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Recommendations to Improve the Cold Chain Management in a Case Company

Helsinki Metropolia University of Applied Sciences

Master's Degree

Industrial Management

Master's Thesis

29 April 2021

Metropolia

The past year filled with studying and working in the middle of the global pandemic has been exceptional in many ways. Despite of the challenging situation and the tight schedule, studying in the Industrial Management programme has been rewarding and pleasant. Even if I am a little bit relieved that this thesis is now completed, part of me would like to continue learning new things.

I would like to take this opportunity to warmly thank my thesis advisor Dr Thomas Rohweder for the guidance with this study. I also want to thank M.A. Sonja Holappa for providing very beneficial advice with the professional language. I thank Industrial Management programme lecturers Dr Juha Haimala and Dr James Collins for instructive lessons providing support for this thesis.

I thank the case company for the interesting subject for my thesis. I am especially grateful to Sini for supporting the thesis and providing me the opportunity to develop my professional skills.

There has been a large group of subject matter experts in the case company working closely with this topic, participating in the workshops and providing their professional expertise to support the work. This study would not have been possible without their involvement. Thank you Aki, Jaakko, Juho, Lotta, Riikka, Rina and Vesa.

The support from my family had a significant impact on my ability to complete this thesis. I would like to express my sincere thanks to Hannu. I appreciate your way to support and encourage me no matter what I intend to pursue. Last but not least I want to thank Niklas for just being there and teaching me the Pomodoro Technique “to eat the elephant”.

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Vantaa
April 29, 2021

Author	Anne Rahola
Title	Recommendations to Improve the Cold Chain Management in a Case Company
Number of Pages	58 pages
Date	29 April 2021
Degree	Master of Engineering
Degree Programme	Industrial Management
Instructors	Dr. Thomas Rohweder, Principal Lecturer Sonja Holappa, M.A, Senior Lecturer

The objective of this thesis was to propose actions to improve the outbound cold chain management of the temperature sensitive IVD reagent products in the case company. The products manufactured in the case company's factory are distributed worldwide. Controlling all steps and procedures in the supply chain on a sufficient level can be challenging and improvement opportunities have been recognised in the current process.

The research approach is design research applying qualitative methods. This study included four stages. At first the current order to delivery process was analysed from cold chain perspective together with the subject matter experts. As a result, the strengths and weaknesses of the current process were identified. In the second phase the existing literature was reviewed in order to find best practices and solutions to tackle the identified weaknesses. The conceptual framework of the thesis was created based on the improvement ideas gathered from the literature. The initial recommendations for improvement of the current process were co-created with the applicable key stakeholders in the third phase. In the fourth phase feedback for the initial proposal was requested from the selected managerial level decision makers and the final proposal was formed based on their comments.

As an outcome of this thesis the improvement recommendations for the case company's cold chain management process are proposed. The implementation of the final proposal provides the opportunity to develop the current process and have better control of transportation.

This study provides practical solutions for the case company to improve the current cold chain management procedures. Controlling the cold chain of the critical products ensures the product quality is maintained also during transportation. It prevents temperature excursions and decreases the risk of the financial loss for the manufacturer. Maintaining the cold chain provides protection to the patient.

Keywords	Cold chain, IVD product, transportation, temperature monitoring, shipment, cool container

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Contents

Acronyms

cGMP	Current Good Manufacturing Practices
CFR	Code of Federal Regulations
CLSI	Clinical and Laboratory Standards Institute
CSA	Current State Analysis
ERP	Enterprise Resource Planning
FDA	Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
IoT	Internet of Things
IQ	Installation Qualification
ISO	International Organization for Standardization
ISPE	International Society of Pharmaceutical Engineering
ISTA	International Safe Transit Association
IVD	In Vitro Diagnostic
OQ	Operational Qualification
PCM	Phase Change Material
PQ	Performance Qualification
QA	Quality Assurance
RCR	Responsible Conduct of Research
RFID	Radio Frequency Identification
SOP	Standard Operating Procedure
WHO	World Health Organization
WI	Work Instruction

1 Introduction

In vitro diagnostic products are used to test and analyze patient samples such as blood or tissue taken from the human body. The purpose of the testing is to detect diseases or monitor a person's overall health to help cure, treat or prevent diseases.

Such products can be temperature sensitive and may require continuous cold storage. Cold chain management of temperature sensitive in vitro diagnostic medical device products is a crucial part of the product life cycle management. Correct environmental conditions of critical products have impact on product quality and enable to ensure optimal shelf life. Suitable packing, storing and shipping prevent damage to end user and financial losses for manufacture.

Controlling all steps and procedures of world-wide supply chain on a sufficient level can be challenging. Complexity of environments in different phases of distribution channel and possible delays during shipment complicate the control of correct conditions all the way to the final destination. Maintaining the cold chain during distribution requires good understanding of product stability, mode of transportation, ambient temperatures during transportation, performance of packing solution and time needed to reach destination. Sufficient control means that the chain is traceable and possible deviations are assessed. Efforts should focus on ensuring that activities add value, are cost-effective and based on robust science and they undergo appropriate risk assessment. Ensuring continuously the correct environmental conditions for critical products provide protection to the patient. (ISPE, 2011)

1.1 Business Context

The case company in this study is an international company developing, manufacturing and selling a wide range of products for research, life sciences, laboratory services and industrial purposes. This thesis focuses on distribution of temperature sensitive in vitro diagnostic reagent products used in health care sector. Products in the scope of this thesis are manufactured at the case company's factory and distributed to several countries all over the world.

The operation of medical device manufacturers is regulated by region and country specific legislations. International regulations concerning in vitro diagnostic medical device products – for example IVD Directive 98/79/EC in EU and FDA Quality System Regulation 21 CFR Part 820 in USA - apply to the case company's business. Additionally, the case company has committed to following ISO 13485 standard describing Quality Management System requirements for Medical Devices.

1.2 Business Challenge, Objective and Outcome

Temperature sensitive IVD products manufactured in the case company's factory are distributed worldwide. The business challenge is to control and assure correct temperature conditions of sensitive IVD products during transportation within all used transportation methods and routes. International shipments include risks since products are not under manufacturer's control during transportation. Manufacturer has to rely on logistics companies and other third parties whose primary focus may not be in the requirements set for diagnostic products.

Currently all procedures and processes may not be fully compliant with all regulatory requirements concerning this business. Therefore, the objective of this thesis is to determine actions to improve the existing outbound cold chain management process of the case company's IVD reagent products. As an outcome of this thesis, an improvement proposal for outbound cold chain management process is created. The improvements help the case company to increase awareness of conditions during transportation, prevent temperature excursions and to ensure high quality products are received by the customer.

1.3 Thesis Outline

This thesis includes seven sections. The first section defines the business challenge, the objective of the study and the planned outcome of the thesis. The second section describes the research approach and design and defines the data used to carry out the study.

The third section is the current state analysis where the current cold chain management procedures in the case company is carefully reviewed and assessed. Based on the results of the analysis the strengths and weaknesses of the current process are defined.

In the fourth section best practices and ways to tackle the weaknesses identified in the current state analysis are searched from the existing literature. The most important and relevant solutions are discussed. At the end of the section four the conceptual framework for the study is created and visualized.

In the fifth section the initial proposal to manage the business challenge is co-created with the applicable key stakeholders in the case company. Recommendations to improve the current process are described and prioritized. The feedback to the initial proposal is collected in the sixth section and the final proposal to improve the case company's cold chain management process is created.

The section 7 draws conclusions and includes the self-evaluation of the study. It includes also recommendations for implementing the suggested improvements into the business process.

2 Project Plan

The previous section described the business challenge behind this thesis as well as the objective and outcome of this work. This section describes the research approach, data collection and analysis methods used in this study. It includes a research design which shows the different stages and the logic of this study.

2.1 Research Approach

Choosing the appropriate research methodology for the problem chosen is vital for successful research. It is necessary to consider the intention and the type of the study in order to find the methods which best enable to meet the set objectives.

Saunders et al. (2016) provide guidance to graduate students of business and management to design a research project and to choose the best strategy and method for a study. Two approaches are described – fundamental and applied research.

The purpose of fundamental research is to expand knowledge of processes of business and management and typically it results in universal principles relating to the process and its relationships to outcomes. The research aims at developing a new or improved theory and findings of this type of research add value to society on a general level. Commonly the research is undertaken by people based on universities, the researcher chooses the topic and defines the objectives and time scale for the research is flexible.

The target in applied research is to improve a particular business or management problem and the research aims to provide a solution to that problem. The new knowledge gained by the research is limited to the specific problem and the findings have practical relevance to certain manager(s) in the organization(s). Applied research is typically undertaken by people based on a variety of settings including organizations and universities. Typically, the objectives of research are negotiated with the originator and the project has a tight timescale.

According to Kananen (2013 p.20) design research produces practical and functional solutions and is conducted in organization in order to improve operations. It combines

development and research by using proper documentation and scientific methods to produce practical solutions to defined business problems.

The nature of this thesis suits applied research more than fundamental research. The research approach in this thesis was chosen to be design research applying qualitative methods. That was considered to be the appropriate approach since the thesis aims to solve a specific business challenge and to improve the case company's outbound cold chain management by recommending improvements. The purpose of the thesis is to develop the specific business case and provide practical solutions to improve the case company's operations.

2.2 Research Design

This study includes four phases which form a process aiming to provide improvement suggestions for the business challenge. Figure 1 illustrates the research design for this study.

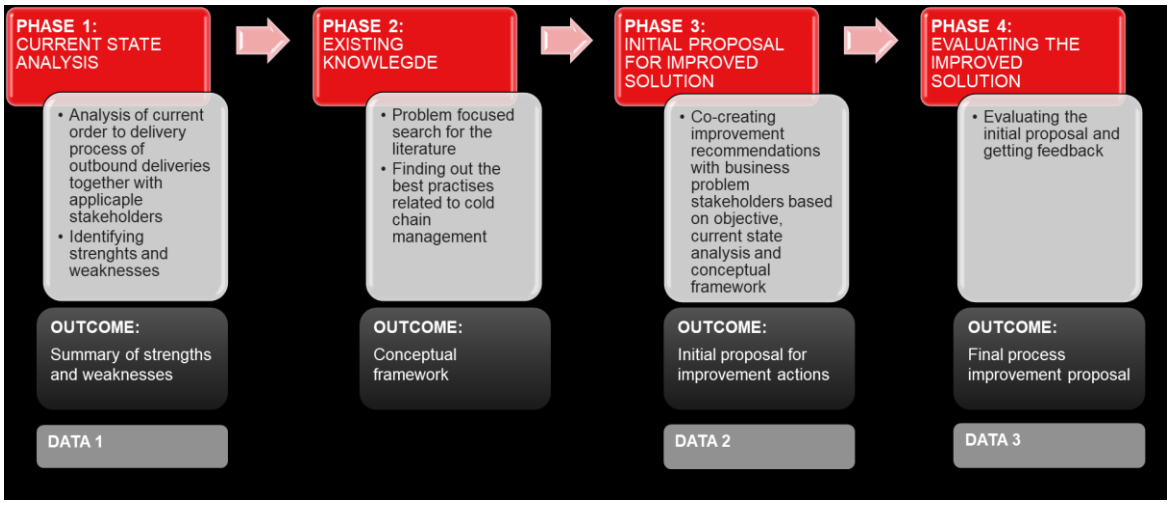

Figure 1. Research design of the study.

The first phase was the current state analysis. In order to suggest improvements to cold chain management it is crucial to have deep understanding of the current process and its strengths and weaknesses. The analysis was conducted by reviewing the current quality management system documents, collecting data from the Case Company's ERP system and having workshops and discussing with relevant stakeholders. The results of

the current state analysis were documented, and the identified strengths and weaknesses of the current process were summarized.

The second phase of the study was the literature review. After the identification of the current process weaknesses the best available practices and solutions to tackle the challenges were researched by reviewing academic literature. The literature search was strongly focused on the identified weaknesses and their possible solutions. Based on the literature search the conceptual framework was created.

The purpose of the third phase was to co-create a solution for an improved process based on the objective, current state analysis and conceptual framework with key stakeholders. As an outcome of this phase the initial proposal for the improved outbound process was suggested.

The fourth phase was collecting feedback for the improved solution. Initial recommendations created in the third phase were presented to two selected managerial decision makers. Based on the comments received in those discussion the final proposal for the partially improved outbound process was created.

2.3 Data Collection

This study draws on a variety of data sources collected in three different rounds (phases 1, 3 and 4 in Figure 1). The methods to collect data for this study included reviewing current quality management system documents, arranging workshops with relevant stakeholders and collecting data from the Case Company's ERP system.

Table 1 shows an overview of data collection during the first round (Data 1) which was the current state analysis. Workshops were arranged with applicable stakeholders and the current process was discussed. Internal documentation related to the current process was reviewed and data from the case company's ERP system was extracted. Table 2 lists the case company's internal quality system documents reviewed during the current state analysis. The review provided deeper understanding of the current process and enabled comparing the real working described in the workshops and the desired state described in the quality system.

Table 1. Data 1 collection for Current State Analysis.

DATA 1					
#	**Source**	**Data type**	**Topic, description**	**Date**	**Documented as**
1	Participants from • Logistics • Customer Service • Quality • R&D	Workshop	Review of current process	5.10.2020	Field notes
2	Participants from • Logistics • Customer Service • Quality	Workshop	Review of current process	18.11.2020 19.11.2020 24.11.2020	Field notes
3	Existing data of current process	Review	Review of Quality System documents related to current process	16.- 20.11.2020	Field notes
4	The Case Company's ERP system	Deliveries	Data of recent deliveries	15.10.2020	Excel sheet
5	Participants from • Logistics • Customer Service • Warehouse • Quality	Workshop	Risk analysis for current process	28.1.2021 25.1.2021 26.1.2021 11.2.2021	Process risk analysis

Table 2. Internal quality system documents reviewed during current state analysis.

#	Content of the document	Number of pages	Description
1	Order-Delivery Process	13 pages	Process description
2	Order handling	34 pages	Working instruction
3	Transaction Screening Procedure	8 pages	Working instruction
4	Handling of temperature sensitive products in dispatch	9 pages	Working instruction
5	Shipping and Storing Temperatures for Diagnostic products	6 pages	List of products and features
6	Cold chain related validation documentation	Several documents	Validations and qualifications related to cold chain critical facilities, equipment and systems

In the second round, Data 2 was collected to gather suggestions from the Case Company for developing the proposal. This data included workshops with applicable stakeholders. Table 3 shows the important variables of Data 2.

Table 3. Data 2 for proposal building.

DATA 2				
#	**Source**	**Data type**	**Topic, description**	**Date**
1	Workshop	Proposal building, documented as field notes	Review of risk analysis and recommended actions	8.3.2021
2	Workshop	Proposal building, documented as field notes	Weaknesses identified in CSA, results of risk analysis, identified best practices and possible solutions	12.3.2021
3	Workshop	Proposal building, documented as field notes	Review and discussion of agreed proposals, final adjustments	26.3.2021

The final data (Data 3) was collected when receiving feedback for the proposal from two selected managerial decision makers. In the third round the discussions with representatives made the primary method of data collection. The discussions were conducted as semi-structured, face-to-face interviews held remotely on Teams. The interviews were recorded as field notes. Table 4 shows the data gathered in this round.

Table 4. Data for the evaluation of initial proposal.

DATA 3				
#	**Source**	**Data type**	**Topic, description**	**Date**
1	Interview: Respondent A	Feedback documented as field notes	Evaluation of initial proposal	1.4.2021
2	Interview: Respondent B	Feedback documented as field notes	Evaluation of initial proposal	1.4.2021

The next section explains in detail how the Data 1 stage described above was carried out for the current state analysis and what the analysis revealed regarding the order-to-delivery process of diagnostic products requiring cold storage.

3 Current State Analysis

The previous section described the research design and approach as well as data collection practices used in this study. This section describes how the current state analysis (CSA) was conducted and what is the current state of the case company's order to delivery process for diagnostic products requiring cold storage. Finally, the strengths and weaknesses of the current process revealed based on the analysis are summarized.

3.1 Overview of the Current State Analysis

The purpose of the current state analysis was to gain deep understanding of the case company's order to delivery process related to diagnostic products requiring cold storage. The focus was on cold chain management and items affecting the correct conditions of the products. The CSA covers all customers and all routes used to deliver diagnostic products from the case company's factory to the first destination which can be a distributor or a final customer.

The workshops were arranged with key stakeholders and all the steps of the process were systematically discussed. The current quality system documents were reviewed in order to investigate how the process is described and how current instructions support work. That also enabled comparing the real execution of work with the planned desired state described in the documentation. The current cold chain related validation documentation was reviewed. Diagnostic products and their features were also reviewed in order to understand how the products differ from each other. The data from the current ERP system was collected in order to understand the amount of deliveries, the most common routes and locations of final destinations. Failure Mode and Effects Analysis (FMEA) was conducted for current process in order to identify and evaluate the process performance. Based on the analysis the strengths and weaknesses of the current process were identified.

3.2 Description and Analysis of the Current Process

The process starts when the customer sends an order. Customer Service handles the order and after that the products are picked and tentatively packed in the warehouse.

After packing the products, the shipment is arranged. Packing is finalized in the warehouse just before the delivery leaves the factory. The carrier takes care of the transportation and the process ends to the point where the customer receives the ordered products. The overview of this process is shown in Figure 2.

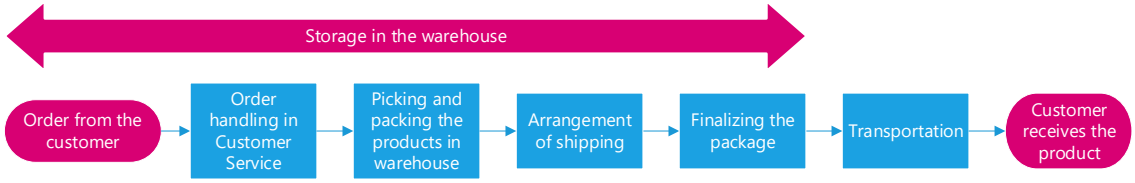

Figure 2. General overview of the order-to-delivery process.

3.2.1 Order Handling in Customer Service

Customer Service handles the order received from a customer and creates a sales order to the ERP system. After that the order confirmation is sent to the customer. That work does not have any impact on the cold chain of diagnostic products. The order completed by customer service triggers a delivery in the ERP system and that is automatically sent to the warehouse.

3.2.2 Storage of Diagnostic Products in the Warehouse

Diagnostic products waiting for the final QA release are stored in a separate cold room outside the warehouse. That is the way to ensure that the products are always pre-cooled before they can be picked and packed for the delivery. The diagnostic products released for sale are stored in the warehouse cold room. It is crucial for product quality to ensure the correct temperature during storage.

Critical facilities related to the cold chain of diagnostic products are validated and continuously monitored with the validated monitoring system which sends an alarm to nominated persons if the temperature exceeds or falls below predefined limits. Fixed sensors are placed to cold chain critical facilities based on temperature distribution studies. There are regular maintenance practices in place for critical equipment affecting cold storage.

Based on the analysis it can be stated that the variables affecting correct product storage in the case company's warehouse are well controlled.

3.2.3 Shipping Stability Studies

Based on the shipping stability studies, certain products are defined in the master data to be so called cool products which are packed to the specific cool containers. There are different containers of different size and the number of products guides which container is chosen. The shipping solutions used for the cool products are single-use containers without return logistics. Other products not defined as cool products are shipped in ambient conditions. Table 5 shows the different product categories based on shipping stability studies. Certain products are allowed to be transported in high temperature (+35…+37 °C) for 3—7 days and certain products can stand temporal freezing during transportation.

Table 5. Categorization of Diagnostic Products requiring cold storage based on shipping stability studies. Letter Y in the table stands for "yes" and letter N stands for "no".

Product Category	Accepted abnormal shipping conditions +35…+37 °C for 3-7 days	Product must be protected from freezing
A	Y	Y
B	Y	N
C	N	Y
D	N	N

When the times and temperatures used in the shipping stability studies are compared with the current real shipments, it can be noted that the studies are not fully up to date with current transportation conditions, and studies do not support the planning of transportation in the best possible way. Discussion with the stability study expert disclosed that the current stress cycles used in the shipping stability studies to test product stability in extreme conditions are not fully up to date with current real transportation times and temperatures.

3.2.4 Picking and Packing

Once customer service has created an order based on the customer request, the ERP system creates a picking list for the warehouse. The list guides the warehouse operator which products are to be picked and how those products need to be packed.

Two types of cold elements are used in cool containers. One type of the elements is prepared in the refrigerator (+2…+8 °C) and the other type of the elements in the freezer (-20 °C). When the products for the delivery are picked, they are packed in a cool container only with cold elements prepared in the refrigerator. After that the container is left to the cold room to wait for leaving the warehouse. Frozen elements are seated to the container just before the container is delivered in order to maximize the container's operating time and to avoid freezing of products in the container during cold room storage.

3.2.5 Arrangement of Shipping

After packing the products for the delivery in the warehouse, customer service organizes the shipment. Depending on the incoterm agreed with the customer the practical arrangement for the shipment can be put in order by the case company or by the customer.

The incoterm used in a delivery is negotiable and the agreed option can be changed based on a customer request by using case specific consideration. The used incoterm has impact on the case company's ability to make decisions related to shipment arrangements. If the customer arranges the shipment, the case company has limited ability to decide the transportation mode and route. In that case the customer can only be informed about identified good practices and requirements set for maintaining the correct conditions. If customer service is responsible for the shipping arrangement, the best available solution is searched in co-operation with the forwarder.

3.2.6 Transportation

The transportation mode for delivery can be a truck or a flight or a combination of different kinds of transportation methods. The final destinations are all around the world. A typical long-distance delivery includes transportation to the airport, one or several flights, waiting time spent in the terminal due to the connecting flight or clearance through customs and

finally transportation from the airport to the final destination. In the worst case it includes also time spent on tarmac awaiting loading before the flight or unloading after the flight exposing products to extreme outside temperatures.

There is not enough data in the case company to provide comprehensive understanding of ambient temperatures concerning all routes and all climate and seasonal variations. In some cases, information is lacking regarding the exact arrival time to the final destination, especially if the customer is responsible for arranging the last mile transportation. Unplanned delays due to flight schedules or customs clearance are possible. Sufficient documented evidence that would confirm that the used packing solution is able to maintain the correct temperature within all routes and all extreme ambient conditions is lacking. That means a lack of documented evidence that the products are constantly kept in the correct conditions during the entire shipment from the factory to the customer.

3.3 Process Map of the Current Process

The flow chart of the current process described in section 3.2 can be seen in figure 3. There are four stakeholders (customer, customer service, warehouse and carrier) described as vertical lanes. Flowchart provides understanding how the process flows and what decisions are made. Speak bubbles indicate strengths and weaknesses identified in the CSA.

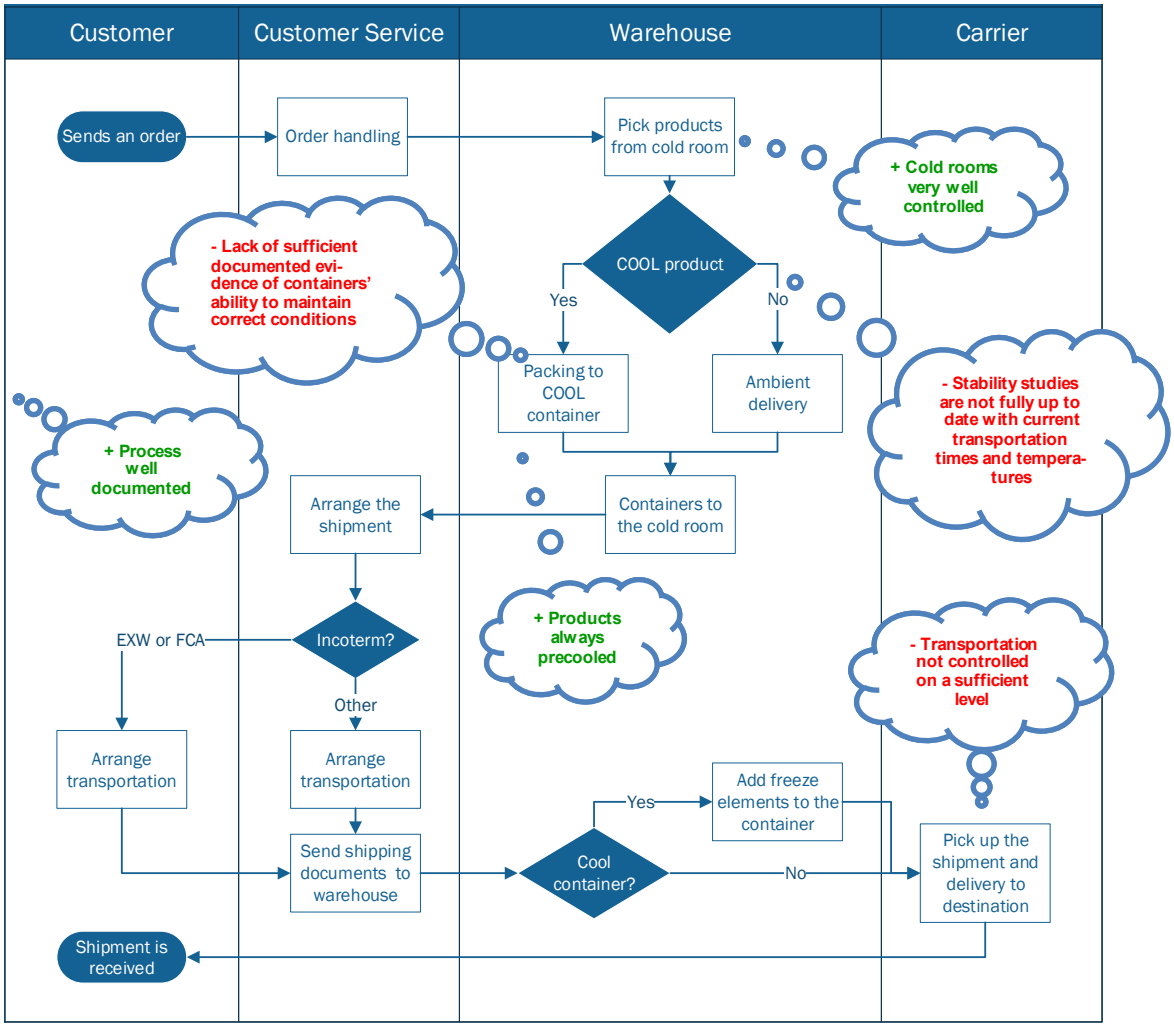

Figure 3. Flow chart of current order to delivery process for diagnostic products requiring cold storage. Speak bubbles indicate strengths and weaknesses of the process.

3.4 Failure Mode and Effects Analysis (FMEA)

After identifying the current process and its' strengths and weaknesses the risks of the cold chain process were analyzed by using the case company's quality system procedure based on FMEA. The potential hazardous situations affecting cold chain management and their potential causes and consequences were discussed in several workshops with cold chain subject matter experts. Severity, probability and detectability of each risk was assessed according to case company's established evaluation criteria.

Clearly the highest risk score was received for those potential hazards which might lead to the situation where the products expose too long time for incorrect conditions during transportation. Based on the assessment that risk required additional mitigations. Possible hazardous situations happening on the case company's manufacturing site were all assessed to be low and current mitigations were seen sufficient. The result of the risk analysis was very well aligned with other observations of current state analysis and it supported the same conclusion as workshops and document reviews - the control of transportation conditions was insufficient.

3.5 Summary of Key Findings of the Current State Analysis

The current state analysis revealed many strengths in the current cold chain management practices. The critical items in the cold chain in the case company's factory are very well controlled. Clear strengths include that the process is described in approved quality system documents, facilities are validated and continuously monitored, and products are always pre-cooled prior to picking and packing.

The weakest part of the process is clearly the transportation of products from the factory to the customer. The identified weaknesses are related to shipping stability studies and transportation. The shipping stability studies are not fully up to date with current transportation times and temperatures and therefore do not support the planning of shipments or handling of possible deviations on the best possible way. All cool containers are not validated according to ISO 13485. There is not sufficient documented evidence that products are always kept in correct conditions during all deliveries which means that the temperature control of shipments is not on a sufficient level.

The key findings of the current process are classified as strengths and weaknesses and listed in Table 6.

Table 6. Strengths and weaknesses of current process identified in the current state analysis.

Strengths	Weaknesses
1. Process is described in quality system procedures and instructions 2. Cold chain critical facilities in the Case Company's warehouse are validated 3. Cold chain critical facilities in the Case Company's warehouse are continuously monitored with validated system which sends alarm if temperature exceeds or falls below predefined limits 4. Fixed sensors used for warehouse monitoring are placed based on temperature distribution studies 5. Products are always pre-cooled prior to packing and delivery	1. Product temperature during transportation within all routes is not maintained and controlled on a sufficient level 2. There is not sufficient documented evidence that the current cool containers are able to maintain the correct conditions inside the parcel in all extreme ambient conditions 3. Shipping stability studies are not fully up to date with the current transportation times and temperatures and do not support the planning of transportation on the best possible way

This section described how the current state analysis was conducted and what kind of strengths and weaknesses were identified in the analysis. In the following section the existing academic literature related to the research topic is reviewed and improvement ideas for the identified weaknesses are searched.

4 Improvement Ideas and Best Practices from Literature

The previous section described the case company's current order to delivery process for diagnostic products requiring cold storage. As an outcome of the previous section, the strengths and weaknesses of the current process were described. The existing knowledge related to tackling the weaknesses identified in the previous section is reviewed in this section. The most important and relevant best practices and solutions to weaknesses identified are discussed. Finally, the conceptual framework for managing cold transportation is created and visualized.

4.1 Maintaining and Controlling Temperature During Transportation

Cold chain refers typically to supply chain maintaining the shelf life of products and preserving perishables during storage and transport from the initial manufacturing location to the end user. It means maintaining continuously the specific required temperature range in order to avoid the product properties to be affected by the possible temperature excursions. It is crucial to notice that maintaining the cold chain cannot improve the product quality, it can only maintain it. Cold chain management aims to provide a safe and effective product to the patient. (Heap 2006, ISPE 2011)

According to Guynes (2018) there are two levels of the cold chain management. The strategic level means planning the required actions and the operational level performing those planned measures. Typically, the operational level means identifying suitable cold chain shipping solutions needed to maintain the required temperature range. Practical sipping solution prevent failures in maintaining the correct temperature which could lead to clinical misdiagnoses. Choosing the proper cold chain shipping solution stipulates thorough understanding of the cold chain management on both strategic and operational level.

According to Yoon (2014) cold chain is a temperature-controlled supply chain which differs from the ordinary supply chain thereby it requires special technology and infrastructure to maintain its value until it reaches the final destination. Maintaining the cold chain comprehensively requires logistical planning and accurate information before shipment. Ensuring the correct product temperature in all ambient conditions regardless of the

transportation mode or temporary outside temperature insists well planned thermal packaging methods. A special requirement for cool shipping is also the need to reach the final destination as soon as possible.

Excessive cold chain packaging is often used to protect the product and to ensure the correct environmental conditions during transportation. Especially one-way shipping of temperature sensitive products in single-use container is a critical part of the cold chain and requires thermally insulated cold chain container. (Singh el al. 2013)

Heap (2006) has described five steps needed to manage the cold chain with success:

- *Know your products and routes*
- *Educate your team on modes of transport*
- *Select the best mode using risk analysis*
- *Use the best provider you can find*
- *Use quality control to manage both planned and unplanned changes.*

Forcinio and Wright (2005) state that the cold chain management is not just maintaining the correct temperature. It can also reduce costs and increase the efficiency of the supply chain. They describe the case where cutting the time needed for cool product transportation resulted also in significant monetary savings. The improvement was based on the finding that most of the shipment time was spent in the customs clearance. Speeding up the customs clearance process was enabled by creating a shipment template harmonized with tariff schedule. When the template clearly laid out all items critical for customs, inspectors were immediately able to see all the information they need to speed up the clearance process. After applying the improved procedure only one shipment out of 70 was held up for examination in the customs clearance. The case shows that even a fairly small well planned and targeted improvement may have significant advancement results.

Kumar et al. (2017) highlight the meaning of quality management system in preventing temperature excursions and the fact that inadequate quality system element can cause temperature excursions. As depicted in Figure 4, critical core quality elements include control of records, deviation management, change control, validation master plan, risk

management, personnel training and awareness, complaint handling procedures and recall management. Good documentation practices have to be adopted in order to ensure adequate instructions and records. If there are incidents from described procedures, they have to be handled and evaluated from the product quality perspective. Change control procedures should guarantee that any changes to design, process equipment or systems are managed in a controlled manner to avoid uncontrolled changes and adverse impacts on validated processes. Validation and qualification strategy for processes and equipment have to be established. Personnel awareness of critical process parameters and procedures for handling complaints and recalls are also crucial elements of quality management system and ensure product quality and patient safety is considered and assessed in all situations. According to the authors deficiencies in these issues have direct impact on temperature excursions. A survey among professionals on pharmaceutical field following cGMP revealed that even if these quality assurance elements are well organized at the manufacturing site, there may be deficiencies during distribution when issues are controlled outside the factory environment.

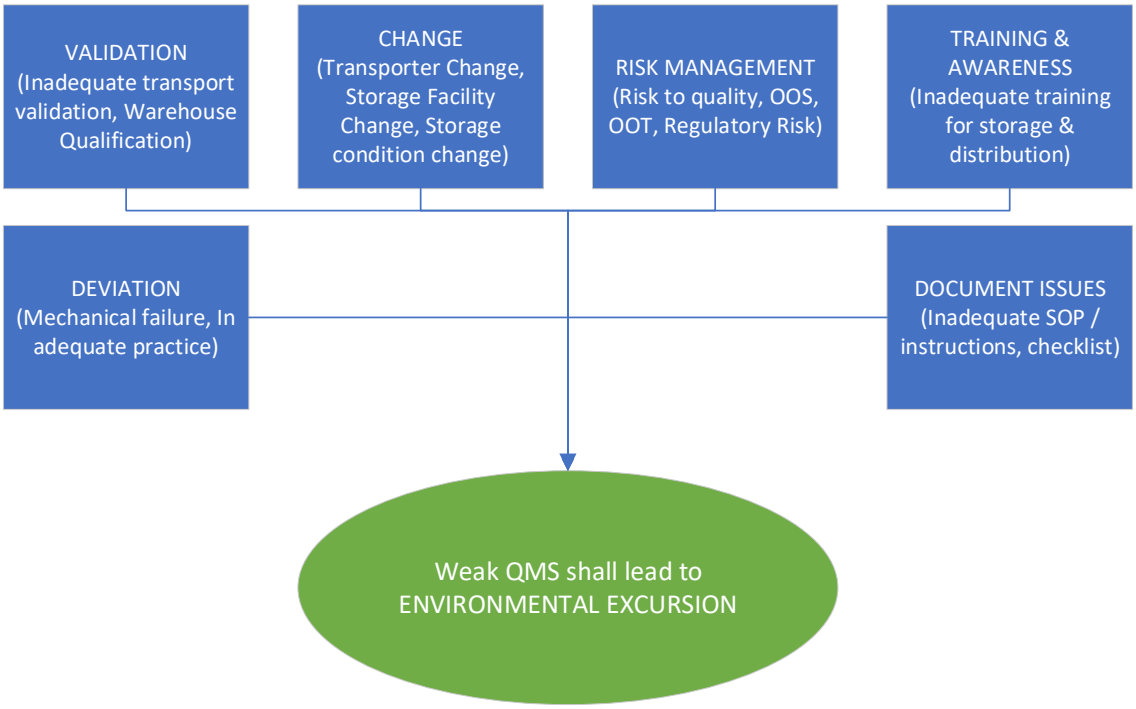

Figure 4. The effect of inadequate quality system to environmental excursions according to Kumar et al. (2017).

4.1.1 Cold Chain Shipping Solutions

The ability to ensure correct temperature during shipment is dependent on the type of container used for refrigeration. Product requirements, duration of transit, shipping routes and methods, ambient temperatures during the shipment and the number of products to be shipped affect significantly the shipping process and need to be carefully considered when choosing the best packaging solution. (Singh el al. 2013, ISPE 2011)

Portable cold chain shipping systems aiming to maintain the product integrity and conditions during transportation can be divided into active and passive systems. (Guynes 2018, ISPE 2011)

Active shipping container is actually a portable refrigerator which includes powered cooling system requiring internal or external power source. (Guynes 2018, ISPE 2011)

Opposite to the active system is the passive shipping containers which maintain the required temperature with preconditioned cool elements. The energy required for cooling is provided by a phase change of a specific material instead of mechanical refrigeration sources. The simplest example of phase change material (PCM) is water and the energy given out when ice melts into water. (Guynes 2018, ISPE 2011)

The active shipping containers may provide the better and longer lasting protection to the product than the passive system. The cooling impact of passive system stops when the phase change is completed, e.g. all ice has turned into water. Passive systems are typically more inexpensive solutions than the active systems. The costs of active systems require return logistics for containers in order to be able to reuse the same containers repeatedly, otherwise the solution is not cost effective.

Huang and Piontek (2017) have developed the solution of passive container utilizing phase change material. The target temperature inside the container was +2…+8 °C. The container's ability to maintain correct internal temperature was tested in extremely low, extremely high and alternating external temperature conditions. The influence of different kind of phase change materials on the time the container was able to maintain the correct temperature conditions was investigated.

Without any PCM the temperature-controlled time under extremely high ambient temperature conditions was less than 1 hour. When water was used as PCM the temperature inside the container dropped to the area of +1…+2 °C for approximately 70 hours meaning too low temperature conditions for the products. When OP5E, an alkane mixture, was used as PCM, the container was able to maintain correct internal temperature under extreme high external conditions for 81 hours. For most of the time the temperature inside the container was between +4…+5 °C which correspond very well the melting/freezing temperature of OP5E. Under extremely low temperature conditions the corresponding times were 1 hour without PCM, 10 hours when using water as PCM and 102 hours with OP5E. Under alternating ambient temperature (at first extremely high temperature following extremely low temperature) the temperature inside the container dropped below +2 °C when using water as PCM. When using OP5E as PCM, the temperature inside the container stayed on required level for 102 hours. The study provides evidence that the insulated container with reasonable selected PCM can be a considerable option for the active containers.

The R-value specific for a certain container material describes the resistance to the transfer of the heat. The higher the R-value is the better the material's ability to insulate heat. Singh et al. (2013) have reported that the R-value together with wall thickness has impact on the length of time the package is able to maintain desired temperature. That finding can be taken into consideration when planning cost effective and practical single use cold chain packaging system. (Singh et al. 2013)

Forcinio and Wright (2005) also highlight the meaning of the R-value in the containers. They describe the case where the packaging providing R-value less than 10 was equipped with the additional insulation material providing better thickness resulting in R-value of 18-22. As a result of the improvement the container's ability to maintain the required temperature increased from 10-12 hours to 36-48 hours.

4.1.2 Monitoring Temperature during Transportation

Despite of all possible controls maintaining the correct conditions during a shipment there is always a residual risk for the temperature excursions below or above the predefined limits due to unplanned delays, extreme ambient conditions, handling mistakes or cus-

toms clearance. Recording the temperature during transportation ensures the temperature has remained within specified range. It documents the maintenance of product quality and enables handling and assessing possible deviations. It also enables to assess possible long-term trends which may indicate changes or problems in the cold chain. Temperature monitoring does not provide protection to the product and product loss may not be avoided by monitoring (ISPE 2011).

Humidity inside the container should also be monitored during the shipment together with the temperature. High relative humidity may cause cold containers to sweat and lose cooling capacity more quickly (Forcinio and Wright, 2005).

There are several techniques available for monitoring conditions during transportation. Forcinio (2006) mentions temperature indicator labels based on phase change chemistry change color in case of unacceptable temperature exposure. Since color change is irreversible, indicators are disposable, but also lightweight and inexpensive (Vivaldi et al. 2020). Disposable electronic temperature indicators state “ok” if predefined temperature limits have not been exceeded. That kind of monitoring provides effortlessly information to the receiver if there are deviations requiring further evaluation, but it does not provide detailed information about the duration of the temperature deviation or exact temperatures the product exposed.

Data loggers are widely used to monitor conditions during transportation (Kumar et al. 2017). They are well available on the market. Loggers can measure temperature and humidity on a predefined interval and the results can be downloaded to computer for review and evaluation. This type of devices requires annual calibration and maintenance in order to ensure accurate information of product storage conditions.

Forcinio (2006) describes also temperature and humidity logging solution based on RFID labels. The same RFID tags used to identify products can include also a temperature sensor. A credit-card-size label with RFID chip can monitor and log environmental conditions at programmed intervals and the data can be retrieved by RFID reader. According to Forcinio (2006) both disposable and reusable solutions exist. According to Vivaldi et al. (2020) RFID tags can be divided into active and passive depending on a power source they use. Active RFID tags typically include a battery and passive tags are powered by external electromagnetic field emitted from the reader. Passive tags are often

preferred due to low costs. RFID tag consists of microchip and an antenna and the data can be accessed by a reader. Depending on the frequency the reader uses, the range where the tag connects to the reader can vary from few centimeters to several meters.

Ruiz-Garcia (2010) discusses challenges and limitations related to RFID technology and provides information that many top pharmaceutical companies are developing RFID solutions for cold chain monitoring, but most of the RFID deployments remain exploratory and results are not published. The lack of long-term experience may prevent implementation of these systems. Automated systems may create a huge amount of data that is difficult to manage and may be a problem for computerized systems. Additional research is needed to have better confidence so that possible false reads are identified and skipped. Temperature loggers are available only for 13.56 MHz HF range which means reading range of about 20 cm. Data rate is also pretty slow for automated system. Metals and liquids inhibit the propagation of electromagnetic waves and complicate the use of RFID technology. Also managing multiple readers in a wide global supply chain can be challenging.

Many authors (Lizhu et al. 2013; Guie 2021; Urbano et al. 2020) discuss shipment tracking solutions based on Internet of Things (IoT) and those technologies are expected to rise significantly in the near future. IoT means a network of devices connected to the Internet in a way they can communicate with each other. Almost any object having IP address and containing embedded electronic system can be connected to IoT. This kind of system enables data transfer over a network without people being involved. Data storage can be local hard driver or the cloud. Software can handle the data, create reports and for example send an alarm to the user if predefined temperature limits are exceeded. (Krogh 2020)

Urbano et al. (2020) describe the design and validation of the tracking system based on RFID tags and IoT. In that system temperature sensors are integrated to RFID tags and the data collected can be transferred to the cloud service by utilizing IoT, RFID, Wi-Fi and mobile telephone network. System registers arrival time and storage conditions during shipment. Cloud service enables all stakeholders and third parties to exploit the collected information. A two-step validation of the system was executed including testing in controlled laboratory conditions which was followed by a real shipment scenario. Calibrated Testo 174H temperature loggers were used in the validation as reference. The

versatility of the IoT and ability to connect different types of systems is seen as a clear strength of IoT based solutions. RFID tags used to monitor temperature were cost effective and testing provided evidence that the system is scalable and suitable for cold chain monitoring. Ability to register timestamps for possible excursions was recognized to be a clear development item. The current state of commercially available solutions was analyzed, and six solutions were identified. According to the authors those systems are typically based on leading technologies, but many organizations do not consider them cost effective yet.

According to Lizhu et al. (2013) IoT provides three important features. It fully utilizes modern technology enabling comprehensive perception of transportation. Accurate real time data monitoring ensures visibility to environmental conditions creating reliable delivery. Using cloud computing allows to manage huge amount of data in intelligent way.

While data from traditional loggers is typically extracted manually in the final destination at the end of the journey, IoT based tracking solutions enable continuous and automated monitoring of the shipment.

4.1.2.1 Choosing the Monitoring System

ISPE (2011) determine several key elements that need to be considered when choosing the suitable monitoring system. The accuracy needed has to be well understood and devices have to be three point calibrated covering the required measurement range. Calibration results or accuracy of the components have to be traceable. If the system can provide a time stamp for the measured values, the accuracy of the internal time measurement component is important. The response time reflects the ability of the system to notice and record a temperature change. Computer system compliance (e.g. with FDA regulations) has to be achieved and maintained. If the system maintains electronically records required to show cGMP compliance, 21 CFR Part 11 may apply and need to be considered when planning the validation. It should also be considered what type of alarms are desired. Typically, alarms are sent if predefined temperature limits are exceeded but some systems may have possibility to send an alarm if the exposure to incorrect temperature exceeds a certain time period. Options for recording intervals as well as time delays for star-up may be required. The way how the system informs user in the

case of alarm – visual indicator, email, text message, phone notification – need to be considered when assessing available solutions.

4.1.2.2 Handling Excursions

The organization should have the procedure in place to handle possible excursions recognized by continuous monitoring. There are two aspects to consider – determination (based on shipping stability studies) if the product is still usable and determination of the root cause of the excursion in order to prevent re-occurrence. In order to be able to assess the root cause the time stamps of monitoring are crucial and enable to trace the place where the excursion happened. (ISPE 2011)

4.1.2.3 Economic Considerations

In a complex and heavily regulated environment cold chain and temperature monitoring is often an unconditional requirement and essential part of the business strategy. These systems are needed in order to ensure product integrity and patient safety. Organizations have a challenge to show compliance with regulatory requirements and find cost effective solutions to carry out the strategy. Choosing low cost devices may be an easy decision momentarily due to small investment but indirect costs may have a lasting impact on the long-term budget. Hidden costs associated with monitoring devices should be considered when choosing a suitable solution for the organization.

The organization is recommended to consider what type of requirements are set for the end user. Possible end user training or a need to provide instructions to the end user may affect the total costs significantly. Choosing an easy to use system reduces additional infrastructure expenditure. Immediate data download capability is a time saving and cost-effective feature.

The reliability of the chosen devices has to be considered. In order to avoid situations where a logger malfunction leads to the interpretation that the product is useless a device type with low failure rate should be considered. (ISPE 2011)

4.2 Cool Containers' ability to maintain correct conditions

ISO 13485:2016 standard requires the IVD manufacturer to

> *validate any processes for production and service provision where the resulting output cannot be or is not verified by subsequent monitoring or measurement and, as a consequence, deficiencies become apparent only after the product is in use or the service has been delivered.*

The standard also states that the organization has to

> *protect product from alteration, contamination or damage when exposed to expected conditions and hazards during … distribution by designing and constructing suitable packaging and shipping containers.*

Validation according to ISO 13485 means obtaining documented evidence based on testing that the validation object fulfills predefined criteria and is fit for intended use. Validation shall be executed according to approved valid procedures and it has to be traceable and documented in detail. There should always be a preapproved plan for each qualification including test cases. Deviation management and change control have to be in place during the whole validation process. A final report is needed to summarize the executed testing in order to close the validation.

Geremia (2017) presents a validation approach which combines GMP and ISO 13485 requirements for medical devices. The validation life cycle seen in Figure 5 is known as V-model due to the shape reminding the letter V. Actions related to planning are described on the left side. User requirements are created to describe what the user expects the system to do. Functional and other detailed specifications describe what kind of technical solutions are needed in order to fulfill set requirements. Qualification testing is shown on the right side. Different levels of testing verify each planning phase. Performance Qualification is the final phase and it verifies the system against user requirements in order to conclude if the system is able to fulfill predefined requirements.

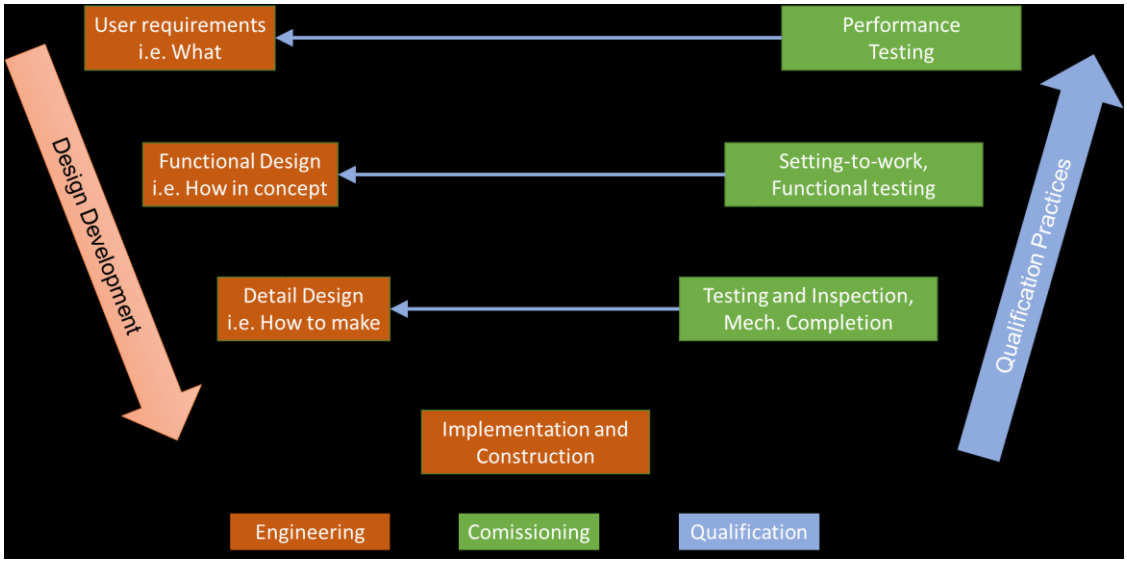

Figure 5. Validation life cycle for medical devices according to Geremia (2017).

Guynes (2018) and ISPE (2011) recommend the cold chain management practitioners to identify the shipping temperatures and to collect the weather data in order to extrapolate the external temperatures during transportation on each route. Based on this data the temperature profiles can be created to describe the outside temperatures during transportation. These profiles can be used to simulate real ambient conditions during shipment when testing the performance of the containers.

ISTA 7E standard provides ready-made temperature profiles for the testing of parcel delivery systems. Profiles are created based on thorough investigation of real temperatures during transportation in different conditions. Profiles are science-based, and they simulate anticipated environmental conditions in parcel distribution network. The standard includes separate profiles for heat and cold circumstances simulating seasonal variations and different geographical locations. ISTA 7E provides standardized methodology to demonstrate the performance of insulated shipping system. The standard is recommended to be used especially in organizations required to show compliance with FDA regulations.

4.2.1 Ongoing Monitoring

After successful completion of performance qualification, the ongoing monitoring procedure for the shipping programme should be established. Monitoring should cover routes

and locations identified to be the worst-case places from the climate, seasonal variation and environmental conditions perspective. Ongoing monitoring is needed since circumstances like environmental conditions or transportation time may change over time and exceed the limits tested in qualification. External conditions during transportation should also be monitored periodically to confirm that they stay in the same range as in qualification. The monitoring should be executed based on risk assessment and predefined procedure. The results of monitoring should be regularly evaluated in order to identify possible problematic shipping routes or unusual trends that may indicate changes in process or equipment. (ISPE 2011)

4.3 Shipping Stability Studies

The purpose of the shipping stability study is to provide evidence that the circumstances the product may be exposed to during transportation do not have an impact on product performance over the whole shelf life stated. (WHO 2017)

Referring to Guynes (2018) stability study is a regulatory requirement to determine the product shelf life and the study has to include the effects of temperature on products during storage and shipping.

According to Forcinio (2006) the product protection during transportation relies heavily on the stability studies. Forcinio is looking at the topic from the pharmaceuticals point of view but the requirements for drugs are so similar to the requirements for diagnostics products that the best practices suitable for pharmaceuticals can be considered also for IVD products. Stability studies are needed since the temperature requirements for shipping may differ from the storage temperature requirements stated in the product label. Temperature excursion studies are needed since it is probable that transportation occasionally exposes products to extreme temperatures due to unplanned delays, customs, weather, mishandling or equipment malfunctions.

ISO 23640 standard requires the IVD manufacturer to *verify that the specified transport conditions will not affect the IVD reagent expiry date*. It also states the following:

> *If transport conditions are simulated, then the protocol design shall be based on the knowledge of the transport conditions. If not already known,*

> *an investigation shall be performed to determine the real transport conditions as a basis for this simulation.*

CLSI stability study guideline (2011) recommends executing a stress test by taking the product through predefined environmental changes simulating the worst-case conditions during transportation. After that the product is placed to normal storage conditions and shelf life testing can begin. The results of transportation simulation testing shall be compared to baseline results from normal storage conditions in order to see if the stress test affected in any way the product stability. Multiple stress test sequences may be needed to address all transport conditions required for the global distribution of the product. Risk assessment, historical data and information from similar products can be used to decide if it is enough to test the product only over the transportation period and not incorporate the long-term study under normal storage conditions.

WHO (2017) notes that understanding how different environmental conditions affect the product quality and when it is not usable anymore helps the manufacturer when troubleshooting post market problems. Manufacturers are recommended to test temperatures between +4…+50 °C for transportation and include cyclic changes to the testing protocol. The possibility of freezing during transportation needs to be considered when planning stability studies.

4.4 Conceptual Framework

The literature review covered the existing knowledge for improving the weaknesses identified in the CSA in section 3. The existing knowledge provided a number of tools and improvement ideas to tackle the business challenge and the identified weaknesses. The Conceptual Framework of this study is created based on best practices and solutions described in existing literature.

The Conceptual Framework built for this thesis contains three key themes as shown in Figure 6 below.

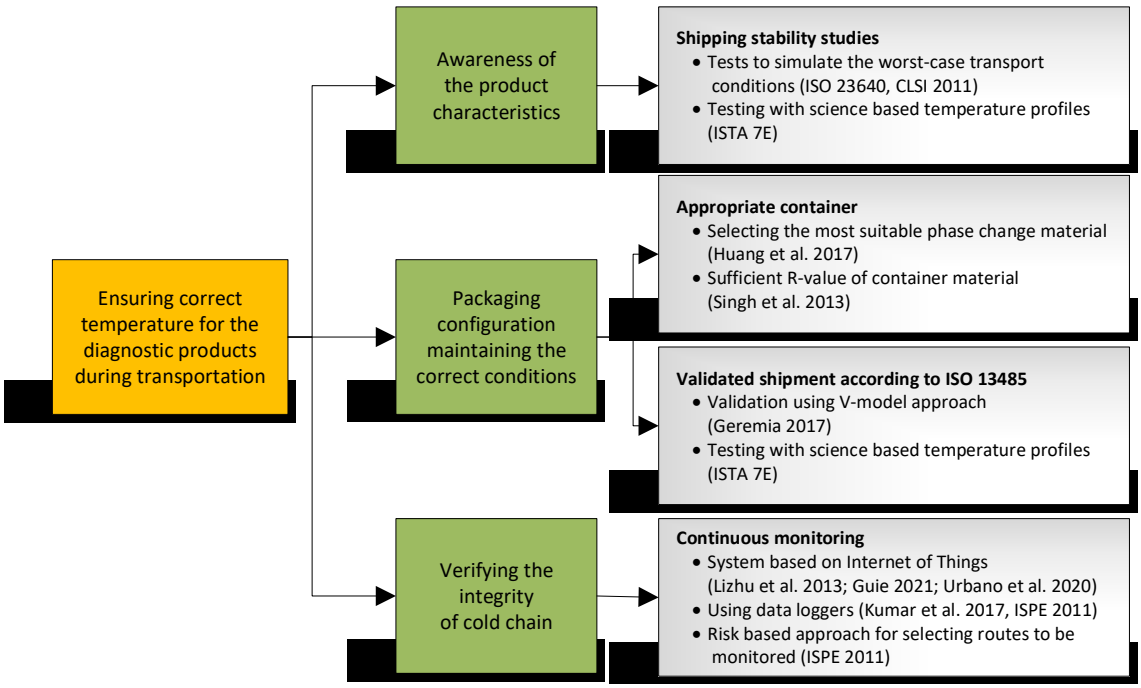

Figure 6. Conceptual Framework of this Thesis.

There are three key themes having a direct impact on ensuring correct transportation conditions for diagnostic products:

1. Awareness of product characteristics
2. Packaging configuration maintaining the correct conditions
3. Verifying the integrity of the cold chain

Awareness of product characteristics means understanding how different conditions product may expose affect product quality. Shipping stability studies are needed to plan transportation methods and packaging configurations. The results of these studies also help to assess possible deviations and temperature excursions.

Suitable packaging is crucial to protect products in all ambient conditions during shipment. Validation provides documented evidence of the container's ability to maintain the required conditions and enable to make a conclusion if the container is fit for intended use.

Despite of all measures there is always a residual risk for temperature excursion during shipment due to unplanned delays, handling deviations, malfunctions, mistakes or customs clearance. In order to ensure correct conditions and be aware of possible deviations, the continuous monitoring of shipments is needed. It also enables to identify and assess possible trends indicating deviations or changes in the process.

In the next section the Conceptual Framework is exploited to eliminate the weaknesses identified in the CSA and to create initial improvement recommendations to the business challenge.

5 Initial Proposal for Cold Chain Management Improvement

This section merges the findings of the current state analysis and the conceptual framework and describes how the initial improvement proposal was built in co-operation with applicable stakeholders in the case company.

5.1 Overview of the Proposal Building Stage

The goal of the proposal building stage was to create improvement ideas for the case company's cold chain management process. The current state analysis revealed that the control and maintenance of correct conditions during transportation of the temperature sensitive diagnostic products require development. Relevant best practice was found from the literature and summarized in the conceptual framework. The proposal for the actions to improve the cold chain management process was co-created in three separate workshops where the identified weaknesses and possible solutions were discussed with the applicable key stakeholders. The proposed actions were agreed together with the participants.

The first step was reviewing the results of the FMEA risk analysis and the identified weaknesses together with the cold chain subject matter experts in the case company. Required mitigations for the risks assessed to have the biggest risk score and solutions to identified weaknesses were co-created with the applicable key stakeholders. In the second phase the identified strengths and weaknesses, results of risk analysis and improvement suggestions were introduced to the wider group of key stakeholders and decision makers including participants from warehouse, logistics, customer service, quality and business operations. Operation and quality directors were involved in the second phase in order to ensure support and resources for the planned actions. Suggestions from the participants were part of the proposal building. In the third workshop some details were discussed in order to make the final adjustments.

5.2 Description of the Recommendations Creation

In the first workshop the results of risk analysis were reviewed. The risk with the highest risk score was clearly the possibility that the products are exposed to incorrect temperatures for too long time during the transportation. Several potential hazard situations that could lead to that consequence were recognized. Especially the situation where the customer is responsible for the shipment arrangements was raised to the discussion. If the customer is not properly informed about the special requirements set for cool deliveries, there is a risk that incorrect choices are made leading to the situation where the products are exposed to incorrect conditions. As a mitigation action, creating instructions for customers was suggested.

A need to have a better understanding of the current containers performance in different ambient conditions was also discussed. A better comprehension would support the shipment planning and choices of different transportation modes. The regulatory requirement to validate the containers was also identified. The concerted decision was to execute validation of the current containers by using V-model.

The risk analysis supported the finding of the CSA that the precooling of products is a strength of the process. However, it was noticed that even if the precooling of the products is not any kind of problem in the current process, the process does not have any element to ensure the precooling of the products in all possible situations. The current process does not prevent that for example the urgent need for a delivery could not lead to a situation where the precooling is skipped. Therefore it was agreed to plan a process element to prevent skipping the precooling step and update the current process accordingly.

The second workshop was started by reviewing the current state analysis and the identified strengths and weaknesses. The ideas raised earlier to improve the current process were presented and discussed.

A need to validate the current containers was agreed. The possibility to use temperature profiles like ISTA 7E was considered. Using temperature profile would require certain outsourced activities since currently available in-house recourses do not enable that type of testing. Since there are some special conditions where the performance of current

containers is not known well enough and where additional understanding would directly support the work of customer service when planning the shipments, it was decided to start the first qualification with in-house testing. The final decision if the temperature profile should be used was postponed and the issue will be reconsidered when the results of the first in-house qualification have been reviewed.

The risk that the performance of the current containers is not sufficient for all challenging routes in all extreme weather conditions was also discussed. Participant 1 suggested to examine possible new solutions to be used beside the current containers when really strong protection to the products is needed. Since Participant 1 has wide experience in the IVD industry, a possibly suitable solution was already mentioned. It was agreed to find out about the availability of the container solution mentioned, and it was also agreed to test the solution in order to see if it could provide better protection to the products than the current solutions.

The risk that a product not allowed to freeze is exposed to too low temperatures during transportation was handled. Participant 2 suggested to rethink the current concept and product groups used to define the packing solution in the shipment. It could be beneficial to plan current procedures in a totally new way, especially if it was possible to introduce a new packing solution providing better protection against freezing than the current one. The current process has just two options – certain products are always packed in a cool container and certain products are delivered in ambient conditions. In addition to the product itself it could be beneficial to consider the delivery route and destination when deciding of suitable package. It could also be a feasible solution to use different cool containers in different routes.

A need to have comprehensive awareness of all ambient conditions during shipments as well as the time delivery needs to reach the final destination was raised in the discussion. That knowledge supports heavily the planning of the container validation as well as planning of shipping stability studies. As a first action the monitoring with single use loggers and with selected routes is started. The second goal is to establish a continuous process for monitoring. That requires a quality system procedure describing selected routes, frequency of monitoring, responsibilities, instruments to be used and reporting methods for the results.

The third workshop was started with reviewing the CSA, CF and already agreed improvement actions. Advanced technologies to monitor the cold chain were discussed. Systems based on wireless technologies such as Internet of Things were recognized. The possibility to automate monitoring and reporting and reduce routine work was seen as a clear benefit. The fact that such an automated system does not require anything from the customer was considered as an excellent advantage. When using data loggers to monitor shipments customers are expected to return data and receiving the results is dependent on external actors. Such systems were seen as later development opportunities once the first prioritized actions have been implemented. It was also commented that since those technologies and commercially available solutions based on these technologies are quite new, it is beneficial to become thoroughly familiar with all features and possible weaknesses. The reliability and operability of the new technology have to be ensured before implementing new solutions.

The fact that the current shipping stability study results do not support the shipment planning and handling of the possible temperature deviations in the best possible way was also discussed. There is an ongoing transition period for in vitro diagnostic medical device manufacturers to implement a new EU legislation (In Vitro Diagnostic Regulation (IVDR) (EU) 2017/746). The case company has an ongoing project targeting to meet the new requirements and to comply with the IVDR regulation. As a part of that project current stability studies are reviewed and assessed. The need to reevaluate times and temperatures used in shipping stability studies will be considered as a part of the ongoing IVDR project.

The current product categorization used to define transportation packaging and possibilities to re-evaluate transportation methods and packages was discussed. Planned actions to better monitor shipments and investigate the performance of current containers may reveal that some products need more protection which typically mean more expensive solutions. Participant 3 had a very good point that there may also be some overpacking and additional understanding might enable to reduce protection with some products meaning monetary savings. A very good suggestion was raised to review the shipping volumes of individual products in order to be able to estimate financial costs of redesigned shipping procedures. The current process to choose a correct pack for each product is very simple and smooth for the warehouse and possible changes have to be

carefully considered to ensure that additional steps in the process really add value to the customer.

5.3 Summary of the proposed improvements

The following recommendations were suggested to improve the control of shipments and develop the maintenance of correct conditions:

1) Monitor selected challenging routes with a single use data logger inside and outside the container in order to increase the awareness of real shipping conditions
2) Create and establish a continuous procedure to monitor the risk based selected routes with predefined frequency
3) Investigate the availability of the possible new container solution and execute preliminary tests for the performance of the container
4) Validate the new container according to ISO 13485
5) Redesign product categories from packing point of view based on the results of container testing and awareness of real transportation conditions gained by monitoring

The following recommendations were suggested to the weakness related to unvalidated containers:

1) Current containers to be validated according to ISO 13485
2) Validation to be started with in-house testing and after reviewing the preliminary results the decision to be made if the testing should continue by using temperature profile

The following recommendation was agreed for shipping stability studies:

1) Executed studies to be reviewed and replanning of the test cycles to be considered from transportation point of view based on the results of the review

The initial recommendations to improve the case company's cold chain of outbound temperature sensitive IVD products are compiled together in Figure 7. The proposed actions concern strength number 5 and weaknesses number 1, 2 and 3 identified in the CSA.

The corresponding recommendations have identification number x.y, where x is the number of the strength/weakness and y is a running number.

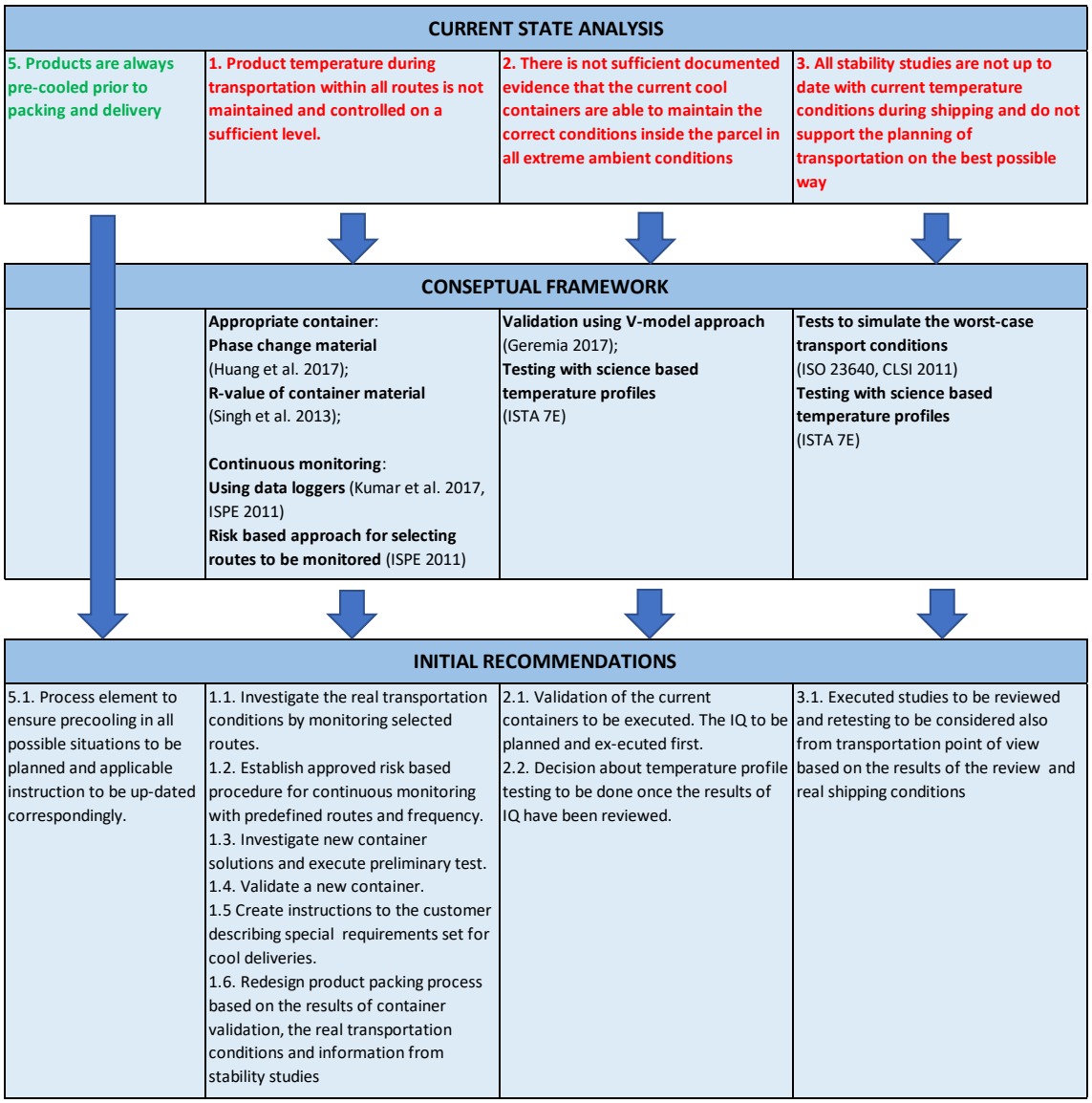

Figure 7. Initial recommendations to improve the case company's cold chain management. Numbers of identified strengths and weaknesses in CSA reflect Figure 6 in section 3.

The priority order of the proposed actions is described in Table 7. All planned actions cannot be executed immediately, and actions categorized in the first group are started immediately. The measures with the second and the third priority order are dependent on the actions in the first category and they will be accomplished once the execution of the first actions allows it. Some actions are dependent on the results of the other actions.

For example, the packing process cannot be redesigned before the results for the container validations exist.

Table 7. Priority order of proposed actions. The number of each action correspond with the number of recommendations in Figure 7.

Priority Order	Proposed Action	Criteria of Success
1st priority	5.1. Process element to ensure precooling in all possible situations to be planned and applicable instruction to be updated correspondingly.	Updated SOP/WI including additional element is approved and released.
	1.1. Investigate the real transportation conditions by monitoring selected routes.	Monitoring results of predefined shipments exist.
	2.1. Validation of the current containers to be executed. The IQ to be planned and executed.	IQ approved.
	2.2. Decision about temperature profile testing to be done once the results of IQ have been reviewed.	Decision of further testing made enabling to complete the validation.
	1.3. Investigate new container solutions and execute preliminary test.	Results indicate possible suitable solution.
2nd priority	1.2. Establish approved procedure for continuous monitoring with predefined routes and frequency.	New procedure established. Continuous monitoring according to released procedure is in use.
	3.1. Executed studies to be reviewed and retesting to be considered from transportation point of view based on the results of the review and real shipping conditions	Current study results summarized, and necessary actions defined.
	1.4. Validate a new container according to ISO 13485.	Approved validation report for new container exists.
3rd priority	1.5 Redesign product packing process based on the results of container validation, awareness of the real transportation conditions gained by monitoring and possible information from stability studies	Possible changes to the current process have been established.
	Create instructions to the customer describing special requirements set for cool deliveries	Approved instruction exists

This section described the co-creation of the initial proposal to improve the current cold chain management process in the case company. In the next section the initial proposal is evaluated, and the final proposal is created based on the key stakeholder feedback.

6 Evaluating the Initial Proposal

This section reports on the results of the evaluation of the initial proposal for improvements presented in the previous section and points to further developments to the initial proposal. At the end of this section, the final proposal including suggested improvement actions to develop the current cold chain management are presented.

6.1 Overview of the Evaluation Stage

The initial proposal was evaluated by presenting the recommendations from section 5 for two selected management level decision makers. Two separate meetings were held with the selected representatives. Both meetings started with the review of the results of the current state analysis, conceptual framework, initial recommendations stated in the previous section and the planned priority of proposed actions. The identified weaknesses and proposed improvements were discussed and feedback and comments from the representatives was requested. The discussions were documented as field notes. The purpose of this stage was to assess the initial proposal from the business and regulatory perspective, evaluate the feasibility and effectiveness of the proposed actions and make necessary adjustments to the proposal in order to create the final proposal.

6.2 Feedback Received for the Initial Proposal

The feedback for the initial proposal provided by the representatives was in general very positive. It was seen that the proposed actions strongly support the needs of the case company, improve the current process and increase the awareness and know-how of the cold chain management process. The fact that the recommendations are concrete and doable measures were seen as a strength of the initial proposal. The proposed actions were considered to develop the current process to the desired direction.

Actions related to controlling and monitoring of transportation conditions were considered well planned steps to develop the process. The priority order of the actions was approved. The action planned to validate the current containers was also approved.

It was seen that the redesigning of the packing process from the product requirement, route and packing solution perspective is not possible to be performed before other actions are executed and additional information of transportation times and temperatures as well as containers' performance exist. Therefore priority class 3 is correct for that action. It was also discussed if there is a risk that the redesigned process is too complex for the warehouse. Representative 2 brought forward a very good point that even a complex decision-making process for packing is not a problem if it is possible to automate it in a way that the warehouse picker receives a ready-made list of what to pick and how to pack the products. When redesigning the process, it has to be considered the possibility that for example the ERP system would be able to automatically create a ready-made picking list based on the predefined logic.

The initial proposal is based on using data loggers to monitor shipments. New technology and a possibility to use wireless monitoring systems was discussed. It was noted that such systems based for example on the IoT are interesting new solutions and it is beneficial to follow their development. It is interesting to hear user experiences of these systems once they become more common. Such a system could be a part of further development after executing all currently planned actions.

The review of current shipping stability studies and possible redesign of current study stress cycles based on the results of the review was seen as a necessary measure. There was a discussion if the required shipping conditions are considered in the current product development process at a sufficiently early stage. When releasing a new product to the market and developing the manufacturing process, also shipping conditions should be considered on a sufficient level in order to ensure that the product can be delivered using valid transportation procedures. Representative 1 suggested adding an action to ensure that the product development process takes shipping into consideration on a sufficient level. Current times and temperatures used in the stability studies were also discussed. It was noted that the test cycles used to carry out the shipping stability studies should be described in the valid standard operating procedure. A task to define stability test conditions in the approved SOP was agreed.

6.3 Final Proposal

The final proposal was created based on the comments and feedback received from the selected management level decision makers. The initial proposal was amended by adding two actions, shown in the green box in Figure 8, related to the shipping stability studies. Action 3.2 aims to ensure that the shipping is considered in an early stage of the product development process in order to confirm that a product can be delivered with the existing process. The purpose of action 3.3 is to ensure that the temperature profiles used in shipping stability studies are described in the approved standard operating procedure. The recommended actions of the final proposal are combined to CSA and CF in Figure 8.

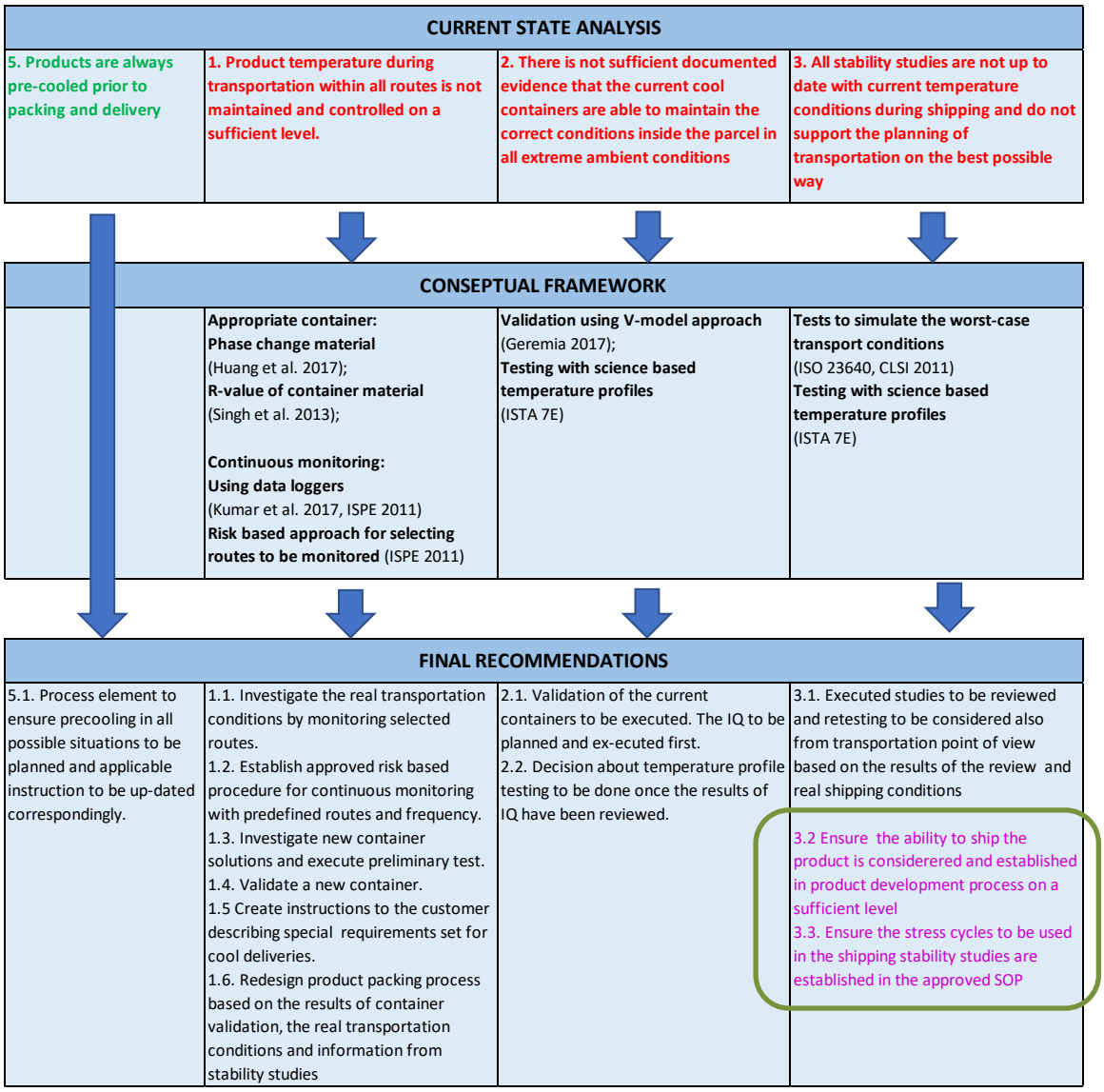

Figure 8. Final recommendations to improve the case company's cold chain management. Numbers of identified strengths and weaknesses in CSA reflect Figure 6 in section 3.

The planned priority order of the recommended actions was also updated with additional actions (shown in the purple box) and is described in Table 8.

Table 8. Final proposal for improvement of case company's cold chain management and the priority order of recommended actions.

Priority Order	Proposed Action	Criteria of Success
1st priority	Process element to ensure precooling in all possible situations to be planned and applicable instruction to be updated correspondingly.	Updated SOP/WI including additional element is approved and released.
	Investigate the real transportation conditions by monitoring selected routes.	Monitoring results of predefined shipments exist.
	Validation of the current containers to be executed. The IQ to be planned and executed.	IQ approved.
	Decision about temperature profile testing to be done once the results of IQ have been reviewed.	Decision of further testing made enabling to complete the validation.
	Investigate new container solutions and execute preliminary test.	Results indicate possible suitable solution.
2nd priority	Establish approved procedure for continuous monitoring with predefined routes and frequency.	New procedure established. Continuous monitoring according to released procedure is in use.
	Executed studies to be reviewed and retesting to be considered from transportation point of view based on the results of the review and real shipping conditions	Current study results summarized, and necessary actions defined.
	Ensure the ability to ship the product is considered and established in product development process on a sufficient level	Product Development Process reviewed and updated if necessary.
	Ensure the stress cycles to be used in the shipping stability studies are established in the approved SOP	Stress cycles defined in the approved SOP.
	Validate a new container according to ISO 13485.	Approved validation report for new container exists.
3rd priority	Redesign product packing process based on the results of container validation, awareness of the real transportation conditions gained by monitoring and possible information from stability studies	Possible changes to the current process have been established.
	Create instructions to the customer describing special requirements set for cool deliveries	Approved instruction exists

The final proposal described in this section was created based on the feedback and comments from decision makers. The final section of this thesis summarizes the study, includes recommendations toward implementation of the planned actions and provides the self-evaluation of the study.

7 Conclusions

This final section of the thesis summarizes the study and the results. It also includes recommendations for the next steps and self-evaluation of the thesis.

7.1 Executive Summary

The objective of this study was to improve the case company's existing cold chain management process. The focus in this study was in temperature sensitive IVD reagent products and in deliveries from the case company's factory to the first customer. Cold chain management is a crucial process which maintains the product quality, provides protection to the patient and decreases the risk of financial loss for the manufacturer. The results of this study help the case company to prevent temperature excursions and to ensure that correct conditions for the temperature sensitive products are maintained also during transportation.

There were four main phases in this study. The first phase was the current state analysis where the current process was reviewed together with subject matter experts. As a result of that phase the strengths and weaknesses of the current process were identified. The next phase was literature review where existing knowledge and best practices were researched from the literature. The conceptual framework for the thesis was created based on the findings of the relevant literature.

In the third phase the initial proposal to improve the current cold chain management process was co-created together with the applicable stakeholders in the case company. Finally, the initial proposal was adjusted based on the comments and feedback received from the managerial decision makers and the final proposal for the improvement of the case company's cold chain management process was created.

The final proposal provides recommendations to develop items identified as weaknesses of the current process. Five actions are proposed to mitigate the fact that currently the product temperature during transportation is not maintained and controlled on a sufficient level. In order to really know the real extreme ambient conditions during transportation on all routes the temperature monitoring of selected routes should be started and established as an ongoing continuous process. Due to the risk that the current containers are

not able to maintain the correct conditions during transportation in all extreme ambient conditions on all routes, a new container solution providing better protection to the products should be examined. When a promising solution is found, it has to be validated according to ISO 13485. Later the redesign of the current packing process should be considered. Once additional information about containers' performance and real transportation conditions exist, it would be beneficial to reconsider how different products should be delivered and if also the route or seasonal variation should have an impact on the chosen packing solution or transportation mode.

Another weakness identified in the current state analysis was the fact that there is not sufficient documented evidence that current cool containers are able to maintain the correct conditions inside the parcel within all extreme ambient conditions. The proposed action agreed with key stakeholders is to validate the containers. The first action is to start testing with in house methods and after IQ to decide if the temperature profiles provided by ISTA 7E standard are used for OQ/PQ testing. The validation provides understanding how the containers perform in different extreme ambient conditions and enables to conclude which containers suit best for each route.

Three improvement suggestions were created for the identified weakness concerning the fact that the shipping stability studies are not fully up to date with current transportation conditions and do not support the transportation planning or handling of possible deviations in the best possible way. The first action needed is a thorough review of the current study results and possible actions needed based on the results of the review. The need for retesting and planning the stress conditions used in the shipping stability studies should be considered based on the results of the assessment and real transportation conditions. It should also be ensured that the product development process pays attention to product characteristics from the shipping point of view before the new products is released. The stress conditions simulating the worst-case shipping conditions used in stability studies should be described in the approved procedure.

Finally, the priority order for the proposed actions were suggested based on the discussions with key stakeholders. All actions cannot be executed immediately and some of them are dependent on the results of the other actions. The priority order has been reviewed and approved by managerial decision makers providing comments and feedback to the initial proposal.

The implementation of the proposed actions improves the current cold chain management process and increases the awareness and know-how of the transportation process. The suggested improvements help to ensure the product quality is maintained also during shipment and prevent damages during delivery.

7.2 Next Steps and Recommendations toward Implementation

The final proposal described the first steps needed to improve the current cold chain management of temperature sensitive IVD reagent products. The recommended actions should be executed in a certain order since some actions are dependent on the results of the other actions. The case company has decided to establish a project with a goal to implement the agreed improvements. The planned timetable for the proposed actions is shown in Figure 9.

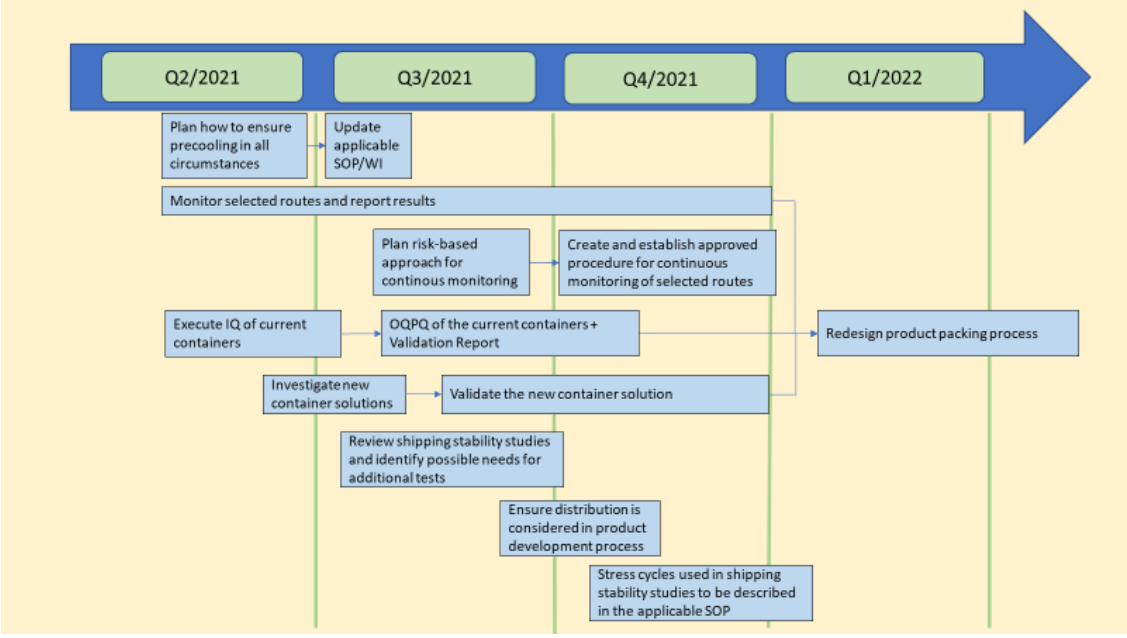

Figure 9. Planned schedule for recommended actions.

The redesign of the packing process can be executed only after the validation of containers and monitoring the selected routes in order to have encompassing understanding what the challenges are within each route and what type of container provides the best protection. It should also be noted that the decision-making process regarding different products, routes and containers cannot be too complex. If a selection seems to be too

complicated it could be evaluated if the ERP system was able to include predefined logic to create a ready-made picking list for the warehouse worker.

Table 9 includes a plan for responsibilities and deliverables to be created as an outcome of the proposed tasks. Ensuring precooling of the products, establishing a procedure for continuous monitoring, including delivery planning in the product development process and establishing shipping stability test cycles should result in an updated or a new SOP. The validations should result in an approved validation report. As an outcome of any review or monitoring a report should be published.

Table 9. Resources needed for the proposed actions and deliverables to be created.

Action	Resources needed	Deliverables
Ensuring precooling in all circumstances	To be executed as a part of the established project	Updated and approved SOP
Monitoring selected routes	Project, warehouse, customer service	Report of the results of the monitoring
Establishing continuous procedure for monitoring selected routes	Quality, warehouse, customer service	Approved and released SOP
Validation of the current containers	To be executed as a part of the established project	Approved Validation Report
Searching a new container solution and validation	To be executed as a part of the established project	Approved Validation Report
Reviewing shipping stability studies and identifying development opportunities	R&D, Quality	Report of the results of the review
Ensuring the delivery of the product is considered in the early stage of the product development process	R&D	Updated and approved SOP
Stress cycles used in the shipping stability studies to be described in the quality system procedure	R&D	Updated and approved SOP

The scope of this thesis covered shipments from the manufacturer to the first customer which can be an end customer or a distributor. Further development after implementing the proposed actions could be to investigate the management of the cold chain in the distributor warehouse and from the distributor to the final customer.

It could be beneficial to follow the development of wireless monitoring systems and consider such a system when further improving the cold chain management process. Automated data collection and reporting could be a practical solution once they are cost effective options.

7.3 Thesis Evaluation

The objective of this thesis was to improve the current outbound cold chain management process and to propose actions how to develop the current process. As an outcome of this thesis several concrete improvement actions for the cold chain management process of IVD reagent products were suggested. The outcome fulfills the initial objective set for the thesis.

Once the proposed actions are implemented, the result is a partially improved process. Implementing the proposed actions help to prevent temperature excursions and to ensure that correct conditions for the temperature sensitive products are maintained also during transportation. The proposed actions help to maintain the product quality and measures provide protection to the patient. The proposed actions decrease also the risk of financial loss for the manufacturer since in the worst case products have to be scrapped if they are exposed to wrong conditions for too long.

The cold chain management of a global supply chain is a complex and multifaceted issue. The actions proposed in this thesis are the first steps needed to improve the current process. Further development can be planned once these actions and the additional information they provide exist.

It can be discussed if all weaknesses of the current process were identified and if all relevant best practices were recognized when reviewing the existing literature. The literature review was limited to publications in English so the risk that something was not found is real. Key stakeholders have participated in the current state analysis and managerial decision makers have assessed the results of the study. The results of this thesis add value and provide an opportunity to develop the current process. A narrower scope would have enabled to dive deeper in certain specific problems. If the scope had covered only deliveries to a certain customer, it might have been possible to execute some tests and collect data for that specific route. The shipping stability studies could also form a

separate study in order to create further proposals to improve that area. It might have been beneficial to search for best practices inside the case company since there are also other sites having temperature sensitive products and they may have faced similar kind of challenges.

It is crucial to conduct the research accurately, honestly and objectively by following the principles of Responsible Conduct of Research (RCR) and ensuring the integrity of the research. Common research evaluation criteria apply to this study in order to confirm reliability, validity, logic and relevance.

7.3.1 Reliability

According to Greener (2008) reliability is another term for consistency. Research has to be auditable and therefore the reader has to be able to repeat the study with the same method and produce the same results, if they so wish. According to Steneck (2017) results should be reported in sufficient detail enabling the reader to assess the conclusions drawn in the study. It does not mean that every single piece of data should be reported since it may contain confidential information of protected processes and products. The data can be processed to understandable, easy-to-read form before it is published. Careful attention to details is needed in order to avoid mistakes.

In this study, reliability was planned to be ensured by the following steps: The significance of findings was discussed in section 7, Discussions and Conclusions. Causes, possible interpretations and limitations of the study were considered and handled. All workshops and meetings including this study were accurately recorded as field notes. All literature reviewed was identified and defined.

7.3.2 Validity

Greener (2008) describes three different kinds of ways to define validity. Face validity means choosing the valid method for research. Construct validity means that the research method really measures what it is expected to be measuring and the method is fit for the intended study. Construct validity is especially important in questionnaires which are not conducted face-to-face since there is no possibility to discuss and clarify

the questions and that may lead to misunderstandings. Internal validity relates to causality which means the relationship between the cause and consequence. Assumptions cannot be made in business research. The key question is if an independent variable account completely for a change in a dependent variable, or are other factors affecting this outcome.

In this thesis, validity was ensured by the careful choice of research design and approach described in sections 2.1 and 2.2. The suitable approach for this study has been discussed and agreed with the thesis instructor in order to choose the best possible approach for this particular case. Workshops in section 6 were conducted as Teams meetings in order to have the possibility to discuss and clarify any unclear questions.

7.3.3 Logic

The study has to be logical. Greener (2008) states that logical structure and argumentation is vital for any audience. Traceability should be established between all findings, conclusions and recommendations suggested.

The logic of this study was ensured by creating a conceptual framework which addresses the identified weaknesses in the case company's business process and solutions based on the reviewed literature. The conceptual framework was further used to co-create the initial proposal together with relevant stakeholders. The structure of the thesis was created in a way that it is logical for a reader describing different phases of the study in chronological order. All steps starting from the business challenge and ending to recommended actions have been thoroughly described.

7.3.4 Relevance

Toffer (2016) notes that research is relevant if it has the potential to improve the decision making of practitioners. Research relevance is reflected in the research question, hypothesis and implications. Relevant research is novel to academics meaning that it helps to understand the relationship between different constructs. It also provides solutions to questions that are meaningful to practitioners working in that field. The researcher has to be able to specify who benefits from the results of the study. It should also be considered if the research question can be answered rigorously.

In this research, relevance was ensured from the beginning when the topic was decided together with the practitioners representing the case company. The research question is a real business challenge requiring improvements. The results of the research will have the biggest relevance to the case company's managers responsible for the cold chain management. Many companies share similar challenges, but this research aims to provide recommendations directly to the case company's situation by stating clearly how the recommended actions would affect the practitioners' decision making.

7.4 Closing Words

Processes and services require continuous development in order to stay competitive and cost effective. Organizations have to continuously identify opportunities for improvements, analyze collected data, plan and implement changes and assess the impact of those changes. The cold chain remains the most important way to protect temperature sensitive products and to ensure that high quality products are received by the customer. Opportunities for development identified in this thesis and implementing those measures can be considered as one cycle of the plan-do-check-act procedure. These cycles should continue afterwards in order to constantly eliminate the weaknesses of the process and to ensure product quality.

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