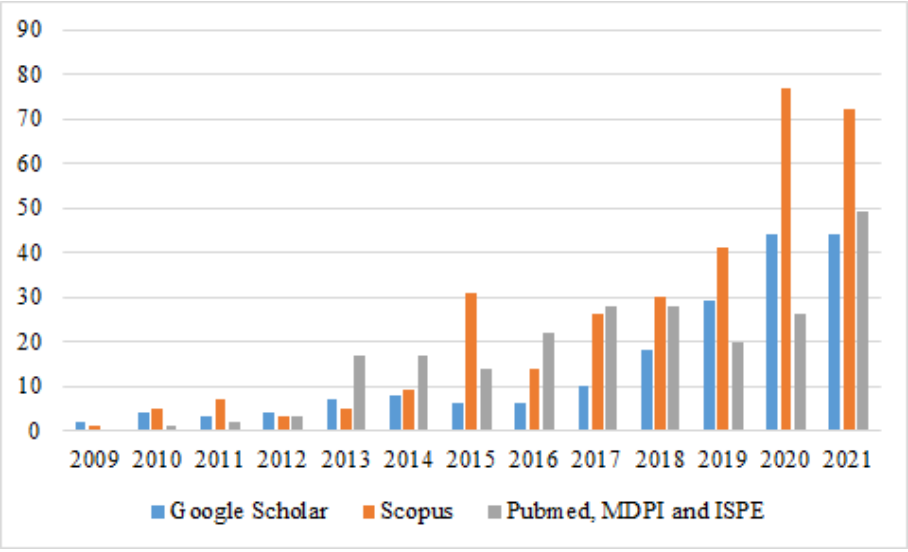

Figure 2. The trend of selected papers that generally can be included on the topics 'Quality Management'; 'Pharmaceutical Industry' and 'Industry 4.0' criteria.

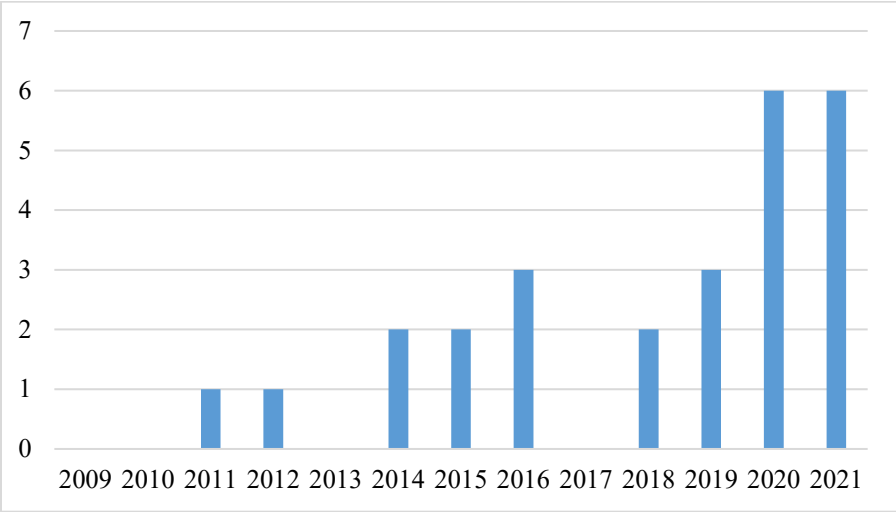

Figure 3. The trend of final selected papers on the study criteria in more specific research

5.3 Proposed Improvements

Based on the study of all the final selected papers, it brings the understanding that can be summarized and become a future challenge of PQS in the industry 4.0 environment and should be studied as a whole single topic that covers:

1. Quality Management in the Pharmaceutical Industry within the regulatory corridor of the PQS, involving:

   - Quality by Design (QbD) as a tool that can assist pharmaceutical companies' efforts towards the market and operational excellence (Grangeia et al. 2019).

   - Typical elements of QbD's PQS through product life-cycle, involve the key elements (ICH 2009; Gandhi et al. 2016; Murphy et al. 2016; Grangeia et al. 2019; Kim et al. 2021):
     - Stage 1, process design that step by step follows the activity to define the QTPP, identify the quality attribute, perform a risk (assessment) analysis, determine the CQA and CPP, determine the design space, and identify a control strategy.
     - Stage 2.1, conduct all facility qualifications that involve the product manufacturing, including the qualification of the building, utility, machine, and equipment used.
     - Stage 2.2, Process Performance Qualification (PPQ) with science-based and risk-based thinking to determine the number of validation batches and using sampling plan standard procedure.
     - Stage 3.1, heightened monitoring on initial commercial batches manufacturing.
     - Stage 3.2, routine product quality monitoring with science-based and risk-based justification to reduce attribute number and sampling plan strategy.
     - Change control management in the product life-cycle.
     - Quality risk management and knowledge management as an enabler (Lipa et al. 2020).

   - Design of Experiment (DoE) and Quality Risk Management (QRM) tools usage in QbD application (Grangeia et al. 2019).

2. Quality Management challenges in general when implementing Industry 4.0, especially in terms of providing resources to achieve it to consider on:

   - Industry 4.0 features that are interconnection, integration, and big data, must support the TQM critical success factor principles (Sader et al. 2016).
   - Reducing costs, energy, improving production process efficiency, responsiveness to customer needs, and product quality are all promoted by the evolution of production systems with the latest technology and tools developed by Industry 4.0 (Pereira et al. 2020).

- Quality professionals in the future must have basic soft skills such as creative thinking, be leaders, know how to communicate and work as a team. Besides their field of competence, they must know new technologies, that is cyber-physical production systems and combine that with the best quality management practices, where their decisions will be based on big data and data mining effectiveness. They have also to be able to make the right decisions based on and supported by data analysis (Santos et al. 2021).

3. Pharmaceutical Industry 4.0 (Pharma 4.0) Challenges in the scope of:

- Industry 4.0 technologies have the potential to transform pharmaceutical manufacturing and logistics platforms through digitization, autonomous systems, robotics, and computing advancements. This requires advancements and innovations that address the various risks and challenges of data, computing, and automation. This new industrial 4.0 manufacturing paradigm should create a business case for adopting new technologies: more control, fewer errors, more responsiveness, and fewer drug shortages. In the future, additional, more accessible, and real-time product quality information will be generated, and it may become more transparent to patients and healthcare providers. (Arden et al. 2021).

- Innovations in Industry 4.0 have provided many improvements and added value to more efficient coordination, communication, and information systems in all corporate organizational functions, especially in the flow of information in manufacturing, logistics, sales, and distribution. Process requirements can be shared and obtained in real-time thereby improving productivity in the pharmaceutical industry. Fast information and quick decisions can increase production continuity so that it can reduce material utilization and energy consumption (Ding 2018).

- Advanced technology such as the use of Cyber-physical-based PAT, a Blockchain and Machine Learning-Based Drug Supply Chain Management, the logistic network is already being developed and contribute to improving the quality performance (Barenji et al. 2019; Abbas et al. 2020; Mostofi and Jain 2021; Kim et al. 2021).

- Data integrity and computer system validation issue to achieve mitigation for PQS risk acceptance (Singh et al. 2018; Steinwandter and Herwig 2019).

5.4 Validation

Validation of selected papers review to confirm this study objective was done qualitatively with two steps verification. First, the analysis conducted by comparing groups of papers that lead to the keywords ‘Quality Management’ and ‘Pharmaceutical Industry’ was checked for compliance with ICH Q10 as the initial final approved guideline for the PQS concept. Confirmation is done by looking at the papers and comparing them with the guideline flow through a checklist tool on the use of keywords in articles including words namely: *pharmaceutical quality system; product life-cycle; quality by design; quality target product profile; quality attributes; process parameters; design space; control strategy; continual improvement; quality risk management; knowledge management; change control; process design; process performance qualification; continued process verification; science-based;* and *risk-based*. Second, the group of papers that lead to the keywords ‘Quality Management’ and ‘Industry 4.0’ was examined by making a comparison to the glossary on standards and IT Architecture that approach on a "Reference Architecture Industry 4.0" - RAMI 4.0, a three-dimensional layer model, as an important step towards implementing industry 4.0 at a practical level (DIN 2016).

6. Conclusion

From the review of all the papers that have been carried out, it can be concluded that the regulatory guide regarding the ICH Q10 Pharmaceutical Quality System as a corridor for the implementation of Quality Management specifically in the pharmaceutical industry has a constructive influence on each other. The concept of total quality management will automatically develop when the pharmaceutical industry is committed to implementing the PQS. Quality Management is built during the product life-cycle, from design, and throughout the commercial production process, covering the entire supply chain from upstream to downstream.

The use of advanced technology in the pharmaceutical industry as the application of industry 4.0 which provides a competitive advantage for the industry itself, in the design and use according to its designation, will support the overall

quality management strategy. The developments that have been carried out include real-time monitoring activities according to PAT needs based on the use of the latest technology.

In addition to cost-benefit considerations in industry 4.0 technology investment, this also demands a challenge for quality professionals to make changes to their competency needs, as an addition to their field of expertise and basic soft skills, the competency in data science, data integrity, and information systems are also required to support appropriate a quick decision making with science-based and risk-based consideration objectives.

Further research is needed to obtain a more enlarging perspective for each stage of the product life-cycle of the PQS on the study-case exploration with advanced technology added value on physical-thing, digitalization, communication, data acquisition, and analysis in terms of product quality assurance and intended to use considerations as the deployment of industry 4.0.

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Biography

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