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Pharmaceutical cold chain and novel technological tools: a systematic review

Cadeia de frio farmacêutica e novas ferramentas tecnológicas: uma revisão sistemática

Giset N. Montoya M.[1], Orlando Fontes Lima Jr.[2], Antonio G. N. Novaes[3], Jose Benedito S. Santos Jr.[4], Jaime A. C. Arias[5]

[1]State University of Campinas, Brasil, natimontoyam@gmail.com
[2]State University of Campinas, Brasil, oflimaj.fec@gmail.com
[3]State University of Campinas, Brasil, antonio.novaes1992@gmail.com
[4]State University of Campinas, Brasil, jbened@gmail.com
[5]State University of Campinas, Brasil, jaime.and.20@hotmail.com

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ABSTRACT
The pharmaceutical cold chain (PCC) deals with specific logistics operational requirements related to product quality, safety, and regulations that make the supply chain management process complex. Also, the pharma industry market growth increases the awareness, in terms of good's temperature monitoring and controlling, of the storage and transportation processes across the network. This study provides a novel approach to PCC, based on a systematic literature review with an extensive analysis of the main aspects that influence the supply chain processes. The major findings highlight the recently worldwide research progress on the PCC subjects related, the challenges involving the PCC and its associated technological advances based on three attributes (product characteristics, vehicle capabilities, and logistics service provider's expertise) and, finally, the impact of technologies and its potential utilization to im-prove the decision-making process on integrated cold chain operations.

RESUMO
A cadeia de frio farmacêutica ou *pharmaceutical cold chain* (PCC) lida com requisitos operacionais de logística específicos, relacionados à qualidade, segurança e regulamentações do produto, o que torna complexo o processo de gerenciamento da cadeia de suprimentos. Além disso, o crescimento do mercado da indústria farmacêutica aumenta a conscientização, em termos de monitoramento e controle de temperatura de mercadorias, dos processos de armazenamento e transporte em toda a rede. Este estudo fornece uma nova abordagem para o PCC, com base em uma revisão sistemática da literatura e extensa análise dos principais aspectos que influenciam os processos da cadeia de suprimentos. As principais conclusões destacam o recente progresso da pesquisa mundial sobre os assuntos relacionados ao PCC, bem como os desafios envolvidos e seus avanços tecnológicos associados, com base em três atributos (características do produto, recursos do veículo e experiência do fornecedor de serviços de logística) e, finalmente, o impacto das tecnologias e seu potencial utilização para melhorar o processo de tomada de decisão em operações integradas da cadeia de frio

1. INTRODUCTION

There have been worrisome logistic problems in pharmaceutical product quality and safety in developing countries such as Brazil. While several public regulations are in place, they have failed to ensure an effective surveillance of the logistics distribution process. In this context, the implementation of efficient traceability systems may significantly reduce profit losses and shortcomings in the pharmaceutical cold chain (PCC).

In general, the supply chain requires systematic and strategic coordination of all activities related to the flow and transformation of inputs, finished goods, information, and financial resources. The PCC refers to a system in which perishable drugs that require low-temperature conditions are always collected in an environment with specific temperature ranges before they are delivered to consumers. The logistics of PCC meets the requirement of high-quality medical products and complies with a thorough temperature control system (Liu and Wang, 2010). To ensure a state-of-the-art logistics in the chain of temperature-sensitive products, it is crucial to consider the harmful effects generated by pathogens or physical agents that occur in an operational environment during each of the processes and cold chain phases.

An efficient temperature control is indispensable to guarantee the quality of the product and avoid economic burden. Considerable progress has been made in recent years in the improvement of surveillance devices, especially in the area of wireless systems (Raab *et al.,* 2011). Wireless Sensor Networks (WSN) integrated with radio frequency identification (RFID) have significantly improved the monitoring of the cold chain (Ruiz-Garcia and Lunadei, 2010). The integration between WSN and RFID is strongly related to the Internet of things (IoT) paradigm.

This study aims to identify the main challenges related to the PCC and its associated technological advances based on three attributes (product characteristics, vehicle capabilities, and logistics service provider's expertise), the progress of recent PCC research worldwide, highlighting the scientific approaches that have been currently used in PCC research, and evaluate the impact of technologies on integrated supply chains. The systematic literature review was used to analyze 124 relevant articles from prominent electronic databases. An extensive analysis of the main issues and challenges that influence the operation processes, on pharmaceutical goods cold chains. As a result, several issues were identified on the PCC structure, and it was pointed out how novel technological tools could be used to overcome them. Finally, a pharmaceutical cold chain literature classification was developed to aid academics and practitioners in stimulating the interest of other stakeholders in this research area.

2. METHODS

The first phase of this systematic review consisted of defining the target problem. The review structure was developed to address specific issues. To assess the evolution of the PCC over time, different geographical and scientific contexts were considered. In line with the objective of this study, the following research questions were addressed:

- Q1: What possible problems are found in the PCC logistic management (Product, Vehicle, and Logistic Operators)?
- Q2: What are the recent advances in PCC research worldwide?
- Q3: Which scientific approaches have been utilized in recent PCC research?
- Q4: What is the impact and added value of the traceability system technology within the PCC context?

Specific search strategies were created to address these questions, as shown in Table 1. The collected bibliography was studied in view of different logistic problems, geographical zones, and recent research methodologies applied to the pharmaceutical drug cold chain (conceptual study, literature review, case study, opinion survey/interview). The next steps consisted of screening and selecting eligible empirical studies in four different stages:

Table 1 – Selection of eligible studies for this systematic review

Step 1- Identification by keyword searching (search strategy)	Step 2- Selection, eligibility and characteristics of the study object	Step 3- Screening and selection of eligible studies	Step 4- Final selection
Identification of potential studies through database searching using primary keywords: pharma, medicine, drug, health, Internet of Things, RFID, traceability technologies.	Secondary keywords: supply, cold chain, pharmaceutical industry, drug distribution, wholesale, Blockchain, IoT, Big Data, Traceability, Analytical Process. Search Databases: EBSCOhost, Compendex, ScienceDirect, Emerald, Google Academic. Search space: Title OR Abstract OR Keywords. Journal type: Academic/scholarly Time filter: Published in the years 2010–2018.	Studies addressing exchange activities between two or more entities related to the management of pharmaceutical cold chain and the technology used. Studies that analyzed pharmaceutical / healthcare industries. Studies that focused on healthcare products other than drugs or medicines. Studies addressing issues in the technology evolution within the PCC.	A quantitative analysis (with and without meta-analysis) was carried out based on data extraction, coding, and recording, found in studies related addressing management issues in the PCC, pharmacy, Internet of things, Technologies and Concepts.

3. RESULTS

The collection of technological and empirical information should be exhaustive and include published studies to avoid selection and/or publication bias (Narayana *et al.,* 2014). The registry must include scales or pre-established criteria to define the validity of studies and filter them based on the authors' criteria. The quality assessment of studies included in systematic reviews is necessary to determine their risk of bias, provide a more accurate background for potential comparisons and guide the interpretation of the outcomes. In accordance with these guidelines, Table 1 describes the flowchart of this systematic review for selection of eligible studies.

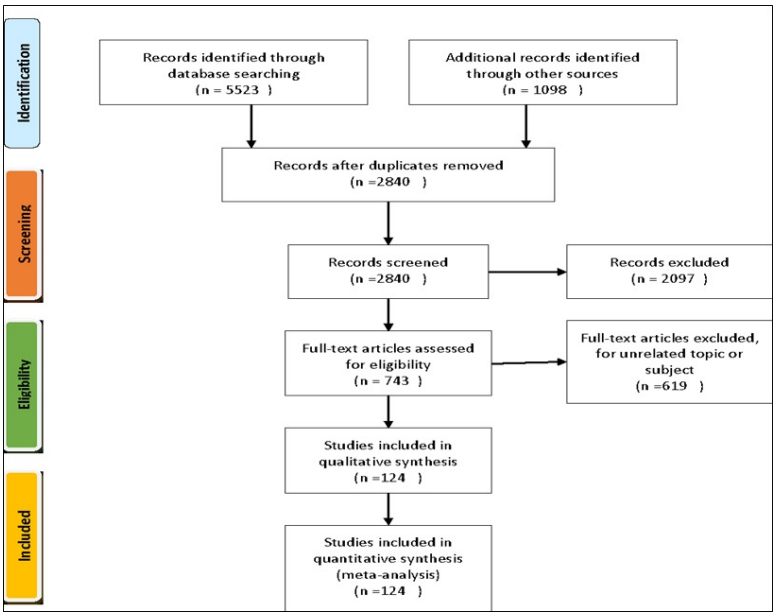

Figure 1. Flowchart of the systematic review in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines

A total of 5,523 titles were retrieved through database searching and 1,098 titles from the list of references in the selected articles. The studies were screened for eligibility based on title and abstract. A total of 2,097 studies that did not address the pharmaceutical drug cold chain were considered out of scope and hence excluded from the analysis. The studies addressing

technologies or application of concepts that could directly impact the logistics in the PCC as well as those determining the use of good practices to improve the quality along the chain using standardized methods were included for analysis. A total of 619 studies that did not meet these criteria were excluded, which led to a total of 124 selected studies (PRISMA flowchart is shown in Figure 1).

The research questions Q1 to Q3 addressed the main topic of study (PCC). Q1 investigates the possible issues found in the PCC in recent years; Q2 approaches the progress in the PCC in different regions worldwide; Q3 analyzes the scientific approaches that have been utilized in current PCC research; lastly, Q4 approaches the impact of traceability identification technologies on the PCC. This type of content analysis combines thematic and descriptive studies, for systematic reviews of the literature. Thus, this paper aims to discuss the cold chain of critical pharmaceutical drugs, focusing on the logistic problems and the use of technology applied to the chain.

3.1. Analysis of logistics in the pharmaceutical cold chain

The pharmaceutical drugs are produced in manufacturing facilities, transported to wholesalers, stored at retail outlets, distributed to pharmacists, and ultimately commercialized to end consumers. Nevertheless, several changes may occur in this straightforward structure as the chain evolves, and viable relationships differ markedly by product characteristics, distribution and logistics service delivery (Parmata, 2016). Therefore, the central dynamic forces of the pharmaceutical industry are distinctive, resulting in strategic and operational variations compared to the rest of the market. Hence, the quality of the service provided in the supply chain plays a significant role in terms of product performance, where effective service quality and transportation management should be considered by logistic operator to address potential issues (Yu *et al*., 2010; Heiskanen *et al.,* 2015).

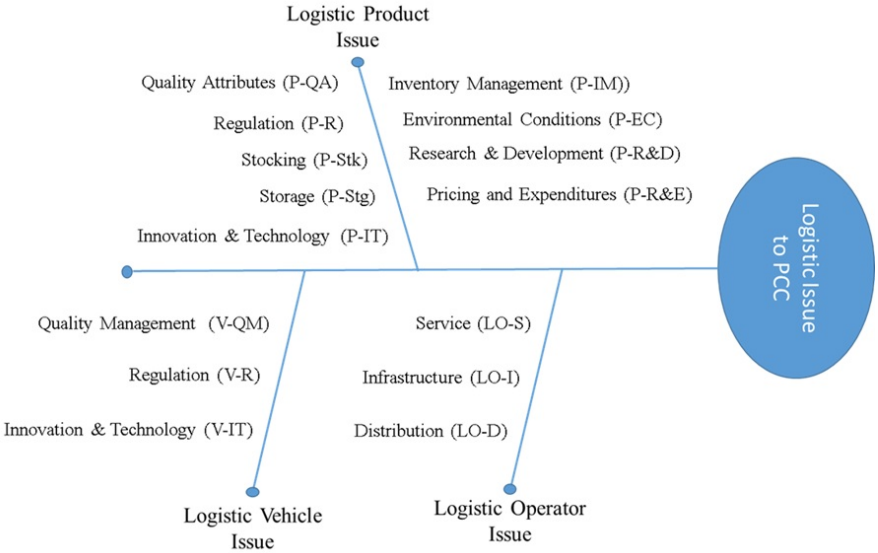

Figure 2. Logistic issues in the pharmaceutical cold chain reported in the selected studies (2010-2018)

Thus, the critical attributes were defined as those characteristics with high operational risk-controlled during the chain (Montoya *et al.* 2018). For the purpose of this review, three research attributes were determined, namely: Product, Vehicle and Logistic Operators. This section

presents the outcomes of Q1 and characterizes the chain of drug supplements. The main issues and sub-issues were grouped and disclosed along the lines in Figure 2 (please see also Table 2).

Table 2 – Logistic Vehicle, Logistics Operator and Product Issue in the PCC

	Sub – Issue PCC		Quantity									References
			1	2	3	4	5	6	7	8	9	
Logistic Vehicle Issue	Quality Management (V-QM)	Refrigeration Systems										(Rossetti *et al.*,2011; Liu *et al.*, 2010)
		Equipment										(Dallais *et al.*,2014; Lee, 2015; WHO, 2010; Oró *et al.*, 2012; Dubreuil *et al.*, 2011)
		Design / Performance										(Defraeye *et al.*,2015)(Liu *et al.*, 2012; Gin *et al.*, 2010)
	Innovation and Technology (V-IT)	Monitors										(Xutao *et al.*, 2010; Chen *et al.*, 2011; Luo *et al.*, 2016; Hribernik et *al.*, 2010; Moreno *et al.*, 2012) (Xiao *et al.*,2016)
	Regulation (P-R)	Government										(Yadav, 2015; Danielis et al., 2013; Yu et al., 2010)
Logistic Operator Issue	Infrastructure (LO-I)	Investment in infrastructure										(Höllein *et al.*, 2016)
		Risk Management										(Mehralian *et al.*, 2012; Jaberidoost *el al.*, 2013; Castillo Santaelena *et al.*, 2017) (Enyinda *et al.*, 2010; 14. Montoya *et al.*, 2018; Jaberidoost *et al.*, 2013)
	Service (LO-S)	Optimal Lead Times										(Ventola, 2011; Chowdary and George, 2013) (Mehralian *et al.*,2010)
		Operating performance										(Vesper *et al.*, 2010; Dadfar and Brege, 2012; IMSHealth, 2010)
		Flexibility and agility										(DE Vries, 2011)
	Distribution (LO-D)	Outsourcing										(Nagurney *et al.*, 2013; Tremblay, 2013)
		Direct Distribution										(Aguas *et al.*, 2016;. Kulkarni and Niranjan, 2013; Wang *et al.*, 2013)
		Indirect Distribution										(Kanavos *et al.*, 2011) (Kelle *et al.*, 2012; Susarla and Karimi, 2011; Baboli *et al.*, 2011; Masoumi *et al.*, 2012)
		Selective Distributive Channel										(Rossetti *et al.* 2011; McCabe *et al.*,2011)(Zimmerman, 2011)
			1	2	3	4	5	6	7	8	9	

Table 2 – Logistic Vehicle, Logistics Operator and Product Issue in the PCC (continuation)

	Sub – Issue PCC		Quantity 1	2	3	4	5	6	7	8	9	References
Logistic Product Issue	Quality Attributes (P-QA)	Active principles										(Woodcock and Wosinska, 2013; Kumru *et al.,* 2014)/ (Marucheck *et al*., 2011)
		Dosage										(Sam *et al.,* 2012)
		Form										(Norman *et al.*, 2017; 43. Allen and Anse, 2013; Arya, 2010)
		Type of Packing										(Shue, 2012) /(Abdellah *et al.* 2015; Chaudhari and Patil, 2012; Elder *et al*., 2016)/(Lawrence *et al.*, 2014)
		Shelf life										(Foroutan and Foroutan, 2014; Ringo *et al*, 2017)/(Chen and Shaw,2011)(Možina *et al*., 2010)/(Laínez *et al*. 2012; Liu and Wang, 2010)
	Environmental Conditions (P-EC)	Temperature										(Zhang *et al*., 2012; bate and Hess, 2010; Zipursky et al., 2014; Donno *et al.*, 2015)/(Oli *et al*., 2017)/(Kartoglu and Milstien, 2014; Kumar and Jha, 2017; Polygongroup, 2017)
		Humidity										(Ghaibi *et al.*, 2014; Duran, 2010; Chung and Peng, 2018)
		Lightness										(Duan, 2011) /(Jensen and Rappaport,2010 ; Caroline *et al.*, 2011)
	Environmental Conditions (P-EC)	Mechanical										(De Weerdt *et al.,* 2015)
		Ventilation										(Song *et al.*, 2014)
	Pricing and expenditures (P-P&E)	Pricing mechanisms										(Heiskanen *et al.*, 2015; Bertoldi *et al.,* 2012)
		Pricing and Availability										(Göllü, 2017 ; Goncharuk and Getman, 2014)
		Decision making for expenses										(Narayana *et al.*, 2012; Pharmerging, 2013)
		Pricing Affecting medical expenses										(Asamoah *et al*., 2012; Taylor, 2010)
	Stocking (P-Stk)	Road / Pallets										(Kheir, 2011; Sharif *et al*., 2010)/(Bauer, 2016)
		Cabinets										(Wandalkar *et al*., 2013)/(Rees, 2011)
			1	2	3	4	5	6	7	8	9	

Table 2 – Logistic Vehicle, Logistics Operator and Product Issue in the PCC (continuation)

	Sub – Issue PCC		Quantity 1	2	3	4	5	6	7	8	9	References
Logistic Product Issue	Innovation and Technology (P-IT)	Chemical Monitors										(Chavan *et al.*, 2014; Nelson *et al*., 2011; Vancea and Viman 2011; Bijwaard *et al*., 2011; Li and Achen, 2011)
		Electronic Monitors										(Çakici *et al.*, 2011; Chircu *et al.*, 2014; Metzner *et al*., 2014, Aung *et al.*, 2011; Hendrik Haan *et al.*, 2013 ; Minghetti *et al.*, 2014; Ruiz-Garcia and Lunadei, 2010; Li *et al.*, 2013,)
	Inventory Management (P-IM)	Alphabetical										(Thomas, 2011)
		Order										(Uthayakumar and Priyan, 2013)
	Inventory Management (P-IM)	Pharmaceutical Form										(Lee, 2015)
		Batch/ lot sizes										(Priyan and Uthayakumar, 2014)/(Agyekum, 2012)
		Cost										(Hatchett, 2017)
	Storage (P-Stg)	Scheduling & planning										(Koster, 2013; Shafaat *et al*., 2013; Wobker *et al*., 2010; Papert *et al*., 2016)
	Regulation (P-R)	Private Entity										(HPRA, 2017; El Shinnawy, 2012)/(Kaufmann 2011; Sangshetti *et al.*, 2017)
	Research & Development (P-R&D)											(Minghetti et al.,2014, Smith *et al*., 2011; Singh et al., 2016)/ (Paul *et al.*, 2010)

Data Analyses
CC Models (with Temperature)
Quality of Novel Technologies
Integration of Informatics Systems
Traceability Technologies
SC Models (without Temperature)
Analytical Technologic Process

Although the analysis of the sub-issues is beyond the scope of this review, some exciting insights into the main logistic issues of the PCC can be obtained from Figure 2. A great deal of academic work involves understanding and suggesting solutions to issue of the PCC (Table 2), classified into 7 categories (Technological resources and PCC concepts), represented by different colors, which are: data analyses, cold chain models (with temperature), quality of novel technologies, integration of informatics systems, traceability technologies, supply chain models (without temperature) and analytical technologic process. These categories will be further described in the section 3.3.

There was a higher number of selected studies published in 2011 (Figure 3), which can be explained by advances in the pharmaceutical industry focused on the application of novel PCC technologies. While changes in the economic and political settings might also have driven the development of the pharmaceutical industry, there seemed to be no real interest of academia to apply their findings specifically to the PCC and its associated issues.

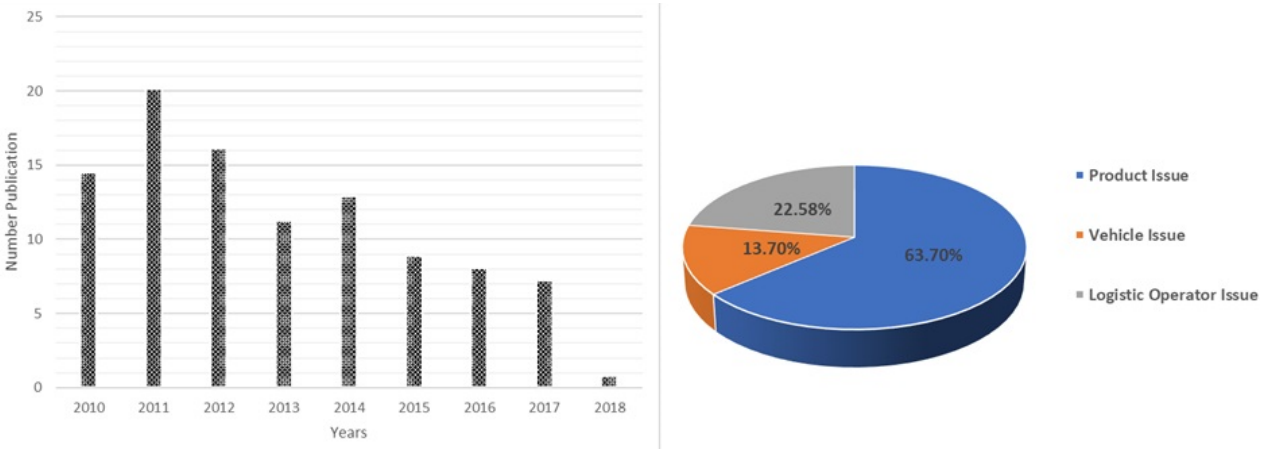

Figure 3. Distribution of published articles on PCC logistic issues by year (2010-2018) and study object

This brings attention to the importance of performing a more in-depth study of the cold chain in the pharmaceutical industry based on new private and governmental regulations, through which new scientific bases could be established and drive further growth in the field. In total, 63.71% of the published studies addressed PCC product issues, whereas 13.71% corresponded to vehicle-related issues and 22.58% to Logistics Operator issues. As seen in Table 3, showed the percentage of studies per year by type of PCC issue. It can be seen that there is a gradual increase in the number of studies concentrated on, P-EC (20%), P-QA (19%), and P-IT (18%) were predominantly related to PCC product issues, whereas V-QM (53%) and LO-D (46%) studies were more related to vehicle and logistics operator issues, respectively. Perhaps, this increased amount of field research has helped the growth of studies using technologies tools and concepts base in data analysis. It also seems that research on logistics operators regarding product distribution has improved the PCC.

Table 3 – Percentage of studies per year by type of PCC issue

Issue to PCC	Sub – Issue PCC	% Total Sub	%Total
Logistic Product Issue to PCC	Environmental Conditions	20%	63.70%
	Quality Attributes	19%	
	Innovation and Technology	18%	
	Pricing and expenditures	11%	
	Regulation	9%	
	Stocking	8%	
	Inventory Management	6%	
	Storage	5%	
	Research & Development	4%	
Logistic Operator Issue to PCC	Distribution	46%	22.60%
	Infrastructure	29%	
	Service	25%	
Logistic Vehicle Issue to PCC	Quality Management	53%	13.70%

The studies have been focused mostly on the value attributes of the product, vehicle and logistics operator, corporate and technological growth strategies, as well as other future issues of strategic and logistical interest, with just a few studies published in recent years (Figure 4). Studies on pricing and expenditures and practice strategies by private or governmental organizations, such as mergers and acquisitions, have accelerated in recent years, indicating new directions for research.

Recently, the management of the PCC has become more complicated because it involves potential interests, human welfare and requires the participation of different stakeholders, such as pharmaceutical manufacturers, wholesalers, distributors, customers, information service providers, and regulatory agencies (Singh *et al*., 2016). The Biopharma Cold Chain Sourcebook of Pharmaceutical Commerce shows that the management of temperature-controlled products reached USD 14.4 billion worldwide in 2018, with a continuous growth rate of 8-9% per year, which is approximately double than that of pharmaceuticals in general (Figure 4). The report by Pharmaceutical commerce (2016), now in its seventh edition, sets logistics costs for non-cold chain pharmacies at USD 78.8 billion, with an increase in growth rate by 4-5% in pharmaceutical volumes. By 2020, the expenditure on PCC logistics is estimated to reach USD 16.7 billion.

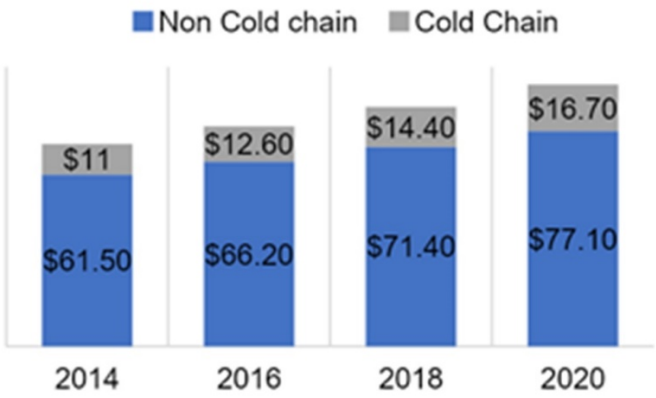

Figure 4. Expenditure in USD on cold-chain and non-cold chain logistics by 2020. Source: Pharmaceutical commerce.

3.2. Logistic issues in the PCC by geographic location and research methodologies

In this section, the selected studies were analyzed based on geographical distribution and scientific research methodologies, as surveyed in Q2. The American and European markets have developed in terms of regulation, financing and provision mechanisms managed by the pharmaceutical industry (Narayana *et al.,* 2012). These blocks account for 81% of the global market of pharmaceutical products (IMSHealth, 2010; MarketLine, 2018a) and are therefore the main drivers of business both in the industry and academia. Figure 5 shows that approximately 76% of the studies selected in this review were carried out in America and Europe, which might have contributed significantly to the peak in the number of studies published in 2011.

The remaining selected studies focused mostly on the Asian market (MarketLine, 2018b). Japan, China and India have dominated the pharmaceutical market in Asia, with pharmaceutical drug distribution higher in China and India, although there is no efficient governmental regulation and there is criticism on development efforts being predominantly made towards Western markets (Rao, 2008).

Historically, some African countries have had poor economic and health development, which continues to be the case today (WHO, 2009). Consistent with this, Figure 5 shows that there are very few studies on PCC logistics in Africa (MarketLine, 2018a). The volume of transcontinental research was also low and reflects the inequality in research efforts among all regions.

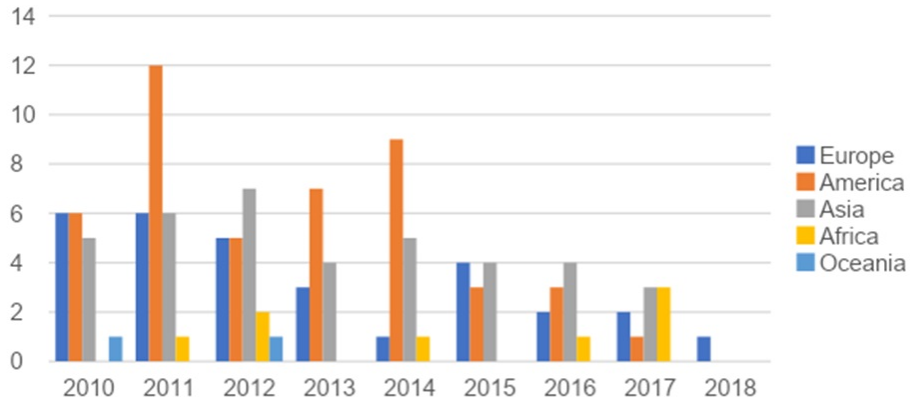

Figure 5. Geographical distribution of selected studies on PCC logistics (2010-2018)

The US market has focused predominantly on behavioral studies at the consumer / medical level while Europe has focused more on the entity's behavior and relationships in the industry through the study of organizational behavior, supply chain issues, and management of operations at the corporate level. This has contributed to the development of high-cost products and marketing activities. Africa and Oceania have focused on issues related to the operational environment and the quality of transport inside refrigerated vehicles, with just a few studies reporting issues in this sector.

Figures 6 and 7 show the main research methodologies utilized in the selected studies, as surveyed in Q3. There was a gradual increase in the number of field studies, with real case studies accounting for approximately 83% of the articles in all the continents. Conceptual studies, literary reviews, and others, such as patent documents, government documents, and the company's research, were also analyzed.

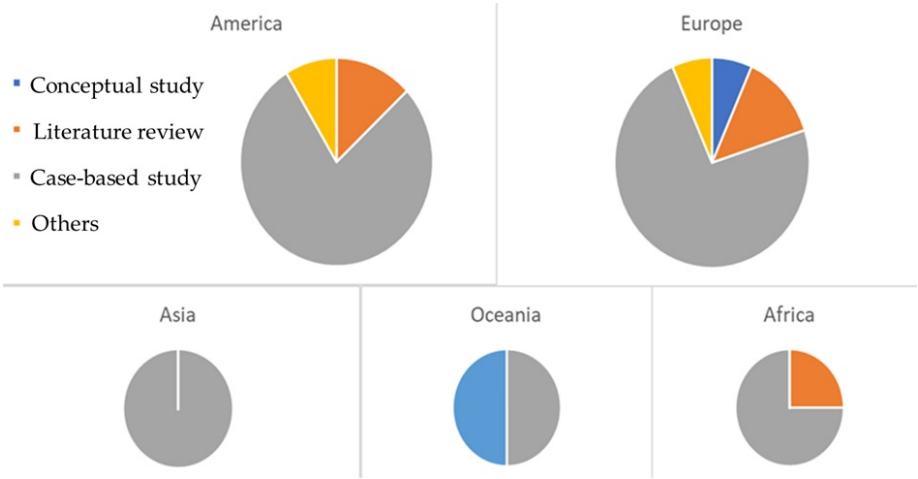

Figure 6. Research methodologies utilized in the selected studies by geographic location

The studies carried out in America, Europe, and Asia showed greater depth and dissemination through a review of several subtopics, as compared to the other areas. The presence of different pricing and political systems in these regions was reflected in the studies. The greater focus on PCC logistics and operations management in manufacturing and services in the European industry indicates that studies in this region have focused more on manufacturing processes and product delivery. The studies carried out in America addressed mainly topics such as information technology, operational environment, attributes of product quality and distribution analysis, and pharmaceutical drug storage and transport.

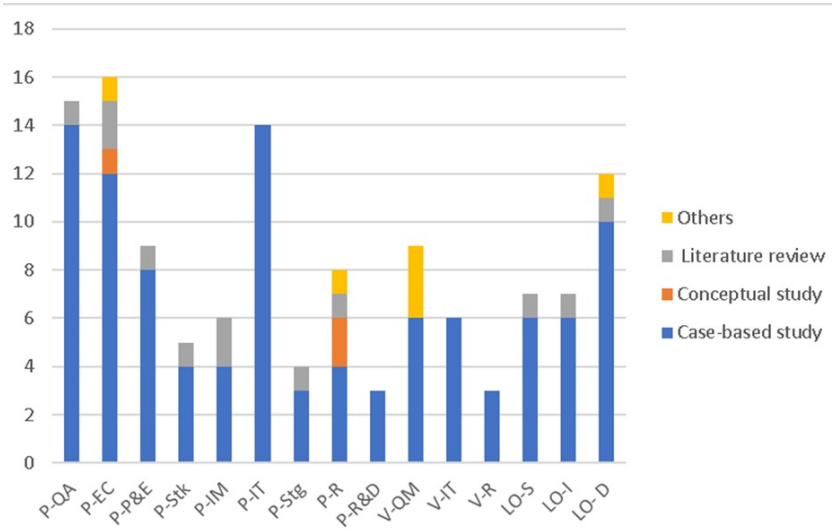

Figure 7. Research methodologies utilized in the selected studies on PCC logistic issues

In any field of knowledge, research development begins with an exploratory analysis (interviews or surveys), followed by case-based studies or theorical and mathematical modeling (which are not discussed herein). Moreover, literature reviews may assist in the analysis of research advances in the field. Throughout the period 2010-2018, there was a gradual increase in the number of literature reviews and conceptual studies, which suggests that research in the field is consolidating and may overcome existing gaps soon.

3.3. Technological resources and PCC concepts

The technological resources and concepts in PCC research are shown in a radar chart (Figure 8), based on the responses obtained in Q4. This type of chart was used for viewing of multivariate data in two quantitative dimensions at the same point on both axes.

As shown in Figure 8, most selected studies focused on CC models (43%). The topics Data Analyses, SC models and Analytical Technological Process were addressed in 21%, 17%, and 14% of the selected studies, respectively. The convergence and increasing integration of specific technologies into a system may support the implementation of traceability technologies, which was addressed in 25% of the studies. In addition, the incorporation and interaction of novel information technologies can enable the analysis of the outcomes in terms of the production process in the pharmaceutical industry. Hence, the transmission and total integration (data analysis/ traceability technologies) tend to be a differential and competitive advantage in the logistics operations of the chain.

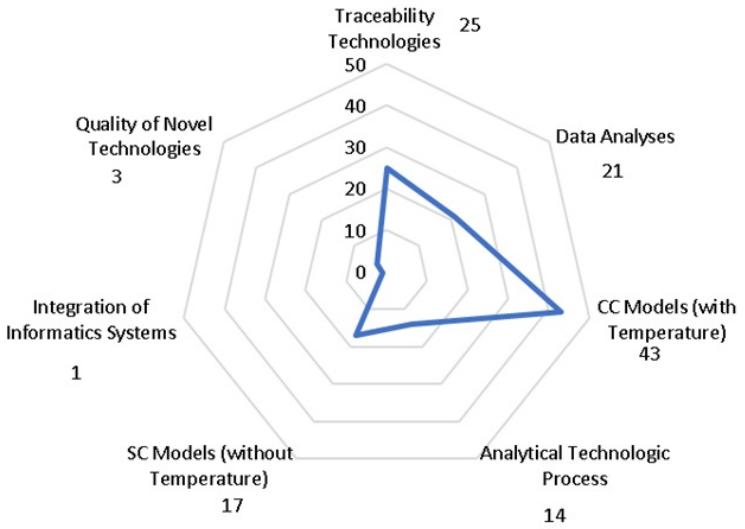

Figure 8. Distribution of selected studies by type of technology and concept

There has been inconsistency in the terminology use for logistic activities, as most definitions have attempted to address the system's ability to track down the product throughout the supply chain (Bosona and Gebresenbet, 2013). Traceability improvement requires that the partners in the supply chain have effective, interconnected information among their systems (Bosona and Gebresenbet, 2013). Within the supply chain, traceability is also highly dependent on the collaboration and coordination of logistics processes and information shared among the stakeholders. Safety and quality aspects can be considered major drivers of traceability systems. It is generally accepted that traceability initiatives behind pharmaceutical products are mainly connected to assure product quality and safety rather than logistics improvement issues. New legislation which has been introduced to address safety and quality concerns is an essential, but not enough, traceability determinant.

The ability to track down and intercommunicate products will significantly increase in the forthcoming years. For instance, the IoT concept is based on the interconnection of different products with the objective of gathering, analyzing and distributing data that can be transformed into real-time information, which is useful for companies to create a competitive advantage within the global market. As previously stated IoT can equip healthcare systems with interconnected devices to obtain a complete panel of the patient's health parameters, although other technological resources or concepts are also involved in the chain.

Accordingly, IoT system applications allow companies to not only maintain the necessary inventory when they need it, but to do the same for customers, by integrating them into the supply chain. IoT applications that span the entire product ecosystem will gather valuable customer information, which can potentially lead to innovative business models, converting supply chain information into a service that companies can sell, create value upon and generate additional revenue. RFID tags are expected to contain more details on a given product and send relevant information (temperature, weather, object damage, traffic conditions etc) to an inventory system.

Another application of traceability system concerns the use of GPS integrated into each product, with a unique identifier. This may also assist in the identification of every single component or equipment the organization needs, which could reduce the amount of lost or stolen goods,

improve the management of stock shortages and overstocks and identify inefficiencies more accurately.

By using information sensors to monitor equipment components, technicians can develop predictive self-learning and diagnostic performance models. Sensors will collect and analyze data on shipping movements from warehouses, distribution and production planning centers, thereby contributing to inventory optimization and efficient customer delivery.

4. CONCLUSIONS

The pharmaceutical industry has revolutionized the development and delivery of medical supplies to the population, which is critical to the success of healthcare initiatives. Therefore, the management of issues in the pharmaceutical cold chain is of interest for both pharmaceutical industry and academia. This systematic review attempted to shed light on the main challenges involving the PCC and its associated technological advances in recent years (2010-2018).

The analysis of PCC logistics described herein provided a broad perspective on the subject. Based on the responses to Q1, different issues can affect the quality of refrigerated pharmaceutical drugs, resulting in irreparable losses in any part of the chain. Three issues attributes were considered in this review: product, vehicle, and logistics operators. The management and resolution of these issues and their corresponding sub-issues may improve product quality, administrative processes, knowledge acquisition, regulation, infrastructure, and the application of new technologies. The studies selected in this review point to an interest of academia regarding the critical role of government requirements during the pharmaceutical process, since depending on the characteristics of each drug, variations in temperature and storage length are permitted without affecting its physical and chemical properties – this is an example where it is useful to know the time length a given drug can be store at room temperature. Nevertheless, it remains imperative to keep good practice measures for conservation of pharmaceutical drugs from the moment they are manufactured until their administration to the patient.

The latest advances in PCC research worldwide suggest that case studies, literature reviews, and mathematical or statistical modeling (not specified herein) can contribute to greater conceptual clarity and technological development, especially in America and Europe. Based on the responses to Q2, there has been an increase in scientific development and manufacturing activities in Asia at the company and supply chain levels under a clinical practice-oriented perspective. Other matters of strategic interest were observed in field studies, conceptual studies and literature reviews carried out in Africa and Oceania. These studies showed an evolution in the management of logistics operators in the pharmaceutical industry towards a more balanced and comprehensive approach.

Based on the responses to Q3, while the large amount of studies carried out in Europe, America and Asia indicates a consolidated and increasing research interest in the pharmaceutical industry, there are many gaps to be yet explored in the field of the cold chain. The increasing interest in critical PCC issues suggests that research efforts have contributed to the development of new technologies that would revolutionize logistics in the pharmaceutical industry. The manufacturing industries and logistics operators must integrate data from multiple sources and automate data collection and analysis to effectively obtain practical information to minimize costs, risks and increase product quality.

Lastly, the responses to Q4 indicate that different technologies and concepts can help pharmaceutical manufacturers remotely monitoring cold chain environments in real time by

integrating sensors into tracking devices with automatic start and stop mechanisms in warehouses, vehicles or shipments, using smartphones or tablets. The temperature or other environmental aspects during any stage of the distribution chain usually results in loss of quality, which significantly decreases the lifespan of the pharmaceutical drug, particularly in case of a prolonged temperature exposure vs. storage length. Consequently, since temperature determines to a large extent the rate of microbial activity, it is the leading cause of product deterioration. A continuous real-time monitoring of temperature conditions to which the pharmaceutical drug is exposed would allow better management of temperature conditions and assist in the creation of a logbook of temperature history in the cold chain.

Furthermore, cold chain models based on empirical research have shown the potential of conceptual and traceability technologies in contextual processes for better decision-making. IoT can be considered a promising resource in the context of PCC to resolve existing issues. The findings presented herein may guide future work by indicating towards where more substantial efforts should be invested in the logistics chain.

Current challenges in the refrigerated transport sector in Latin America, highlight the need for efficient logistical support and temperature maintenance throughout the logistics chain. Among the international strategies to overcome these issues and increase system efficiency is the active control of refrigeration conditions and temperature stability via traceability systems, with the incorporation of new technologies, for example, IoT or blockchain. Other strategies include incentives and the creation of new regulation by the government or non-profit institutions together with companies for pharmaceutical and health industry solutions across the globe.

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