



Distribution of dialysis fluids

- Is transport and storage optimised from a
temperature point of view?

Authors: Linda Nilsson
Matilda Wallergård

Supervisors: Annika Olsson, Lund's Institute of Technology
Per Kjellstrand, Gambro AB
Theodor Sandström, Gambro AB

Preface

The thesis is the final part of our Master Degree in Industrial Engineering and Management respectively Mechanical Engineering. The degree is awarded by Lund Institute of Technology, Lund University, Sweden.

This report is a presentation of our thesis, which was carried out under direction of Gambro Research and Development, in September 2003 to January 2004.

We would like to thank everyone at Gambro who has contributed with their knowledge and support to this thesis. Most of all we want to thank Per Kjellstrand, who has provided us with knowledge on a completely new field and for spending hours proofreading our report.

Moreover we would like to thank all the employees at EM5 for making us feel welcome. It made our days in the office and especially the coffee breaks much more valuable.

The field trip to Italy was also an experience we never will forget. It contributed with lots of valuable information to the report, and also an insight of the Italian food and wines.

Last but not least we would like to thank our supervisor Annika Olsson at the Division of Package Logistics, Lund Institute of Technology and Ernst Wehtje at Bioett AB.

Lund, January 2004

Linda Nilsson & Matilda Wallergård



Abstract

The background to this thesis is the fact that high temperature during transport and storage, degrade the glucose of peritoneal dialysis fluid (PD-fluid), into a toxic substance. Research at Gambro has shown that exposure to high temperatures can destroy the PD-fluid in just a few hours, requiring months to repair. With this knowledge it became important to monitor the temperature, and evaluate which temperatures the product is exposed to in the distribution chain. This to conclude if the product will reach the patient with high quality, guaranteeing well-being.

The focus of the research has been to clarify which temperatures the PD-fluid is exposed to during distribution from production to the patients. The centre of attention has been the distribution between Italy and Sweden, where the three-compartment bag (trio) has majority of market shares. It is the conventional PD-fluid, not the trio that is harmed due to high temperatures. All the same, the study of this thesis should be seen as a pilot case and the experience gathered can be applied to any distribution chain, supplying conventional fluid or not.

To analyse if the distribution chain is optimised from a temperature point of view, an in-depth mapping was made. Monitoring the temperature and taking part of previous temperature studies identified critical points in the distribution chain. Interviews, observations and document reviews were moreover an important part of the research strategy. Throughout the research, the authors evaluated existing temperature awareness among the stakeholders.

By monitoring the temperature and taking part of previous temperature studies, it was concluded that critical temperatures exist, mainly due to transport. The PD-fluid was exposed to temperatures below the restricted 4°C a couple of times. In one case the fluid was exposed for a temperature below zero. To avoid this, tempered trucks are recommended.

From evidence in previous studies by Gambro, it was obvious that temperatures above the restricted 30°C occur. This happens in the worldwide container transports. Gambro has to consider reefer containers in those cases where there is a risk for the conventional PD-fluid or any temperature sensitive goods might be subjected to temperatures exceeding 30°C.

The warehouses in Italy and Sweden have a good control of their warehouse temperatures, which are regularly monitored.

There is a huge lack of temperature awareness among the Gambro stakeholders, and this is according to the authors, the explanation why the temperature control is lost during transport. On the whole the warehouse temperature is controlled, but as soon as the product is in the hands of an external actor, the control is lost. With an increased awareness about why the conventional PD-fluid is temperature sensitive, most critical handling in the

distribution chain could be avoided, and thereby decrease the need for temperature-controlled transports.

As a second part of the thesis a temperature monitoring system, developed by Bioett AB, was evaluated to conclude if it indirectly could indicate the quality of the conventional PD-fluid.

The Bioett system could to some degree monitor the temperature, and reflect the total amount of glucose degraded, but for which purpose? To be successful for Gambro, the monitor system has to indicate if it affects the quality or not, which the system does not. The biological activity of the glucose in the PD-fluid, which is time- and temperature dependent, is more complex than the Bioett system and it can therefore not indicate the quality of the PD-fluid.

It is the authors' believe that with an improved awareness, transport and storage will be optimised, since the control throughout the distribution chain will be improved. Involved parts will have a better understanding and guidance and thereby take on correct actions if anything out of the ordinary would take place.

Contents	
1 Introduction.....	1
1.1 Background	1
1.2 Problem formulation	2
1.3 Objective.....	2
1.4 Delimitations.....	3
1.5 Gambro AB.....	3
1.6 Outline of the thesis.....	4
2 Methodology.....	7
2.1 Research approach	7
2.1.1 Case study as a research strategy	7
2.1.2 Scientific validity	7
2.2 Data collection.....	8
2.2.1 Interviews.....	8
2.2.2 Observations	9
2.2.3 Document reviews.....	10
3 Our research design.....	11
3.1 Research strategy	11
3.2 Research process	11
3.3 Data collection.....	11
3.3.1 Quantitative data.....	11
3.3.2 Qualitative data	12
3.3.3 Validity	13
3.3.4 Reliability.....	13
3.3.5 Objectivity	14
4 Kidney failure	17
4.1 The kidney.....	17
4.2 Peritoneal dialysis	17
4.3 Peritoneal dialysis fluid.....	18
4.3.1 Drawbacks of the PD-fluid.....	19
4.3.2 3,4-DGE	20
4.3.3 PD-fluid causing less cytotoxicity	22
5 A temperature controlled distribution chain.....	23
6 Good Distribution Practise	25
6.1 Storage.....	25
6.2 Transportation	25
6.3 Inspection	25
7 The Bioett system	27
7.1 Application	27
7.2 TimeTemperatureBiosensor (TTB).....	27
7.3 Bioett Activator	28
7.4 Bioett Detector	28
7.5 Bioett Monitor System.....	29
7.6 Limitations.....	29
8 Previous Temperature Studies	31

8.1 Studies by Gambro.....	31
8.1.1 Transport Temperature Study	31
8.1.2 Transport Vibration Study	31
8.1.3 Warehouse Study	32
8.2 Studies by International Safe Transit Association	33
8.2.1 Background.....	33
8.2.2 Result.....	33
8.3 Studies by University of Seafaring	34
8.3.1 Background.....	34
8.3.2 Result.....	34
9 Container Climate	37
9.1 The external climate.....	37
9.1.1 Temperature	37
9.1.2 Humidity	37
9.1.3 Condensation	37
9.2 The cargo.....	38
9.3 Choice of container.....	38
10 Gambro supply chain structure	39
10.1 The network of distribution centres and satellites	39
10.1.1 PD-fluid markets	40
10.2 Planning the global supply	41
10.3 Planning the operational work	41
11 Distribution of PD-fluid	43
11.1 The physical flow	43
11.2 The order flow	44
11.3 Production Canosa.....	44
11.3.1 Suppliers.....	44
11.3.2 The production process.....	45
11.3.3 The warehouse	46
11.3.4 Shipments to Mirandola	46
11.3.5 Complaints.....	46
11.4 DC Mirandola.....	46
11.4.1 Incoming goods	47
11.4.2 Storage.....	47
11.4.3 Shipping	47
11.5 Prisma	48
11.6 DC Lund.....	49
11.6.1 Planning deliveries.....	49
11.6.2 Incoming goods	49
11.6.3 Nonconforming goods	50
11.6.4 Storage.....	50
11.6.5 Shipping	51
11.7 Schenker AB	51
11.7.1 Distribution	51
11.7.2 Timetable	52

11.7.3 Electronic Data Interchange.....	52
11.7.4 Loading requirements	52
11.7.5 Temperature requirements	53
11.8 The pharmacy	53
11.8.1 Deliveries from DC Lund	54
11.8.2 Storage.....	55
11.8.3 Transport Service.....	55
11.8.4 Reclamations	56
11.8.5 Apoteket AB in the future.....	56
11.9 The patient	57
11.9.1 Dialysis treatment.....	57
11.9.2 Delivery frequency	57
11.9.3 Storage routines	57
11.9.4 Patient holidays	58
12 Empirical Study.....	59
12.1 Presentation of empirical study.....	59
12.2 Initial trial period.....	59
12.2.1 Result of the trial test period.....	60
12.2.2 Adjustments as a resulting effect.....	61
12.3 Final test period.....	61
12.3.1 Result of the final test period.....	62
13 Analysis.....	65
13.1 Distribution of PD-fluid	65
13.1.1 Transport	65
13.1.2 Warehouses	66
13.1.3 Temperature awareness	67
13.2 Temperature studies.....	68
13.2.1 Temperatures harming the PD-fluid	68
13.3 The Bioett system.....	69
13.3.1 Difficulties in monitoring an ambient chain.....	69
13.3.2 Early warning system	70
13.4 Is the TTB applicable for Gambro?	70
13.4.1 The true temperature reaction.....	71
13.4.2 A reversible TTB reaction.....	71
13.4.3 The initial value of 3,4-DGE.....	72
13.4.4 A complex distribution chain	72
13.5 The PD-market.....	73
13.6 Cost savings in the distribution chain	73
13.6.1 Transport routines.....	73
13.6.2 Order routines.....	74
13.6.3 Stock Keeping Units	74
14 Conclusion	75
14.1 Transport and storage.....	75
14.2 Awareness.....	75
14.3 Quality improvement.....	76

14.4 The TTB – in securing the quality?	76
References	77
Appendix 1	79
Appendix 2	80
Appendix 3	81
Appendix 4	82
Appendix 5	83
Appendix 6	84
Appendix 7	85
Appendix 8	86
Appendix 9	87
Appendix 10	88
Appendix 11	89
Appendix 12	90

1 Introduction

This introducing chapter will present the background to the thesis and the reasons for its origin. The chapter will also include the problem formulation, the purpose and the delimitations of the thesis. Finally the structure of the report is presented.

1.1 Background

About 1.2 million individuals in the world suffer from kidney failure and they can only survive when supported by regular dialysis treatment. The dialysis product market is characterized by a stable year-on-year increase. One contribution is a change in priority; today patients are treated, who yesterday were considered non-treatable. At the same time treatment is improving, providing patients with an even longer lifetime. Other factors contributing to a market increase are an increased frequency of welfare diseases like diabetes and hypertension and increasing resources in emerging markets.

The industry trend of globalisation and consolidation is giving three big global companies 70% of the renal product market. As a result, these companies, besides from producing bigger quantities, have to market, sell and distribute to more remote markets.

Gambro is a company, which is a global leader in renal care, healthcare services and blood component technologies. One of the treatments involves a daily use of four 2-2.5-litre bags of peritoneal dialysis fluid for each patient, which means a very complex distribution chain. The dialysis fluid is distributed to the patient's home and an on time delivery is vital. The dialysis fluid is stored and transported at room temperature to provide the patient with a good-quality product. Gambro is today aware of the possibility of reduced quality in warmer countries, such as in central Europe and around the equator.

A recent study, performed by Gambro, has shown that high temperature at storage and transportation might cause a degradation of the peritoneal dialysis fluid, giving toxic substances. Today there is no clear view about which temperatures the product is exposed to during transport and storage. Therefore this issue needs to be acknowledged and investigated by Gambro, for the safety of the patient.

Bioett AB is a company in Lund, which has developed a system for quality assurance of a temperature controlled supply chain. Their core product, a programmable biosensor, monitors the transport's accumulated temperature load, over a specified period of time. Bioett's biosensor has so far mainly been functional for distribution of frozen and chilled goods, but the applicability for room-tempered goods is under development.

Cooperation between Bioett and Gambro is in progress, with the aim to develop a biosensor suitable for room-temperature controls in the supply of peritoneal dialysis fluids.

1.2 Problem formulation

The aim of this thesis is to investigate if the distribution chain includes deficiencies, leading to variations in temperature. Could these possible temperature variations influence the peritoneal dialysis fluid negatively, as having a damaging effect on the quality? The question will be answered by the following studies:

- Mapping the activities of the distribution chain, including the production in Canosa Italy, the distribution centre in Mirandola Italy, the distribution centre in Lund Sweden, the medical retailer, the end consumer and the transports in-between.
- The transport temperature as a function of time will be monitored from Mirandola to Lund with a mechanical temperature logger.
- The accumulated transport temperature will be monitored by a temperature system developed by Bioett AB.

By clearing which temperatures the Gambro distribution chain holds, and how they affect the quality of the peritoneal dialysis fluid, the following questions will answer to if transport and storage is optimised, from a temperature point of view:

- How is the fluid concentration of toxic substances affected by temperature variations in transport and storage?
- Are the actors of the supply chain aware of the risk with exposing peritoneal dialysis fluid to high temperatures?
- Are there any handling recommendations for the peritoneal dialysis fluid?
- If there are any recommendations, are they lived by?
- Will the data from the mechanical temperature loggers correlate to the information stored in Bioett's biosensor?
- Is Bioett's biosensor suitable for room-temperature controls in the supply chain and can the biosensor indirect be an indicator of the quality of peritoneal dialysis fluids? If not, how can it be adjusted to fulfil Gambro's needs?

1.3 Objective

The objective of the thesis is to map the distribution of the peritoneal dialysis fluid, from producer to the end consumer, focusing on the variation in temperature. The mapping will give the employees at Gambro a deeper insight about how the peritoneal dialysis fluids are handled during transport and storage. Furthermore the objective is to, with help of empirical studies, conclude if the temperature monitoring system, developed by Bioett AB is an appropriate tool to reveal gaps in the distribution chain. It will moreover be concluded if Bioett's system in some way, due to temperature results, can indicate the quality of the fluid.

1.4 Delimitations

The mapping of the distribution chain will start with the production in Canosa and end with the end consumer in Sweden. The mapping will include handling, storing, transport and more, but focus on variations in temperature.

When mapping the distribution of peritoneal dialysis fluids from production to the Swedish patient, the authors will come across information and questions about the distribution to other destinations. When the information is considered of interest for the employees at Gambro, it will therefore be included in this thesis. It should though be notified that this mapping will not be in detail.

The measurements of the temperature will only occur between the distributions centres in Mirandola and Lund. This choice is made by Gambro, for the reason not to make the investigation too extensive.

A limitation to the temperature study is the choice of season. In this thesis the temperature will be monitored in October to December, when no high summer temperatures occur. It would be of interest to monitor the temperature through the whole year, but this is limited by the twenty-weeks work period of this thesis.

The temperature data will only show the temperature surrounding the pallets of fluid, not the actual fluid temperature. This thesis will not consider the heat conductivity of the fluid-bags and the cardboard boxes. It should be known that the bag, and especially the cardboard box have some protectiveness against the surrounding temperature. Moreover it is known that the box in the core of the pallet is the least influenced by surrounding temperatures.

1.5 Gambro AB¹

Gambro is a leading medical and healthcare company with 20 900 employees in 40 countries. It all started when Professor Nils Alwall invented the first plate dialyser. The industrialist Holger Crafoord realized what a great innovation this was and founded Gambro 1964 to develop and market the invention.

Gambro's three main activities are to produce dialysis products, to operate dialysis clinics and to supply blood bank technology. These activities are organised into three business areas, Gambro Renal Products (GRP), Gambro Healthcare and Blood Component Technology (BCT). Gambro Renal Products creates and supplies dialysis machines, dialysers, bloodlines and dialysate concentrates. Gambro Healthcare operates about 963 dialysis clinics and provides treatment to about 53 500 patients. The third business area, BCT provides technology, products and systems to blood centres and hospital blood banks.

¹ <http://www.gambro.com>, 2003-09-09

2002 the turnover was 27,6 billion SEK and Gambro Renal Products represented 32% of the income, Gambro Healthcare 61% and BCT 7%.

Gambro Renal Products offers a wide range of products for the three main areas hemodialysis, peritoneal dialysis and renal intensive care. The market share for Gambro Renal Products is about 32% and for peritoneal dialysis the market share is about 2%.

1.6 Outline of the thesis

Chapter 1 – Introduction

This introducing chapter will present the background to the thesis and the reasons for its origin. The chapter will also include the problem formulation, the purpose and the delimitations of the report. Finally the structure of the report is presented.

Chapter 2 – Methodology

The aim of this chapter is to provide the methodological theory, to develop the research design, presented in the next chapter.

Chapter 3 – Our Research Design

The purpose of this chapter is to present the chosen research strategy as well as the methodology used in the research process. Further on, registered case study data is critically analysed, to guarantee a high quality result and conclusion.

Chapter 4 – Kidney failure

This chapter provides an understanding of the human's kidney, the consequences of kidney failure and thus the importance of satisfactory dialyse treatment. The intention is also to give an insight on which negative effect high temperatures have on dialyse fluids and thus the patient.

Chapter 5– Temperature controlled distribution chain

A definition of a temperature controlled distribution chain is presented. The chapter also presents its complexity and the meaning of being frozen, chilled or ambient.

Chapter 6 – Good distribution practise

This chapter contains recommendations, by the commission of the European Communities, on quality-conscious storage, transportation and handling.

Chapter 7 – The Bioett System

The structure and the elements of the Bioett system will in this chapter be outlined. The reader will be familiarised with the technique of the system and its limitations.

Chapter 8 – Previous temperature studies

This chapter summarises three different temperature studies, answering how the external climate influences the inner climate of a truck or container. The studies are accomplished by three unrelated sources, where one is Gambro.

Chapter 9 – Container climate

This is an overview of the three main factors, influencing the inner climate of a container; the external climate, the cargo and the type of container.

Chapter 10 – Gambro supply chain structure

The Gambro network of distribution centres and satellites is described, and how the global supply is coordinated. Furthermore it is presented how the operational work is planned and which IT-system that is used.

Chapter 11 – The distribution of peritoneal dialysis fluid

This chapter is a mapping of the fluid distribution from Italy to Sweden. The introduction of the chapter includes a summary of the physical flow and the order flow, followed by a thorough investigation of all the included parts of the distribution chain.

Chapter 12 – Empirical study

The chapter describes the purpose of the study, how it was planned and performed, and ending with a presentation of the result.

Chapter 13 – Analysis

The problem formulation of the thesis will be answered, giving an insight of the distribution chain, existing temperatures and how they will affect the quality of the product. Moreover the system of Bioett will be evaluated, in terms of how it is suitable for an ambient temperature chain. Most important, it will be concluded if the Bioett system is a valuable tool in securing the quality of dialysis fluid, and thereby the safety of the patient.

Chapter 14 – Conclusions

This is the last chapter of the report, where the most important thesis conclusions will be summarised.

The report ends with references and appendices. To facilitate the reading, appendix 1 is a summary of useful words and definitions.

2 Methodology

The aim of this chapter is to provide the methodological theory, to develop the research design, presented in the next chapter. If nothing else is mentioned the theory behind this chapter is from Yin² and Bell³.

2.1 Research approach

Three overall aspects should be approached when to choose an appropriate research strategy. Which type of question posed, the extent of control the researcher has over actual behavioural events, and the degrees of focus on contemporary as opposed to historical events. These three conditions are each differently related to the five major research strategies: experiment, survey, archival analysis, history and case studies.

2.1.1 Case study as a research strategy

In general a case study can be said to deal with issues regarding the relationship between different factors, interplays among several variables, in a given situation. Furthermore it is said that a case study involves a limited number of respondents, such as one person, a group of persons or an organisation.⁴

A case study is favoured when a “how” or “why” question is being asked about a contemporary set of events over which the investigator has little or no control.

When a research strategy is chosen, the next step is to design the process. Yin defines the process as: *an action plan for getting from here to there, where here may be defined as the initial set of questions to be answered, and there is some set of conclusions (answers) about the these questions.* The main purpose of the action plan is to guaranty high quality answers, to the formulated question.

2.1.2 Scientific validity

Case studies rely on analytical generalization, meaning that the investigator is striving to generalize a particular set of results to a broader theory. For example if another organisation, working under similar conditions, may relate their actions and decisions to the results of the original case. A single case study may present an important contribution to knowledge development and theory foundation, but the validity is of course improved with an increased number. There are three situations where the single case study is preferred:

² Yin Robert K., “*Case Study Research: Design and Methods*”, Second Edition, Volume 5, Sage Publications, 1994

³ Bell Judith, ”*Introduktion till forskningsmetodik*”, second edition, Studentlitteratur, Lund, 1995

⁴ Axelsson, J, ”*Scientific considerations and research design*”, extract from Arbetsmiljödriven kvalitetsutveckling,

- A critical test of a formulated theory.
- An unique or unusual situation.
- Access to an area, which previously has been denied.

The quality of a research design, including worthiness, credibility, conformability and data dependability can be established by applying the four tests summarised below:

- *Construct validity*: establishing correct operational measures for the concepts being studied.
- *Internal validity*: establishing a connecting relationship, whereby certain conditions are shown to lead to other conditions, as distinguished from spurious relationships.
- *External validity*: establishing the field to which a study's findings can be generalized.
- *Reliability*: demonstrating that the operations of a study – such as the data collection procedures can be repeated, with the same results.

2.2 Data collection

A good case study will use as many sources of evidence as possible to reach the objective. No single source has an advantage over the other; in fact they complement each other. The most commonly used methods are interviews, observations and document reviews.

2.2.1 Interviews

Interviews are an important source of evidence, as a well-informed respondent can provide important insights into a situation. The respondent can also provide shortcuts to prior history of the situation and help identify other relevant sources of evidence.

There are three different aspects of the interview that will be presented. First of all the choice of interview, secondly the choice of respondent and last how to record the interview.

Type of interview

There are three types of interviews: informal conversations, guided interviews and standardized interviews. They differ from each other in the construction of the questions, as being more or less structured.

An informal conversation, of an open-ended nature, is often critical to the success of a case study. This interview will give both facts and opinions about events, which will give the interviewer a deeper insight into a matter. An open conversation has the advantage of flexibility and the respondent's perception of relevancy. The disadvantage is that the data, because of the diversity in responses, can be hard to analyse. A way to avoid subjectivity is to seek for contrary evidence as hard as possible.

In the guided interview, the respondent will be interviewed for a limited time and guided with help of a number of key words. The questions must be carefully worded, not leading, so the respondent will provide his own fresh view of the matter. A guided interview has the advantage of being easier to handle without being restrained by specific questions, risking important issues to be missed out.

The last method, a standardized interview, is more like a survey. The questions will be the same and in the same order to make the analysis easier. A big disadvantage with the standardised interview is that important issues might be missed, because of poor recall and inaccurate articulation. Interview data should be corroborated with information from other sources to approach this problem.

Selection of respondents

Respondents are the second issue of importance and the selection is usually chosen according to if the method is quantitative or qualitative. Qualitative methods focus in depth on relatively small samples collected purposefully, whereas quantitative methods typically depend on larger samples selected randomly.

Recording the interview

The interview can be documented by taking notes, by tape-recording or by filming. Tape-recording is the most common way of documenting the interview, since all that have been said can be kept, reviewed and analysed. It is also an advantage for the interviewer since she can review her own effort, and improve the interview until next time. The disadvantage is that the tape-recording can have a hampering effect on the respondent.

Filming the interview is a good technique if the purpose is to document body language and other non-verbal behaviours. As with tape-recording this can have a hampering effect on the respondent, usually even worse.

Making notes is an easy way of registering information, but with the risk of losing information. It is significant to make notes of gathered information, reflections and analysis, soon after the interview.

2.2.2 Observations

There are mainly two different kinds of observations: Direct observation and participant observation. They can be regarded as different levels of researcher involvement, more or less structured.

For an inexperienced researcher, it is preferable to use a structured way of collecting data, to achieve as much valuable information as possible. Irrespective if the observation is direct or participant, structured or not, it is

important to keep the study objective. Being more than one observer is the best way to attain objective and reliable information.

2.2.3 Document reviews

The information collected from a document can be either from a primary- or secondary source. A primary source is defined as, information arising during the project, for an example minutes from a meeting. A secondary source is an interpretation of a document from an earlier research, for example a book or an article based on a primary source.

The main benefit from documents is to corroborate and supplement evidence from other sources. If the documentary evidence is conflicting rather than corroboratory, there is a reason to inquire further into the topic. Document reviews are also a way of finding new questions about communication and networking within an organization. Yin says: *“An experienced investigator reviews previous research to, not only answer what is known on a topic, but also develop sharper and more insightful questions about the topic”*.

3 Our research design

The purpose of this chapter is to present the chosen research strategy as well as the methodology used in the research process. Further on, registered case study data is critically analysed, to guarantee a high quality result and conclusion.

This thesis will test the already formulated theory that high temperatures in the distribution chain exist and effect the fluid negatively. The thesis will also answer if Bioett's Time Temperature Biosensor is a valuable tool; to secure the quality of the fluid, by a temperature monitored distribution chain.

To answer to the title of the thesis, the authors as a first step had to be familiarised with a completely new field; PD-fluids and their time-and-temperature dependent reaction. To evaluate the distribution chain, out of a temperature point of view, it had to be known how the PD-fluid reacts to different temperatures. There has to be a parallel between existing distribution temperatures and its effect on the fluid's quality, to know if the distribution is optimised or not.

3.1 Research strategy

A case study as a research strategy was chosen whereas this thesis was subjected to a specific organisation, a specific situation, which contemporary events we had no or little control over. Our task was to draw conclusions from relationships between different factors to provide good-quality answers to the case question above. The data collection, analyse of the results as well as the conclusions are of both qualitative and quantitative character to give as much validity to the case study as possible.

3.2 Research process

The action plan (figure 3.1 page 15) of the thesis is as a whole built upon a quantitative research method, with statistics as empirical data. To give more validity to the thesis, the research was complemented with qualitative research methods such as interviews, observations and document reviews.

3.3 Data collection

3.3.1 Quantitative data

The statistical data was gathered over a period of eight weeks, including two intervals. The first interval was a trial period during two weeks to secure that everything was going as predicted. This was to guarantee that all involved parts in the distribution chain had the correct information and understanding about the proceedings. Moreover there was time in-between the two periods to evaluate and modify the theory. The second interval was a six-week test period that was providing us with the data to be evaluated.

3.3.2 Qualitative data

During the whole research process, the qualitative data collection was ongoing. At the start of the research, the collection of information was less structured, with the purpose of getting a deeper insight into the matter. This understanding was a prerequisite, giving us the possibility of proceeding with more structured key questions. The qualitative data collection was in the start to triggering further questions, while it in the end was more a tool to support and supplement evidence.

Interviews in the distribution chain

Both conversational and guided interviews were made throughout the thesis. In the beginning of the thesis the authors, gathered information, by conversations at coffee breaks and spontaneous interviews in the hallway. As time went, the authors built up a network of contacts, and more guided interviews (appendix 2-5) were made. The questions to be answered became clearer over time, and thereby the respondents were chosen. One interview would lead to a deeper insight, but also revealing missing pieces of information. This would then initiate a second interview, with a second respondent necessary.

None of the interviews were tape-recorded. The authors documented the information by taking notes both during and after the interviews. It was considered to be the best way of documenting the interview, since the time and place of the interview was not always planned. By spending much time at Gambro, closeness to the respondents were provided and thereby the questions could be re-asked. Since the risk of losing information was minimal, a tape-recorder seemed unnecessary.

Patient interviews

To full-fill the map of the distribution chain, Italian and Swedish patient interviews (appendix 6) were made. The twenty interviews were structured telephone interviews, carried out by the authors and an Italian employee at Gambro.

A dialysis nurse at the University Hospital in Lund made the selection of Swedish patients. Ten random patients were chosen to represent the storage routines of Gambro's peritoneal dialysis patients on the Swedish market. The Sales company in Italy helped the authors to track ten Italian patients, equally spread out into the country. The intention was to gather patient information from two different markets, and thereby see how and if storage- and handling routines differ. The number of patients was chosen, with consideration of not being too many. Telephone interviews limited the selection, but it was the best way to get quick answers and the possibility to ask sequel questions.

The Swedish dialysis nurse and the contact person at Italian Sales, contacted the patients on forehand to achieve approval of their names and telephone

numbers to be handed out for an interview. In Italy an ethical committee was contacted to get authorization of the interviews.

Observations

Observations were made throughout the distribution chain to get a satisfactory picture of the included parts. The authors visited the production unit in Canosa Italy, the distribution centre in Mirandola Italy, the distribution centre in Lund Sweden, a hospital, a pharmacy, and moreover the transport supplier in Sweden and one of their terminals.

The observations were more or less structured. They became more structured over time since the authors gained experience, and learned what to look for.

Document Reviews

During the whole thesis document reviews of primary- and secondary sources were made. The authors tried to come across previous studies, which could be complementary to their own test results. Literature was studied to develop the authors' knowledge and make it possible to ask valuable questions during interviews and observations.

3.3.3 Validity

The quantitative part of the case study was designed with two test periods providing data, to reach a high validity. The statistical data collected, were from two different sources of evidence: Bioett's biosensor and Gambro's temperature loggers. Moreover, the authors reviewed previous logged temperatures, between Gambro's distribution centres and different worldwide markets, done by Gambro at randomly selected shipments.

The validation of the test was dependent on the people handling the goods in the distribution chain. It was a condition that the right information and knowledge were provided to the people responsible at the distribution centre in Lund and Mirandola. They would otherwise be a risk, being the source of failure, not adding or reading the temperature loggers and the self-adhesive labels correctly. This would give incorrect statistical data and the validity of the research would decrease.

3.3.4 Reliability

The reliability of the statistical data could be threatened by loss of information caused by external circumstances, such as the plastic bag being too wet, or the self-adhesive label being lost or torn.

The interviews in the distribution chain were of conversational and guided art, which could lead to information being lost, which was critical to the reliability. The authors, always taking good notes and afterwards comparing them in-between themselves prevented this risk.

The structured patient interviews were critical to the reliability; since the respondents were too few to represent the whole peritoneal dialyse patient population. The authors knew this, when selecting the number, but a bigger survey was not necessary for the purpose. The purpose was to give the reader an insight, into the handling and storage of the fluids in the patient's home.

Both the authors, knowing that two observers would give a more qualitative observation, always carried out the observations together. People notice and experience things individually, seeing things in different perspectives, securing valuable information not being lost.

3.3.5 Objectivity

The authors of the thesis are familiar with the importance of being objective in their data analysis, to provide good validity and reliability.

In an interview of conversational or guided art, it is easy to accidentally ask leading questions and therefore jeopardise the objectivity of the data collection. More structured information forms can prevent this, but it was never an alternative for the research in the distribution chain. An open conversation has the advantage of flexibility and the respondent's awareness of relevancy.

The lack of literature on the subject of this thesis, gave the authors no choice, but to read articles. They are often written, influenced by subjectivity. To secure valuable theoretical knowledge, the articles were always reviewed critically.

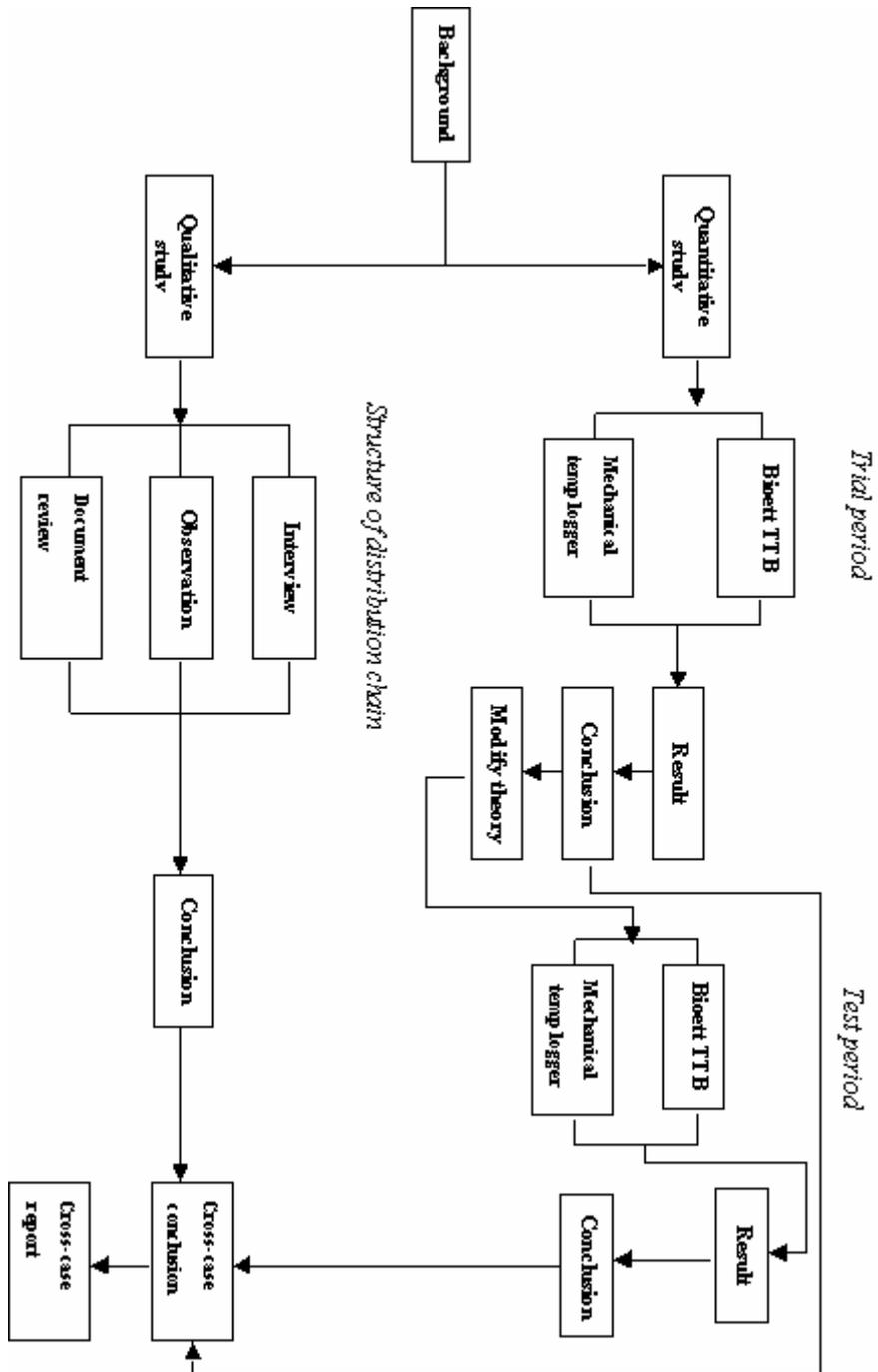


Figure 3.1 The action plan of our research process

Our research design

4 Kidney failure

This chapter provides an understanding of the human's kidney, the consequences of kidney failure and thus the importance of satisfactory dialysis treatment. The intention is also to give an insight on which negative effect high temperatures have on dialyse fluids and thus the patient.

4.1 The kidney⁵

About 1700 litres of blood pass through the kidneys every day. Their main functions are to clean the blood from waste products, remove excess fluid, keep normal body chemistry and produce important hormones. The excretion product is urine. If the kidneys stop working it may be a temporary problem, called acute renal failure. In this case the kidneys can be fully recovered. With a persistently decreased kidney function, referred to as chronic renal failure, the kidneys will never recover.

There are different treatments for chronic renal failure depending on the capacity of the kidney. In worst cases kidney transplantation is the best option, as it can give the patient his/her remaining life back. If the kidney function has declined to about 10% of normal, the patient can be described a special diet, which can delay the start of the dialysis treatment. When only 5% of the kidney function remains, dialysis treatment is needed. There are two kinds of dialysis treatment: hemodialysis and peritoneal dialysis. Hemodialysis purifies the blood outside the body by an artificial kidney. The treatment is performed three times a week for 3-5 hours. In peritoneal dialysis a cleansing fluid is brought into the patient's abdominal cavity, 3-4 times a day, where the peritoneum acts as a dialysis membrane.

4.2 Peritoneal dialysis

Peritoneal dialysis requires plastic bags with dialysis fluid, sterile bloodlines, and in some cases a special machine that helps the circulation of the fluid⁶. The patient has a permanent catheter in the lower abdomen, through which the dialysis fluid is introduced to the peritoneal cavity (figure 4.1). The peritoneal cavity is covered by a thin membrane, the peritoneum, which serves as the dialysis membrane. The peritoneum contains blood vessels and an extensive network of capillaries. When the peritoneal fluid is instilled, the vessels open up and the peritoneum's blood-flow increases. The waste products and the excess fluid in the blood move across the membrane by diffusion. The waste products and the excess fluid are thus removed to the dialysis fluid, which is then removed from the body.⁷

⁵ Gambro Basics, educational material

⁶ <http://www.gambro.com>, 2003-09-09

⁷ Gambro Basics, educational material

There are two different types of treatment modes, Continuous Ambulatory Peritoneal Dialysis, CAPD and Automated Peritoneal Dialysis, APD. CAPD is used without any machines and can be performed at any clean, well-lit place. The cleansing dialysis fluid flows into the peritoneum via a catheter. After a few hours the fluid is drained out and replaced with fresh dialysis fluid. It is close to a continuous process. The fluid exchange is performed four to five times a day. Each exchange takes about 30 minutes. A portable machine, connected to a catheter, is used in the APD treatment. The exchange takes place during nighttime while the patient is asleep. The treatment is ongoing 10-12 hours every night and the patient usually carries fluid in the peritoneum during the day as well.⁸

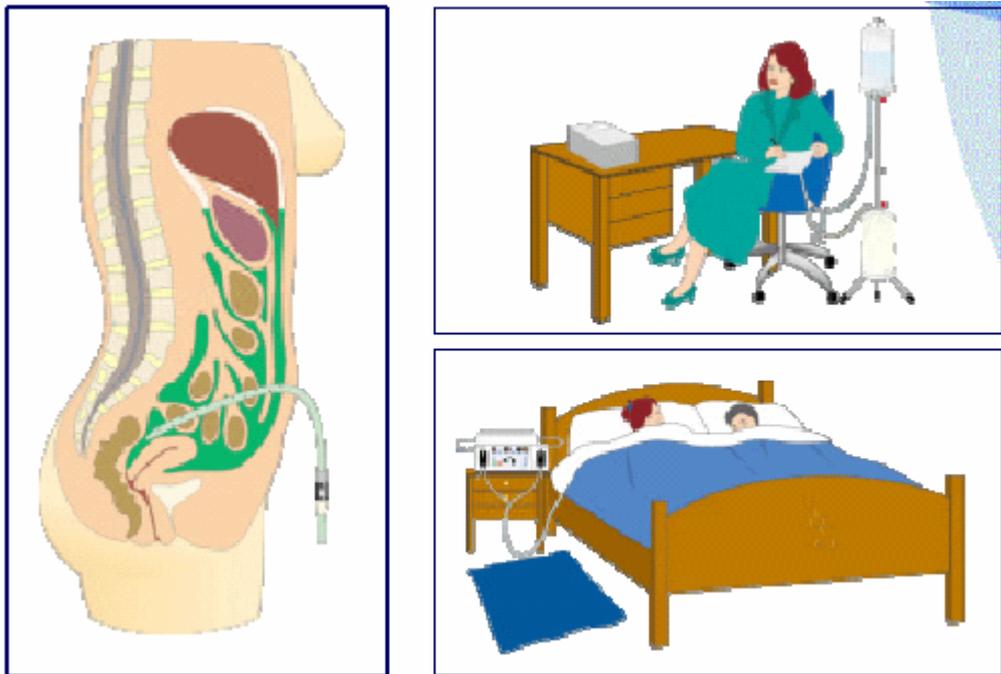


Figure 4.1 Peritoneal dialysis

4.3 Peritoneal dialysis fluid

The peritoneal dialysis fluid (PD-fluid) contains electrolytes, buffer and osmotic agents. The electrolytes are among others Sodium (Na^+), Calcium (Ca^+) and Chloride (Cl^-). The composition of electrolytes is close to that of blood plasma and the reason is to avoid diffusion of the life-important electrolytes from the blood to the dialysis fluid. For example, if the sodium concentration in the dialysis fluid is too low, the sodium from the patient's blood will move to the dialysis fluid. It may lead to so called hypovolemia

⁸ <http://www.gambro.com>, 2003-09-09

during the dialysis, with low blood pressure and muscular cramp as a consequence.⁹

One of the kidney's functions is to generate bicarbonate (buffer), which takes care of the acids formed in the body during the metabolism. Patients with kidney failure cannot produce bicarbonate and the dialysis fluid must provide a buffer. For many years bicarbonate was used as buffer, but due to some practical problems with bicarbonate it is nowadays replaced by lactate.¹⁰

The third component in a dialysis fluid is an osmotic agent. Normally glucose is used because it is cheap and non-toxic¹¹. The glucose prevents the body from drowning in water, since it helps to remove excess fluid and waste products from the blood. Depending on the amount of water needed to be removed, different glucose concentrations are used, for example 1.5, 2.5 or 4.0%. In production of the PD-fluid, bacteria is exterminated by heat sterilization at about 120°C.¹²

4.3.1 Drawbacks of the PD-fluid

During the heat sterilisation, glucose is degraded to glucose degradation products (GDPs). Several of the GDPs have been identified, for example 3-DG, 5-HMF and 3,4-DGE, but the main point of the GDPs is still unidentified. A high amount of GDPs is suggested to be one factor limiting the long-time survival of the peritoneal membrane. The GDPs might also be the reason for patients' death and inflammation of the peritoneum i.e. peritonitis.¹³

There are two kinds of peritonitis: bacterial and chemical. Bacterial peritonitis is when bacteria from the patient, the environment, the equipment or the exit site of the catheter, are brought to the peritoneum and cause an infection. Compared to biological peritonitis, there is no bacterial growth at chemical peritonitis. GDPs cause chemical peritonitis and it may be suspected that they increase the risk for bacterial peritonitis.¹⁴

One case of serious outbreak of chemical peritonitis was observed and documented in Turkey 1996. Within one month, 21 patients out of 55 in total, presented symptoms of peritonitis. They were all using PD-fluid with the same lot number and the colour of the fluid was darker than usual. The researcher concluded a high level of acetaldehyde as the reason behind the peritonitis cases. Another conclusion was that a second degradation product might have

⁹ Gambro Basics, educational material

¹⁰ Ibid

¹¹ Erixon Martin et al, "*PD fluids may be perilous if used too soon after sterilization*", Gambro AB, Lund, 2003

¹² Gambro Basics, educational material

¹³ Erixon Martin et al, "*PD fluids may be perilous if used too soon after sterilization*", Gambro AB, Lund, 2003

¹⁴ Ibid

been the source of the peritonitis. It should be noted that further investigation on this matter was not preceded.¹⁵

Recently the most reactive and toxic GDP, in the PD-fluid, has been identified, 3,4-dideoxy-glucosone-3-ene (3,4-DGE).¹⁶ It is suspected that the 3,4-DGE was the GDP that caused the outbreak of chemical peritonitis in Turkey.¹⁷

4.3.2 3,4-DGE¹⁸

As mentioned above, glucose is degraded into GDPs during heat sterilisation. It is known that 3,4-DGE probably is the GDP, causing chemical peritonitis and therefore it is important to fully understand its reaction to high temperatures. Figure 4.2 is a simplified illustration of the most important GDP reactions, to ease the understanding of the thesis.

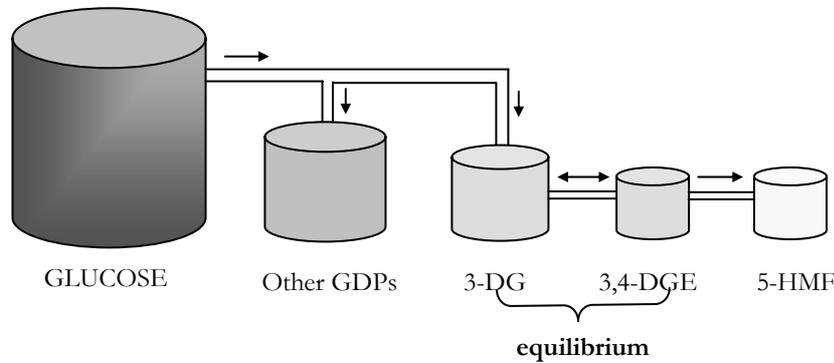


Figure 4.2 Glucose degradation products

The concentration of the toxic 3,4-DGE is dependent on by which speed glucose is transferred from the big tank, and how quickly the 3-DG is transformed to 3,4-DGE. Both the reaction speeds are dependent on temperature, but the speed from the big tank is negligible in comparison to the speed between the 3-DG and the 3,4-DGE.

After heat sterilisation 1-2% of the glucose is transferred to GDPs, where 30% is divided in-between 3-DG and 3,4-DGE. There is a temperature dependent equilibrium between the 3-DG and the 3,4-DGE. The 3,4-DGE contains 3% of the equilibrium volume. To ensure quality by a decreased level of GDP, absorption tests of 5-HMF are made.

¹⁵ Tuncer Murat et al, "Chemical peritonitis associated with high dialysate acetaldehyde concentrations", Nephrol Dial Transplant 15: 2037-2040, 2000

¹⁶ Linden Torbjörn et al, "3,4-Dideoxyglucosone-3-ene (3,4-DGE): A cytotoxic glucose degradation product in fluids for peritoneal dialysis", Gambro AB, Lund 2002

¹⁷ Erixon Martin et al, "PD fluids may be perilous if used too soon after sterilization", Gambro AB, Lund, 2003

¹⁸ Kjellstrand Per, Senior Scientific Advisor, Gambro AB, interview 2003-11-19

Researchers at Gambro suspect that the concentration of 5-HMF, will only reflect the total amount of glucose degraded. This measurement will therefore not show the true concentration of the toxic 3,4-DGE.

In this thesis the authors choose to define quality as a low 3,4-DGE concentration.

Influence from storage temperature

Directly after heat sterilisation, the concentration of 3,4-DGE is very high. As the fluid cools down the concentration will decrease. A low temperature is necessary to reach low levels of 3,4-DGE. The lower the temperature is, the slower is the decrease in GDPs.

Exposing the PD-fluid to high temperatures, even for a short period, will once again increase the concentration of 3,4-DGE. It is important to remember that the required time to decrease the level of 3,4-DGE, will take much longer. The quality of a PD-fluid can thus be destroyed in just a few hours, requiring months to repair. The reaction of the 3,4-DGE is illustrated in figure 4.3.

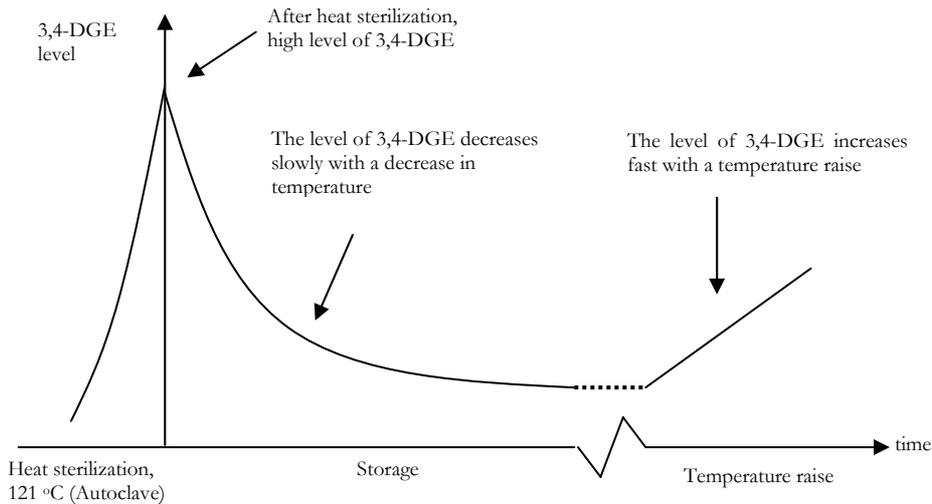


Figure 4.3 The reaction of 3,4-DGE

Experiments have shown that the temperature is the single most important factor for glucose degradation during storage¹⁹. Recommendations are to store the PD-fluid in 4-30°C.

The reaction rate between 3-DG and 3,4-DGE has not yet been fully determined but experiments have been done and together with the Arrhenius-formula approximate reaction rates are calculated. Figure 4.4 illustrates how quickly the reaction increased, with only small temperature increases, giving

¹⁹ Kjellstrand Per et al, "Storage may be as detrimental to PD fluids as heat sterilization", Gambro AB, Lund 2003

what is likely to be dangerous levels of 3,4-DGE. The experiment was using a PD-fluid, 50 days after sterilisation, exposed to 25 and 40°C, to obtain preliminary rate constants. As figure 4.4 illustrates, it took five days to reach what is suspected to be the dangerous level of toxic 3,4-DGE.

Temperature (°C)	Time
30	160 days
36	20 days
40	5 days
46	15 hours
50	4 hours
56	30 min
60	7 min

Figure 4.4 Approximate time required at a certain temperature giving a critical level of 3,4-DGE.

4.3.3 PD-fluid causing less cytotoxicity

The three-compartment bag (trio), figure 4.5, is providing the patient with the possibility to choose between three different glucose concentrations. The trio has a reduced amount of GDPs, compared to the conventional PD-fluid, figure 4.6, and it is thereby not as sensitive to high temperatures. The conventional PD-fluid has approximately ten times the amount of GDPs compared to the trio. The trio has been successful and therefore the Gambro conventional PD-fluid market, in industrial countries, is decreasing in favour for the trio.



Figure 4.5 Trio, the three-compartment bag



Figure 4.6 The conventional PD-fluid

5 A temperature controlled distribution chain

This chapter presents the definition of a temperature controlled distribution chain, its complexity and the meaning of being frozen, chilled or ambient.

A temperature controlled distribution chain includes all storage and transport facilities necessary to ship a temperature sensitive cargo, from the manufacturer to the end user. Nowadays the distribution chain is becoming more and more complex. Generally it involves several transit locations, storage and handling by different parties including airports and docks, a variety of transport facilities such as aircraft and trucks. Moreover the demand of faster, smaller and more frequent deliveries is increasing. The complexity of the distribution makes it harder to control the temperature at storage and transportation, which is highly significant for the quality of the product.²⁰

The UK Medicines Controls Agency reports that 25% of all serious deficiencies of medicinal products, recorded by medicinal inspectors, were related to bad control and monitoring of storage and transport temperatures²¹. It is the responsibility of the producer, to secure the quality and shelf life of the product, by clarifying in which temperature range it is to be stored and transported. A temperature controlled distribution chain is characterised by the demand of being frozen, chilled or ambient.²²

- For frozen goods a temperature, below -18°C must be maintained in all parts of the storage unit. The temperature should be monitored and recorded daily.
- The demand on the distribution of a product needing to be chilled is to keep the temperature between the freeze point and 8°C. The product must not freeze, since the protein of the product might denature. Freezing may also cause physical unstableness.
- There are many definitions of ambient storage requirements. Some say that the product has no requirements on temperature, other say that the temperature of the cargo should keep the external air temperature at a transport. The authors of this thesis define ambient temperature as room temperature, 25°C.

²⁰ Kayum Robert, "Temperature-controlled distribution in the health Care industry", Business Briefing PharmaTech, Business Briefings Ltd, London, 2002

²¹ Kayum Robert, "the supply chain is no longer a weak link in the global Pharmaceutical industry", Pharmaceutical Manufacturing and Packing Sourcer, Samedan Ltd, London, 2002

²² Taylor John, "Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products", the Pharmaceutical Journal, vol 267, London, 2001

A temperature controlled distribution chain

6 Good Distribution Practise²³

This chapter contains recommendations, by the commission of the European Communities, on quality-conscious storage, transportation and handling.

Good distribution practice, published by the commission of the European Communities, is a quality assurance, which ensures that products are consistently stored, transported and handled under recommended conditions.

The quality system should ensure that:

- Observations of the storage conditions, including transportation, are made at all times.
- An adequate turnover of the stored medicinal products takes place.
- The products are stored in appropriately safe and secure areas.
- A tracing system that enables any faulty product to be found and an effective recall procedure.

6.1 Storage

When arriving at the distribution centre, the products must be protected from bad weather during unloading and it is preferable if the arriving area is separated from the storage area. In the storage area the temperature should be monitored and recorded periodically and the result should be reviewed regularly. The temperature equipment should indicate when the specific temperature range is not maintained. To ensure stock rotation there should be a “first in first out” system. It is also important to check expire date on the products. If a product is beyond expiry date it should be separated from usable stock and should not be sold or supplied.

6.2 Transportation

The transportation of medicinal products must be arranged in such a way that their identification is not lost and the products must be traceable. The goods should not be subject to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to attack by microorganisms or pests. If the product requires controlled storage temperature, it should also be transported with controlled temperature.

6.3 Inspection²⁴

In certain cases when an inspection is made and the guidelines are not followed, the company can be charged a penalty fee. The company will also lose some of their goodwill and good-quality reputation.

²³ Council Directive 92/25/EEC

²⁴ Sjögren Anette, Qualified Person, Gambro AB, interview 2003-10-02

7 The Bioett system²⁵

This chapter outlines the structure and the elements of the Bioett system. The reader will be familiarised with the technique of the system and its limitations.

7.1 Application

The Bioett system is a tool to secure the quality of temperature sensitive goods, by monitoring the time- and temperature effect of the supply chain. It has been applied in frozen- and chilled supply chains, where temperature conditions during handling, storage and transport are crucial to ensure the quality of a product.

The system will monitor the temperature in the supply chain and reveal if the chain has been subjected to temperatures, possibly disadvantaging the product quality. Live checks in the supply chain, will identify critical points and help in managing logistics and distribution to better quality.

7.2 TimeTemperatureBiosensor (TTB)

Bioett has developed a programmable biosensor, which measures the accumulated effect of the temperature, of the transport, over a period of time. The biosensor, in the form of a self-adhesive label (figure 7.1), is a unique combination of electronics and biochemistry.

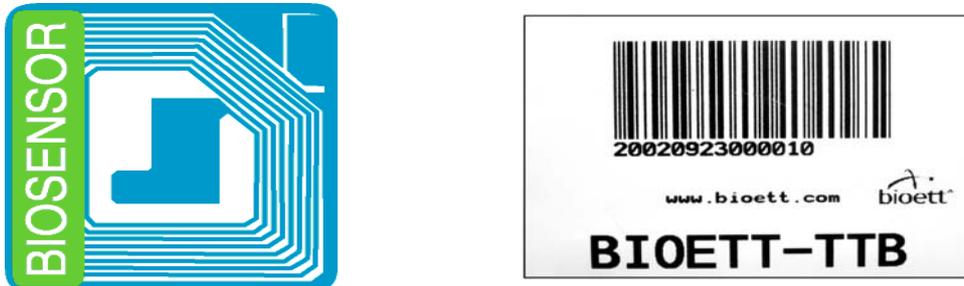


Figure 7.1 An illustration of the TTB

The electronics consists of a passive radio frequency circuit, which is a well-spread technology, used for detecting theft in stores. The circuit is modified in a way that it is broken by a biosensor containing an enzyme that is responding to temperature changes. The enzymatic reaction increases the electrical signal from the circuit. As the temperature rises, the enzymatic reaction rate increases and the electrical signal will increase in intensity. The enzyme reaction can be seen as a clock, which increases its ticking speed with an increased temperature. The enzyme reaction is based on the Arrhenius formula and is

²⁵ <http://www.bioett.com>, 2003-10-01

differently set according to if the TTB is monitoring a chilled- or frozen supply chain. It is the enzyme composition that indicates at which speed the electrical signal should increase. Different TTBs are obtained by varying the amount of enzyme, supplying chains from a few days up to a few months, to be monitored. Chilled as well as frozen supply chains are covered by the system.

The TTB was originally developed to secure the chilled food chain, at a constant temperature. The TTB signal increases with a constant value every unit of time. The predetermined value is set in line with the present distribution chain and to which a normal temperature it is subjected. When the product suddenly is exposed to temperatures exceeding the normal temperature setting, the TTB will increase its predetermined value and signal that it has been exposed for a higher temperature.

A TTB for frozen food chains has also been developed. The enzyme reaction will only react with temperatures exceeding -18°C . The signal value will add on every time the product is subjected to temperatures above -18°C , and the final value will indicate to which extent the frozen supply chain has been broken. By indirect means, a below temperature performance will effect the shelf life.

The TTB is the part of the Bioett system that will follow the product throughout the supply chain. It is placed on the secondary package (carton), where it easily can be scanned.

7.3 Bioett Activator

The activator (figure 7.2) is a machine producing the TTBs. When the TTB is manufactured it will directly activate the enzyme in the TTB and thus set the starting point for the TTB.

The activator is designed to produce up to 1500 TTBs per day, in order to label every carton. In most cases the activator is located at the customer, since it is important to activate the TTB as close to the production as possible. In Gambro's case the TTBs are manufactured and thus activated at Bioett and then frozen to pause the reaction. The TTBs will be kept frozen until used by Gambro.

The activator also contains a bar code printer, giving each TTB a unique identification that allows traceability.

7.4 Bioett Detector

The detector (figure 7.3) is a handheld scanner, used to read the TTB's electrical signals at chosen points along the distribution chain. The electrical signal is translated to a value, which the detector reads and stores.



Figure 7.2 Bioett's activator



Figure 7.3 Bioett's detector

7.5 Bioett Monitor System

Information from the detector will be downloaded to a server and stored in a database. In the database, the information reveal whether there are any deviations in the temperature controlled distribution chain.

The values from the TTBs will be plotted in a graph with a regression line. The line will show the predetermined value, which is set by the normal temperature of a specific distribution chain. On forehand it will be decided how much the plotted values are allowed to differ from the regression line to be in the allowed interval. If the plotted value for a specific transport will be plotted outside this area, it is a sign that the transport temperature has been too high.

7.6 Limitations

One limitation with the TTB is that it demands many readings of the TTBs, to get a fully evaluation about the transport. With few readings it is hard to indicate where the temperature possibly has been out of normal. To store temperature information along the whole test interval, a temperature logger can be used as an alternative.

Another limitation for the research in this thesis, is that the self-adhesive label is placed on the outside of the pallet's shrink film. This is where the temperature will be registered, not inside the secondary package (carton) that contains the plastic bags of dialysis fluids, where the temperature control is critical. This is mainly a problem during seasons where the temperature diverges most from 20°C. For example, during the summer when the pallets are exposed to sun radiation; the chances of having the same temperature, on the inside and the outside, are the smallest.²⁶

²⁶ Olsson, Ousbäck, "Säkerställande av en oavbruten kylkedja", master thesis, Lund Institute of Technology, Lund 2003

8 Previous Temperature Studies

This chapter summarises three different temperature studies, answering how the external climate influences the inner climate of a truck or container. The studies are accomplished by three unrelated sources, where one is Gambro.

8.1 Studies by Gambro

8.1.1 Transport Temperature Study²⁷

2000 Gambro executed temperature studies of the worldwide transportation between different distribution centres and markets. The study took place during one year and the intention was to evaluate existing temperatures in the distribution chain. Mostly container transports were evaluated.

The result (appendix 7) revealed several transports with temperatures above 30°C. This was mainly in the summer months June, July and August. Most eye-catching was the transports to Malaysia. The temperature was above 30°C every month. The highest measured temperature was 36°C and it occurred in transports to Saudi Arabia and Yemen. The evaluation of the study resulted in reefer containers and tempered trucks in the distribution from DC Lyon, France to USA, Canada, Australia and Japan.

8.1.2 Transport Vibration Study²⁸

Gambro has during 2002 and 2003 performed transport vibration tests, with the intention to evaluate if it may have a damaging effect on the product. The logger used in these tests also registered temperature, which has been of value for this thesis.

Four test episodes were studied (figure 8.1): three from Sondalo, Italy to Lund, Sweden and the fourth between Sondalo, Italy and Busan, Korea. The test intervals included storage before transport.

Between Sondalo and Lund the means of transportation was truck and between Sondalo and Busan it was by boat. A refrigerated container was used in the sea transport to Korea. All tests were performed during summer except one in November, between Sondalo and Lund.

The average temperatures monitored between Sondalo and Lund were 23.6, 25.4 and 18.9 °C. The maximum temperatures documented were 28.1, 28.8 and 22.9 °C.

Between Sondalo and Busan the maximum temperature was 28.4°C and the average temperature was 24.8°C. The container shipment by sea showed a stable temperature of 18 °C.

²⁷ Joachimsson, Ingvar, Manager Quality and Control, Gambro AB, 2003

²⁸ Flank Peder, Development Engineer, Gambro AB, Transport Studies, 2003

	Sondalo-Lund	Sondalo-Lund	Sondalo-Lund	Sondalo-Busan
Max	28.1	28.8	22.9	28.4
Min	19.9	17.1	9.9	17.9
Average	23.6	25.4	18.9	24.8

Figure 8.1 Temperature results from the vibration study (°C)

8.1.3 Warehouse Study²⁹

2001 a study was made by Gambro to evaluate the temperatures of six warehouses in Asia. It was performed during the summer. It can be noted that the worldwide warehouses in general do not have air-conditioning, but fans. The warehouse temperatures are regularly monitored.

The result from the study (figure 8.2), shows average temperatures between 23-31°C, with more than half over 30°C. The highest peak is measured to 38°C in the Koga warehouse.

Warehouse	Period 1		Period 2		Period 3		Period 4	
	June 2001		July 2001		August 2001		September 2001	
	Average 24h	Peak	Average 24h	Peak	Average 24h	Peak	Average 24h	Peak
Hong Kong	-	-	-	-	31	35	31	34
Taipei	-	34	30	34	31	35	30	34
Koga	-	-	-	-	28	38	24	29
Tokyo	23	27	29	34	28	32	25	30
Ilsan	23	26	24	28	24	28	22	27
Shanghai			29	32	27	29	26	28

Figure 8.2 Warehouse temperatures in Asia

²⁹ Joachimsson Ingvar, Manager Quality and Control, Gambro AB, 2001

8.2 Studies by International Safe Transit Association³⁰

8.2.1 Background

In summer 2001 ISTA, International Safe Transit Association, undertook a research project to identify and document extreme high temperatures in a steel-sided trailer. The project took place in the hot climate in the United States' southwest. It should be noted that data were collected in a worst-case manner. The data is not typical for vehicles in general and only a small part of the cargo were exposed for the highest temperatures.

To collect the data a battery-powered temperature logger was used, which monitored both the temperature and the humidity. The project included seven trips, starting in Dallas and ending in Phoenix. Each trip took 48 hours, except for two that, due to holidays, took 112 hours respectively 90 hours. A climatic centre provided data on outside temperatures and it varied between 17-38°C. Normally the outside night temperatures were below 25°C and the maximum temperatures occurred in the afternoon.

8.2.2 Result

The most eye-catching inner temperature result was an one-hour peak of 58°C. This occurred in an outside temperature of 38°C.

Three transport studies, each of different distance and external temperature, showed for how long the inside trailer's temperature was kept above a certain temperature (figure 8.3). Note that the time of the maximum temperature is accumulated over the total transport time.

Time of transport (hours)	External Temperature (°C)	Inner Temperature (°C)	Accumulated time (hours)
48	20-35	>38	13
		>49	3
90	20-40	>38	18
		>49	1
112	21-41	>38	28
		>49	7

Figure 8.3 Temperature results on a trailer's inner climate.

A conclusion of the tests was also if the humidity inside the trailer was high, the trailer temperature was low even though the outside temperature was high. The graphs from two of the trips can be found in appendix 8 and 9.

³⁰ http://www.ista.org/Knowledge/ISTA_Temperature_Report-2002.pdf, 2003-10-21

8.3 Studies by University of Seafaring³¹

8.3.1 Background

A meteorology study group at the Warnemünde-Wustrow University of Seafaring, Germany studied internal temperatures of a container during 1970. The group investigated, which influence solar radiation, has to the temperature inside containers. The containers used were standard containers with monitoring equipment.

Chapter 9 will include a fully presentation of which factors that influence the inner climate of a container. This chapter will furthermore give an explanation to a standard container.

8.3.2 Result

The study resulted in a definition of four different climate groups, each differently influenced by the solar radiation (figure 8.4).

- Class A: This class means less than 3 hours of sunshine per day and occurs primarily in Central Europe during autumn and winter months. The influence of solar radiation was small and the temperature inside was on average 2.0°C above the outside temperature.
- Class B: Means 4-8 hours of sunshine per day and describes the climate of autumn and spring months in Central Europe. The solar radiation has a weak effect and the inner temperature of the container was on average 5.2°C above the external temperature.
- Class C: This type of climate describes the summer in Central Europe and means up to 12 hours of sunshine a day. The effect of solar radiation is moderate and the temperature inside the container gets on average 11.5°C higher than the outside temperature.
- Class D: The last class of climates illustrates a subtropical climate with more than 12 hours of sunshine a day. The solar radiation has a strong effect and the inside temperature is on average 17.3°C higher than the outside.

It should be noted that the deviation between inner and external temperatures in classes presented, are showing average temperature results. Therefore the temperature might be higher. For class D, 25.5% of the values measured, had a temperature difference between inside and outside of 20-25°C. In this case the container temperature measured 50-55°C.

³¹ <http://www.containerhandbuch.de>, 2003-10-21

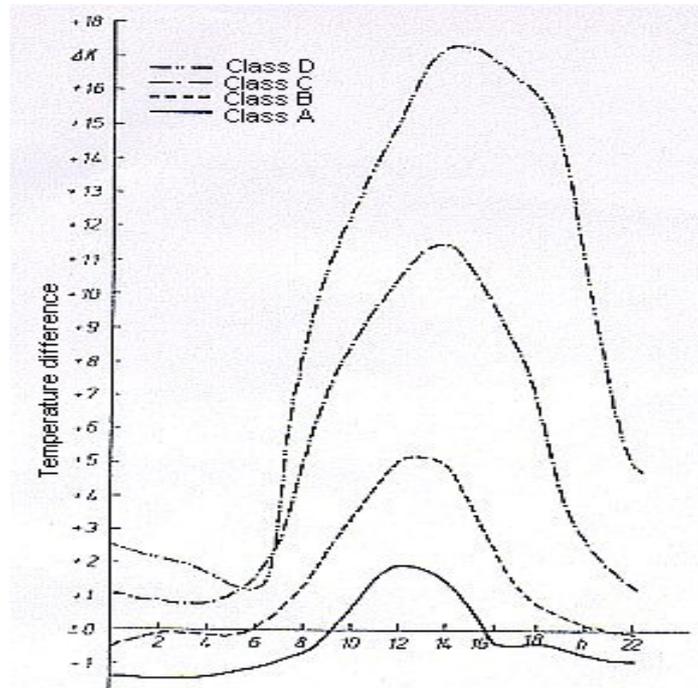


Figure 8.4 Average daily variations in overheating of the air inside a container, plotted by radiation class.

Previous temperature studies

9 Container Climate³²

This chapter overviews three main factors, influencing the inner climate of a container; the external climate, the cargo and the type of container.

9.1 The external climate

The climate inside a container is affected by the external climate conditions determined by the transport route, the season, the time of day and the weather conditions, such as rain or sunlight. It is hard to predict how the container climate will change, as the conditions vary greatly, from one transport operation to another. Still it is important with an awareness of how the factors interact when assessing the risk of transportation.

9.1.1 Temperature

The air temperature inside a container is, apart from the sun radiation, affected by the external air temperature and wind. As an average, the internal air temperature is higher than the temperature of the external air.

Substantial temperature variations inside the container occur, due to the variation in levels of solar radiation over a day. The variation in temperature is most extensive directly under the roof, where the solar radiation is the strongest and hence the greatest heat exchange. As the container is being exposed to rainfall, the roof will also cool of more rapidly than, for example, the sidewalls.

The air inside the container will be heated above the external air temperature even under normal conditions, but the temperature variation of the cargo will not be as noticeable. This means that the temperature in the heart of a cargo adapts to changing external temperatures rather slowly.

9.1.2 Humidity

The humidity conditions in the container has to do with internal factors, such as the characteristics of the cargo and its packing. Additional moisture in the container, for example rain or snow, will increase the humidity. Incoming outside air usually has no negative impact upon humidity. Since the temperature prevailing inside the container is generally higher than the outside temperature, incoming air will reduce relative humidity.

9.1.3 Condensation

Any mass of air has a dew point temperature. Condensation forms when air is cooled below its dew point and as general rule there is always a risk of condensation when cold surfaces come into contact with warm and moist masses of air.

³² <http://www.containerhandbuch.de>, 2003-10-14

9.2 The cargo

The cargo including the wooden pallet, its contents and the surrounding package material also influences the container's inner climate. In a closed container, the cargo is always the largest source of moisture and therefore it is important to load the cargo as dry as possible.

The water content and the biotic activity of the cargo, interacts with the humidity, ventilation and temperature conditions. The cargo strives to establish an equilibrium moisture content, by releasing water vapour into the container air, when temperature is rising. Vapour will reach the cold container wall and roof, giving condensation. Despite sunshine during the day, the container roof will not dry, giving a continuous increase in condensation. As a result water will start to drip onto the cargo.

Necessary requirements for storage climate conditions are based on the level of water content and biotic activity.

9.3 Choice of container

The choice of container is as equivalent to the container's cryptoclimate, as the cargo and the external climate. The theory above relate to conditions in a closed standard container. Wear and tear over the years in use is the reason why the standard container is not absolutely water vapour tight. Especially the door is a source of leakage, where moisture will find its way in and result in condensation. An open or refrigerated container would respond differently to the external climate.

A refrigerated container (reefer) is an insulated container with a built-in refrigeration system. The reefer is capable of maintaining the temperature of a demanding cargo that has to be kept frozen, chilled or warm.

The container contains a motor generator, which provides the container with electric power when it is on a route inland. Whenever the container is shipped on a vessel or placed in a terminal, it is connected to the power source onboard or to the power source of the terminal.

Containers with insulating behaviour, low heat-transfer value of the walls, are optimal for short voyages of precooled cargoes. The insulating effectiveness is not to be trusted, for longer voyages. Moreover the limited heat exchange might delay the desired temperature adjustment of the cargo. A cargo loaded in colder conditions will arrive in tropical ports at a lower temperature than the surrounding, creating condensation.

10 Gambro supply chain structure

This chapter describes the Gambro network of distribution centres and satellites, markets and how the global supply is coordinated. Furthermore it is presented how the operational work is planned and which IT-system that is used.

10.1 The network of distribution centres and satellites³³

Gambro has a worldwide network of distribution centres (DC) and satellites, located close to the main markets, coordinated by global transports. There are in total six DCs: four in Europe, one in USA and one in Korea. The DCs are responsible for the global supply, while the satellites only supply the demand of a specific market.

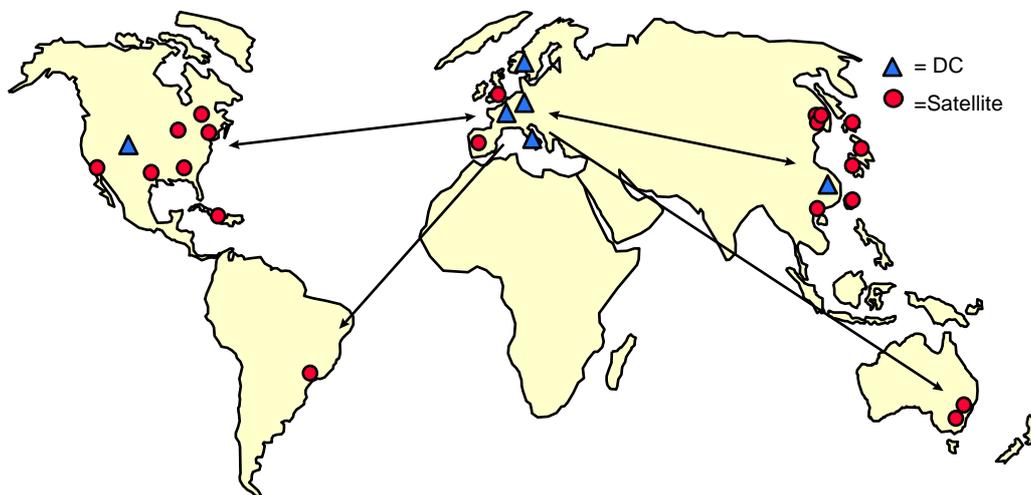


Figure 10.1 The global supply chain

A satellite is defined as a terminal receiving goods, from either a DC or a production unit. At the satellite, the goods will be consolidated with other incoming goods or broken into smaller shipments. The storage space of a satellite is substantially smaller than of a DC, since they supply a smaller market. A DC not only supplies a bigger market, but also other DCs or satellites.

Market size or economical aspects are reasons behind the placement of a satellite, while a DC is closely related to the production unit. For example there are many satellites in Northern America, for economical reasons. Each satellite

³³ Sandberg Per, Manager DC Lund, Gambro AB, interview 2003-09-17

is supplying a small market, since the cost of land transportation is very high, compared to the rest of the world.

10.1.1 PD-fluid markets³⁴

Gambro has in total 2850 PD-patients, which covers 2% of the world market. Conventional PD-fluid covers 90% of the world's PD-patients, which is not in favour for Gambro. Only 10% of Gambro's PD-fluid portfolio is conventional fluid and the other 90% is the three-compartment bag (trio). The business growth for PD in total was in May 2003 more than 20%.

More than half of Gambro's PD-patients are located in Europe and the single largest market is Korea. Korea has 40% of Gambro's total patient population. Gambro conventional PD-fluid markets are mainly Europe, but also Korea and Kuwait. The markets for the trio are almost the same but with Australia and Canada in addition. Gambro provides PD-fluids to some countries under description, for example Libya. This means that the PD-fluid is not registered in these countries and therefore a description is needed. Figure 10.2 illustrates both conventional and trio markets, with the exception for the description countries. For divided markets see appendix 10.

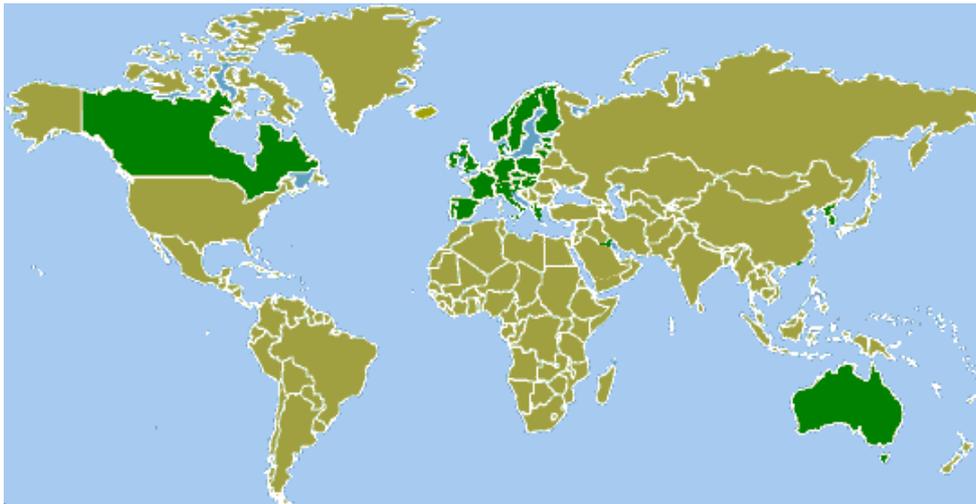


Figure 10.2 Gambro PD-markets 2003

³⁴ Gambro AB, Intranet, 2003-12-09

10.2 Planning the global supply

The global supply chain planner is responsible for the overall coordination of the supply chain (figure 10.3), securing stock availability and managing total supply chain stock levels. Furthermore the global customer service level and internal service level, between the DC and satellite, has to be set and guaranteed.

10.3 Planning the operational work

Different IT-systems are used among the Gambro affiliations, where Gambro Sweden uses SAP R/3.

i2 is an interface, gathering data (inventory, in-transit stock, orders, shipments to end customers and fixed production plans) from the five main local IT systems. i2 is covering the DCs in Lund, Mirandola, Denver and Hechingen and the satellites in Madrid and Huntingdon. All sales subsidiaries, covering five continents, are providing a rolling twelve-month statistical forecasting based on historical sales in i2.

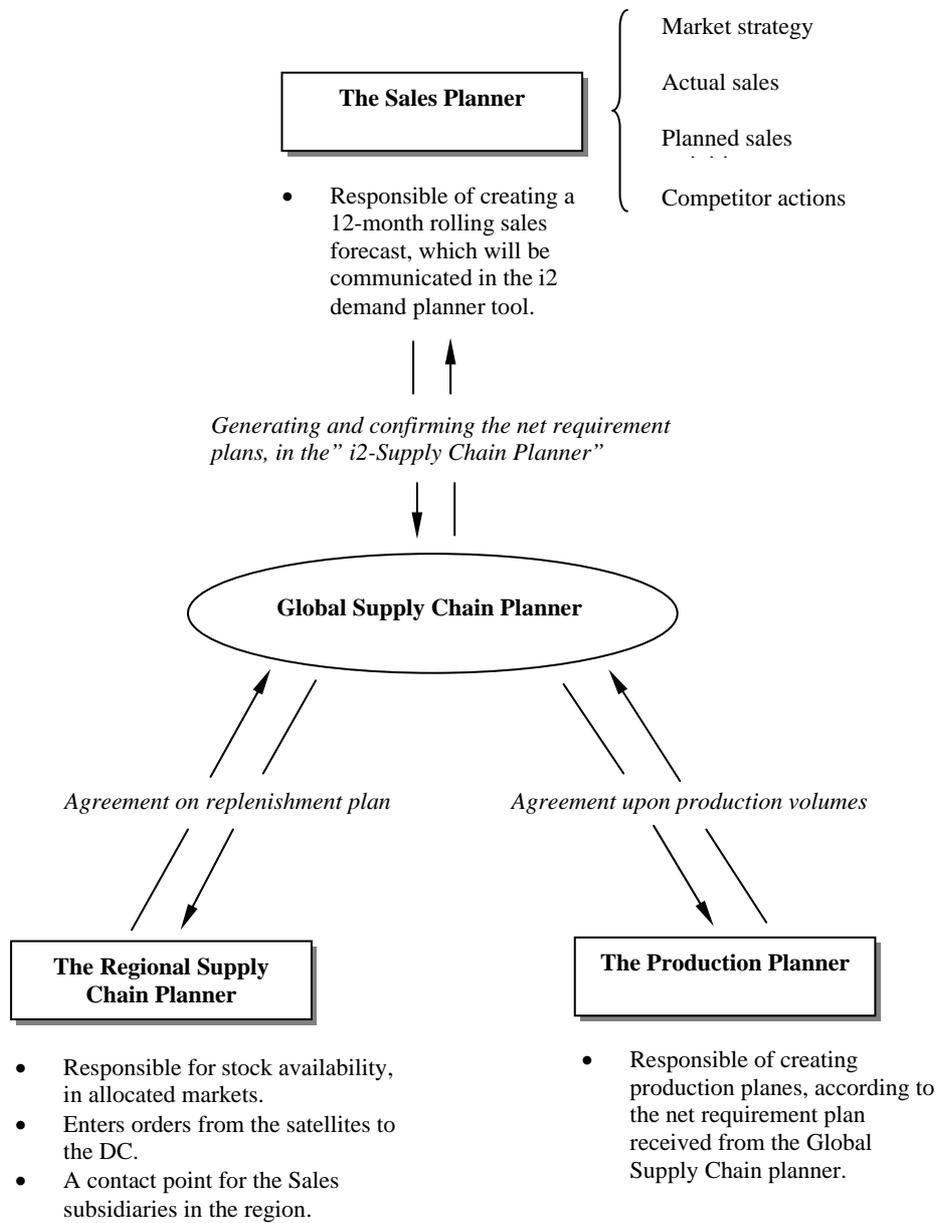


Figure 10.3 Illustrating the global supply planning

11 Distribution of PD-fluid³⁵

This chapter is a mapping of the PD-fluid distribution from Italy to Sweden. The introduction of the chapter includes a summary of the physical flow and the order flow, followed by a thorough investigation of all the included parts of the distribution chain.

11.1 The physical flow

The distribution chain of PD-fluid consists of several actors, starting with the production in Canosa. Finished goods will be delivered to the distribution centre in Mirandola. From Mirandola the PD-fluid is distributed to all global markets, via distribution centres and satellites. This thesis is focusing on the Swedish market. To reach the Swedish market, the PD-fluid is transported to the distribution centre in Lund, from where it will be spread out to different pharmacies in Sweden. The PD-fluid will reach the patient, via a pharmacy.

Figure 11.1 views the actors of the distribution chain from Italy to Sweden. Section 11.3 to 11.9 will more in detail describe the different actors of the distribution chain between Italy and Sweden.

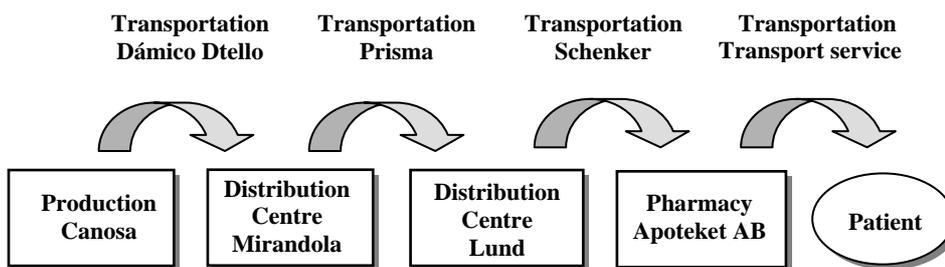


Figure 11.1 The distribution of PD-fluid from Italy to Sweden.

³⁵ If nothing specific is mentioned, all information in this chapter is gathered through interviews and observations. The Gambro Intranet has also been a source of evidence.

11.2 The order flow

The order flow, summarised in figure 11.2, is reversed compared to the physical flow. It is the customer demand that indirectly triggers the production, a so-called pull-strategy. A pull-strategy, producing towards actual demand, requests good visibility of information and co-ordination.

The patient, who is in monthly contact with the pharmacy, initiates the order flow of the PD-fluid. The pharmacy puts in an order to Swedish Sales every third or fourth day. Swedish Sales informs DC Lund via the SAP/R3 system, about the required delivery. DC Lund initiates an order to DC Mirandola via fax. The order is received in Mirandola and is placed in the Italian IT-system. The order will, when delivered, change the stock level and therefore an order to the production is made. With the same IT-system the main part of this process could have been eliminated.

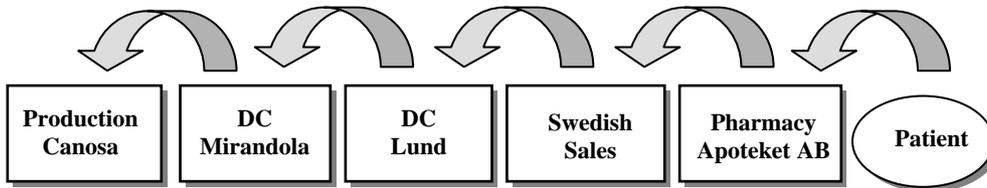


Figure 11.2 The order flow of PD-fluid

11.3 Production Canosa

In year 1988 the Gambro group decided to produce dialysis fluid in Italy, to cover the domestic market. The production started in Bologna 1989, with a new plant in Canosa 1995 that could produce for the Gambro affiliates in Europe. An enlargement of the Canosa plant was made in 2002, due to an increase in the PD-fluid market. The plant has a maximum production capacity of 12 million litres per year and with further investment the capacity can be increased to 20 million litres per year. The production in Canosa is planned to meet the net requirement plan, received by the global supply chain planner (figure 10.3).

The plant produces both conventional and trio PD-fluid but as the market for trio is growing, only 10% of the production is conventional fluid. Canosa produces 150 stock keeping units (SKUs), which is because of all different sizes and mainly because the different labels required for different countries. It is currently under progress to reduce the SKUs, by combining different languages and requirements in the same label.

11.3.1 Suppliers

Canosa has in total 20 raw material suppliers, where five cover 80% of the total volume and turnover. Direct material (dM) covers 60% of the total

manufacturing cost (TMC) and 90% of the dM cost is due to the plastic components.

11.3.2 The production process

There are one hundred three shift employees, producing PD-fluids after a three month rolling forecast, communicated in the i2 demand planner tool. The production is evenly balanced through the year and the forecast is weekly updated from the DC Mirandola for five weeks ahead.

The production process is divided into six steps:

1. Water for injection

The raw water is chemically pre-treated, softened, treated for pH adjustments, double-stage reverse osmosis and distilled.

2. Preparation of solution

The preparation of solution is made in tanks of stainless steel, where raw material is added to 10.000 litres of water. The finished solution of 12.000 litres is filtered and pH adjusted, before the final filtration of carbon dioxide.

3. Filling of bags

Production operators perform the filling of the bags using a two-lined automatic filling equipment. There is one fully automatic line. By weighting the bag in the beginning and end, the dosage is checked at regular time intervals. Before reaching the vacuum packing station, the bag will be marked with a lot production number, expiry date and other variable data.

4. Packing under vacuum

After the automatic vacuum packing, the bag is loaded on a trolley and brought to the sterilisation by an automatic loading/unloading system.

5. Sterilisation

The sterilisation process is carried out in an autoclave, with a temperature of 120°C. This process will give a completely sterile bag of fluid but with an increased level of GDPs.

6. Packing

Each bag is submitted to visual inspection and, in groups, put into a carton box. The box is labelled with an identity and a bar-code for traceability.

In the production unit it was observed that the PD-fluids were packed before they were completely cooled down to room temperature. The temperature was approximately 40°C. The fluid bags packed together, will insulate each other and will therefore decrease in temperature rather slowly. The last batches before the weekend, will be packed and labelled on the following Monday. These bags will therefore have time to cool down, and reach the warehouse at room temperature.

11.3.3 The warehouse

The warehouse has 2500 pallet spaces, including raw material and finished products.

The packed and labelled carton boxes are brought to the warehouse, where they before shipment to the distribution centre in Mirandola, will be in quarantine for fifteen days. It is important not to release the fluid too soon after sterilisation, since the level of GDPs will be extremely high. As section 4.3.2 describes, it is ultimate for the decrease in GDPs to have a slow decrease in temperature after the high temperature sterilisation.

The temperature of the warehouse is not controlled and therefore there is no possibility to either cool or heat the inside temperature. The temperature can during summer, exceed the temperature requirement of 30°C.

11.3.4 Shipments to Mirandola

There are shipments to Mirandola every day, Monday to Friday, two to three times a day. The transport supplier is Dámico Dtello and during the authors' visit to Canosa, it could be observed that steel sided trucks were used. It could also be observed that the truck was loaded by the warehouse operators.

The truckloads for Mirandola are always full, giving room for 38 pallets. A double-truck has room for 60-80 pallets. One pallet includes the same volume of fluid, but the amount of bags can vary according to the size of the bag.

The distance to Mirandola is 500 kilometres and if Mirandola is reached late at night, the truck is parked until unloading the following morning.

If no emergency appears, the finished products are always distributed through the distribution centre in Mirandola. The PD-fluids will be distributed directly from Canosa, under consideration that the quarantine time has expired, when the hospital demand is urgent.

11.3.5 Complaints

All customer returns of the PD-fluid, shall be sent and evaluated by the production in Canosa. The goal for the production is to have less than ten returned bags per 100 000 produced units. Today the level is reached by five bags out of 100 000 produced units. The complaint is in most cases cosmetic, where the bag can be dirty or leaking.

11.4 DC Mirandola

DC Mirandola is an automatic controlled warehouse with 28080 pallet spaces and equipped with a conveyor system. An automatic warehouse is considered to be the best choice because of the high volumes handled. The risks with an automatic warehouse are machine failures and human mistakes.

DC Mirandola stores PD-fluid, PD-equipment, raw material for the production in Mirandola (Dasco), finished products from Dasco (monitors, PD-lines, bloodlines). The PD-fluid is distributed to other DCs, satellites and the Italian market.

11.4.1 Incoming goods

The PD-fluid from Canosa arrives to DC Mirandola, Monday to Friday. Incoming goods are received between 06-22 o'clock and two or three shipments from Canosa arrive any time during the day.

When the pallet is unloaded by one of the DC operators, an ID-label is placed onto the shrink film. The ID-label identifies the kind of goods on the pallet and is required for tracing the products in the automatic warehouse. The pallet is transferred to another operator who inspects the pallet with goods to secure that there has not been any transport damages on the package. The same operator labels the wooden pallet with a second ID-label made for the conveyor system. When labelled and inspected the pallet is moved to the conveyor band, where it will be registered as inventory. The conveyor band moves the pallet to a station where one of sixteen trolleys transfers the pallet into storage.

11.4.2 Storage

The computer system selects a pallet place according to the size of the pallet and the storage availability. To minimize the effect of machine failure, pallets including the same goods are evenly spread between the shelf rows. A lift picks the pallet from the trolley and places it at the chosen position. The PD-fluid is stored for an average of three weeks. It was observed that the storage area was dark with no windows.

Temperature control

The storage temperature is controlled by air-conditioning and is monitored in five places every second hour. The temperature is approximately 10°C in winter and 25°C in summer. The warehouse manager will be notified and take measures, if the temperature reaches 28°C. According to the quality manager in DC Mirandola this has never happened.

11.4.3 Shipping

When an order is registered, the computer system will select goods according to expire date and if possible from the same production batch. The pallet is placed on a trolley and moved along the conveyor band. An order for another DC or satellite is usually including one or more whole pallets, and thereby there is no need for consolidation. The conveyor band will move the pallet directly to the outgoing gate where the pallet manually will be moved to the shipping area.

A domestic order, for an Italian hospital requires more work since the order is smaller and more complex, including different products. One order might require a part of a pallet and therefore the pallet needs to be broken. In this case the remaining pallet has to be repacked or consolidated with another broken pallet, before returning into storage. The returned consolidated pallet of PD-fluid might include different batch numbers and different expiring dates. This pallet will be marked with a label, saying mixed pallet.

The pallet will be stored at the shipment area for a maximum three hours until shipment. Shipments to DC Lund depart every day at all times. Customer Service in Mirandola orders the truck via telephone, on a day-to-day basis.

11.5 Prisma

Gambro's transport supplier in-between Italy and Sweden is the Austrian transport company, Prisma. Prisma is also used for shipments from DC Mirandola to DC Hechingen in Germany.

There are 1400 kilometres between DC Mirandola and DC Lund and the transport time is altogether approximately 41 hours. After leaving DC Mirandola, at approximately two o'clock in the afternoon, there is a 6,5 hour drive to Prisma's terminal on the border between Austria and Germany. The truck will be parked at the terminal over night, leaving at approximately eight o'clock the following morning. The truck will travel across Germany, reaching the ferry terminal in Travemünde at approximately eight o'clock in the evening. The ferry to Trelleborg, Sweden does not leave until eleven o'clock at night, but the three hours in-between is scheduled time for customs. The ferry will arrive in Trelleborg, the following day at six o'clock in the morning. The truck will reach its end-destination, DC Lund, around 07:00, unloading at 07:30. Figure 11.3 summarises the transport between Mirandola and Lund.

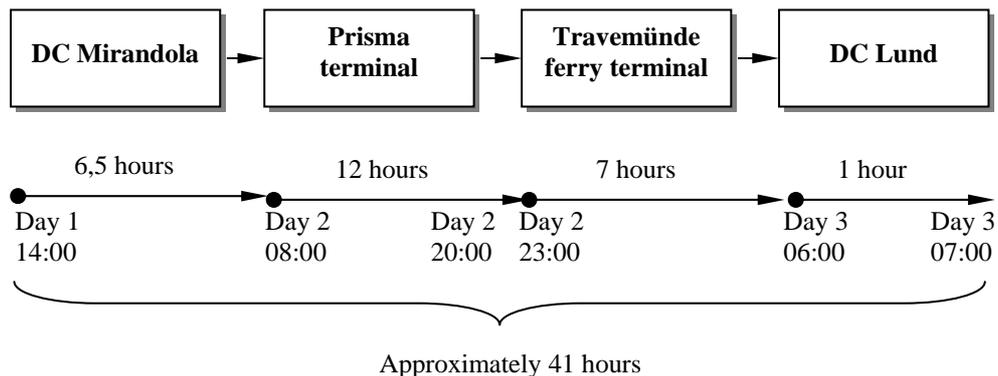


Figure 11.3 The time schedule for a shipment between DC Mirandola and DC Lund.

Shipments leaving Mirandola on a Thursday or a Friday, will not reach Lund until the following Monday. Over the weekend the goods will be stored at Prisma's terminal. There is no reloading or added load at the terminal. The

truck, inclusive its load, will be parked outside until Sunday morning, leaving at approximately eight o'clock in the morning.

There are no tempered shipments of PD-fluids, even though this is recommended, during the cold months of the year. This can result in frozen PD-fluids, giving a fracture to the plastic bag. Furthermore there are no temperature-regulated shipments during summer. According to the employees at DC Lund, Prisma's trucks are always equipped with black covers. They have never experienced receiving shipments from a steel sided truck.

11.6 DC Lund

DC Lund (appendix 11) has a manual controlled warehouse, with 6500 pallet spaces in-house and 6000-8000 pallet spaces outsourced to a warehouse in Malmö. PD-fluids are only stored in the Lund warehouse. DC Lund supplies, not only the Scandinavian countries with Gambro's products, but also approximately 90-95 other countries. From DC Lund PD-fluid is distributed to Scandinavia, Greece, the Czech Republic, Estonia, Kuwait, Latvia, Macedonia, Lithuania, Libya, Australia and Kenya. Markets in developing countries are gradually growing, while the home market for conventional PD-fluids is decreasing. The customer's demand varies and depending on the order, the pick-ups can be of all sizes. Orders from clinics are often big and synchronised, while the description orders can be very small and individual. For these reasons, the supply chain becomes very complex, and therefore a manual warehouse is considered to be the best choice.

11.6.1 Planning deliveries

According to the customer's order, Swedish Sales plans the deliveries and arranges a pre-delivery note, booking the goods for each order in the warehouse. Swedish Sales can in the IT-system, SAP/R3, view the orders received and order confirmations sent out together with delivery dates. This information will be sent to SAP/R3 Delivery as a pick-up order prepared so that the confirmed delivery date can be met.

With the pick-up data forecasted, the regional supply chain planner will contact the distribution centre and notify them of the dates on which the goods have to leave to be delivered on time.

11.6.2 Incoming goods

Shipments from Mirandola arrive every weekday, apart from Tuesdays. The goods usually arrive 07:30 – 08:00 in the morning. During normal conditions, one week includes arrivals from six to seven trucks. Incoming goods are received, weekdays between 07.20 am to 14.00 pm.

The arriving goods are unloaded into the receiving area, where the warehouse operator performs checks required for acceptance. First, it is visually secured that the packing has not been damaged, such as being torn or damp. As a

second step, the goods are identified by making an association between the product data and the pallet handling code. It is secured that product identification and quantity will match what is indicated in the system (SAP).

11.6.3 Nonconforming goods

Nonconforming goods will be segregated in a special area (NOC) and appropriately identified to ensure that it is not inadvertently used. Goods that have expired or are close to expiration or have been declared nonconforming by the manufacture are also placed in the NOC-area. To reduce the risk of products reaching the expiring date too quickly, it is under progress to block arriving goods that previously have been stored for more than 240 days.

According to the Warehouse Manager³⁶, the most common cause of damage during transport is exposure to condensation and moisture. The goods often arrive without top seal and wrapped with a type of plastic not suited for the transport conditions. With improved packing routines in Canosa, these damages could be eliminated.

Another problem, related to shipments from DC Mirandola, is when the pallet includes different batch numbers. The reason for this is described in section 11.4.3. The consolidated pallet cannot enter the warehouse directly, without being unpacked and sorted. The process is very time-consuming.

11.6.4 Storage

Received goods are processed in order of arrival, “first in first out”, to ensure stock rotation. The goods are stored from floor to roof, from the shipping area to the NOC area (see appendix 11), with no fixed placement. This means that the goods are stored on the floor and close to the shipping area if there is storage place available. This logic of storage placement is to facilitate the picking and make it efficient.

Temperature storage conditions

The storage area is equipped with temperature recorders to indicate when the specific temperature range has not been maintained. The floor- and middle level is regulated to keep 25°C, while the roof level is regulated to 30°C. When the temperature rises above the set temperature, the Warehouse Manager and the Quality Assessment Manager will be notified and decides upon swift measures. The system’s limitation is that the warehouse temperature cannot be cooled, only raised. To avoid exposing the PD-fluids to high temperatures, they are stored at the lower level during summer time. Monthly temperature reports are written and documented. So far, there have been no temperatures above 30°C, but during summer it is quite common with temperatures above 25°C.

³⁶ Berggren Claes, Warehouse Manager DC Lund, Gambro AB, interview 2003-09-18

11.6.5 Shipping

All pallets included in a truckload are stored together, in the part of the shipping area, intended for the same destination. The shipping area is divided into a domestic- and an international part, where Sweden, Denmark and Finland are considered domestic.

The truck driver loads the goods, by backing up against a weather-sheltered gate. The weather-sheltered gates prevent the goods from being exposed to the outside weather conditions. When container shipments are sent, the warehouse operators will load the goods outside.

International goods will be provided with shipping documents, faxed to the warehouse, from the division of Order Handling & Shipping. The domestic shipping information is assessable to the warehouse via SAP/R3. When the shipping document is handed over to the truck driver, the external transport company is responsible for loading the goods.

11.7 Schenker AB³⁷

Gambro's transport supplier for shipments within Scandinavia is Schenker AB, which is a worldwide logistic company. In Sweden they have 26 terminals and 400 cooperating haulage companies located all over the country. Each haulage company is specialised on its own route, usually covering an area set by postal code.

The responsibility of the shipment is handed over to Schenker when the shipping document is signed at the DC. Depending on the size of shipment and its destination, one of Schenker's external haulage companies will collect goods at DC Gastelyckan in the afternoon, five days a week.

11.7.1 Distribution

There are different ways of distributing the goods to its customer. If the order from DC Lund weights over 1000 kilos or if the destination is in the nearby area, the goods will be sent directly to the customer. Direct deliveries are usually to the pharmacy in connection with a big hospital, providing dialysis. Examples of direct PD-fluid deliveries are: Lund, Malmö, Borås, Göteborg and Danderyd. Smaller shipments, with different end destinations, will be consolidated and transported to Schenker's terminal in Malmö. At the terminal the shipment will be brought together with other goods going for the same- or nearby destination. The choice of consolidation has to, besides from being the most cost effective, provide the customer with on time delivery.

The consolidated shipment will leave Malmö the same day as arrival between five and seven in the afternoon, going directly to the customer or to another

³⁷ Gröndahl Lars, Customer Service Manager, Schenker AB, interview 2003-10-07

terminal. This is how the PD-fluids are spread out into the country, getting closer and closer to the end customer.

There are deliveries to Denmark twice a day, to Norway once a day and to Finland once a day, every day but Thursdays. These deliveries always go direct to a terminal in the destination country, except for one delivery once a week to Finland. This Finish shipment is consolidated with other goods in Värnamo.

11.7.2 Timetable

Destinations south of Gävle, has a maximum travel time of 24 hours, while destinations north of Gävle has a maximum travel time of 48 hours. Schenker guarantees on time deliveries and for Gambro, they reached this by 94% in August 2003.

At a visit to the terminal in Malmö it could be observed how quickly the reloading was performed. The arriving truck from Gastelyckan, with a pallet for Sundsvall, unloaded in one end of the building and immediately it was picked up and transported to the leaving truck, at the terminal's opposite side. This delivery for Sundsvall, which was a further away destination than 1000 kilometres, was loaded on a swapbody, to enable a combination of road- and rail transportation. The swapbody was transported by road from the terminal in Malmö, Fosie and moved to a train in Spillepengen, going by train to Sundsvall. At the end station the swapbody was moved back to a truck. Transportation like the one described will take slightly longer, 1-3 days, but it is more cost effective and environmental.

Goods can be transported by air, but never in normal cases, only when the delivery is urgent.

11.7.3 Electronic Data Interchange

Gambro does not book transport for each outgoing order. They use Electronic Data Interchange (EDI), which is an electronic exchange of business information between organisations in a structured format. This provides Schenker with the possibility to monitor Gambro's transport need, on an every day basis. Information visible to Schenker is what kind of goods to be transported, delivery time, volume and weight, together with other special requirements that might exist.

11.7.4 Loading requirements

Gambro specifies the pallets of PD-fluid, not to be loaded on top of each other by buying the transport, not in volume or in weight but in share of a full load. Ordering a full load, floor to roof, gives the signal to the transport supplier to not double-stack the PD-fluid.

According to Schenker two pallets of PD-fluid might be loaded on top of each other, but this is only by mistake. If the outcome is damaged goods, Schenker is responsible.

11.7.5 Temperature requirements

Gambro has to specify if the goods are to be transported and stored in a certain temperature interval, by clarifying it to Schenker. During cold winter months (November-March), the Warehouse Manager or the Sales Manager at Gambro, determine if the transport should be ordered with a special temperature requirement. During summer there are no requirements on a temperature-controlled transportation from Gambro.

If Gambro orders the PD-fluid to be transported above 4°C, there are specifications from Schenker preventing the fluid from freezing. Over night the PD-fluids are never kept loaded in a truck or container. Isolating blankets can be used, but according to one interviewed truck driver, this is rare. In really cold weather, heating equipment is used.

11.8 The pharmacy

Apoteket AB is the Swedish pharmacy and is a government-owned and non profit-orientated company. Apoteket AB's main task is to supply patients, wherever they live, on the right time, with the medicals needed. There are 900 local pharmacies in Sweden.³⁸ The PD-fluid is a medical product and has to be distributed by Apoteket AB³⁹.

Out of the 900 pharmacies there are thirteen that distribute Gambro's PD-fluids to 136 dialysis patients (figure 11.4). The patient figure varies according to the death- and transplantation rate. The pharmacies are centralised in connection with one of the bigger Swedish hospitals, providing dialysis treatment. Gambro's market strategy is to concentrate the sales to the largest hospitals, with the largest PD-patient population. By doing so they will gain experience and knowledge, and step-by-step move into smaller markets.⁴⁰

³⁸ <http://www.apoteket.se>, 2003-10-23

³⁹ Lindahl Ulf, Manager of Swedish Sales, Gambro AB, interview 2003-11-03

⁴⁰ Ibid

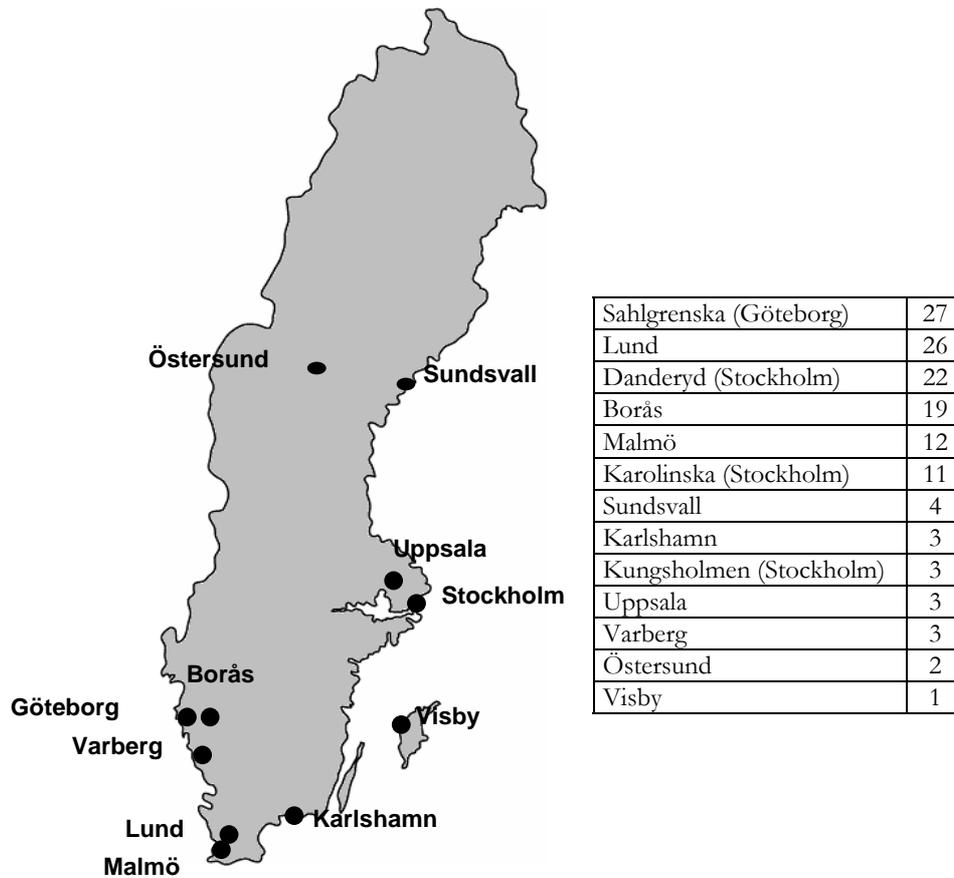


Figure 11.4 Pharmacies distributing Gambro's PD-fluids and the number of patients for each pharmacy.

In this thesis the authors visited Lund's University Hospital and their pharmacy. To cover the need of their 42 patients registered for peritoneal dialysis, the pharmacy has one separate storage facility, intended for dialysis products only. The people working with the pharmacy's dialysis products, the so-called Dialysis Group, are in close contact with the hospital's dialyse division and the transport service provided by Region Skåne. Other pharmacies distributing PD-fluid have a different distribution system due to their few patients.

11.8.1 Deliveries from DC Lund

Once a year, the preliminary supply need is planned in line with the previous year's consumption and the clinic's current patient information. Out of the 42 patients, 26 are using Gambro PD-fluid.

The pharmacy will every third or fourth day, at lunchtime, send a booking to the Gambro Sale Company. A delivery, from DC Lund, will arrive the following day at three o'clock in the afternoon. If urgent, a delivery can be made the same day. Each delivery usually includes 10-15 pallets of Gambro products and

these are always moved directly into storage. It is very important that there is a person on duty when goods arrive. If the delivery, for some reason is delayed, someone has to work overtime to receive the goods. Under no circumstances the goods are allowed to be kept outside the storage facility.

11.8.2 Storage⁴¹

Arriving goods from DC Lund are not always sorted by best-before date. Some of the goods arriving might have less lasting time, than the goods already in stock. This is why the pharmacy does not process “first in first out”. According to the pharmacy warehouse manager in Lund, this happens maximum ten times a year with goods from Gambro. To guaranty quality, expire date is always the priority of stock rotation. Gambro does not accept reclamations of goods out of expire day. These goods are the responsibility of the pharmacy and it is up to them how to eliminate the expired product (section 9.6.4). PD-fluids, out of expire day, are emptied in the sink by someone in the Dialysis Group. There is no money refund on these products. To prevent this loss, PD-fluids are labelled with yellow stickers when there are three months left to the expiring date.

The goods are stored, from floor to roof, wherever room is available. The storage facility has fluorescent lights in the roof, radiators and windows along one side. The temperature is kept at 20-25°C, besides during summer when it gets up to 28°C. Air conditioning is installed in the building, but it is not always working.

At a visit to the pharmacy storage facility, the authors could observe that PD-fluids occasionally were kept by the window, exposed to sunlight as well as heating from the elements. It was also noted that the storage facility was not provided with theft alarm.

A patient’s order, including all products needed for the home dialysis treatment is arranged on a pallet, one or two days before being picked up by Transport Service. As a demand from Läkemedelsverket (Apoteket AB’s supervise authority) every box of PD-fluid, has to be opened and visually quality checked by the pharmacy before delivery. This is to secure the safety of the patient.

11.8.3 Transport Service⁴²

Transport Service, supplying Region Skåne with transport, is handling deliveries of dialysis products. They have a transport route, planned according to where the patient lives and when the delivery is needed. Each patient’s delivery frequency is depending on the individual storage ability, where the patient lives and how big the consumption is. Deliveries from the pharmacy

⁴¹ Roos Stig, Apoteket AB, the hospital pharmacy in Lund, interview 2003-10-17

⁴² Ibid

can be made once a week as well as once every six weeks, depending on the patient's request.

The sequence of deliveries is also made out of economical- and environmental aspects. One transport route can include one to ten dialyse patients. The truck used for deliveries, is a specific truck equipped with a fridge for chilled medical products and a heating system keeping the PD-fluids from freezing. The truck usually arrives at the pharmacy 07.30.

11.8.4 Reclamations⁴³

Gambro has different ways of handling reclamations. In all cases it is important to remember that the product, under no circumstances will be accepted to return to the DC Lund warehouse. An exception is if the PD-fluid is packed on an un-sealed pallet.

- A complaint from a patient means that the PD-bag must be returned to the pharmacy. Gambro is contacted and if there is a desire, the bag will be returned to Gambro for evaluation. In this case the bag will be sent to DC Lund and they will return it to the production unit in Canosa. If Gambro decides not to do an evaluation, the pharmacy will discard the PD-fluid by emptying it in the sink.
- Gambro is forced to accept and refund a PD-fluid reclamation from the pharmacy, when there are more than three months left to expire date. If the expire day is due, it is too late for a reclamation and then the pharmacy will discard the PD-fluid.
- As it is business customary, Gambro will always accept reclamation of wrong quantity orders and the change in order products. According to the Swedish Sales Manager, reclamations due to a patient transplantation or the death of a patient will be accepted and money refunded. Though the pharmacy in Lund claims that there is no money refund for the returned goods from ending patients. The drop of patients is 10% a year for the pharmacy in Lund.
- Damaged good during transport, is a matter between the haulage company and the pharmacy. Gambro will not be involved.

11.8.5 Apoteket AB in the future⁴⁴

Within a couple of years Apoteket AB plans to centralise their pharmacies. The plan is five major DCs, so called distance pharmacies, which will supply the local pharmacies and the hospitals with big volume products. Today 20% of the products represent 80% of the volume, distributed by the pharmacies. This

⁴³ Lindahl Ulf, Manager of Swedish Sales, Gambro AB, interview 2003-11-03

⁴⁴ Ibid

is the reason behind the centralisation, which will result in a less complex distribution chain for medical products.

11.9 The patient

Each patient use in general four PD-bags, containing two litres, a day. The two-litres PD-bags are packed in a carton, including four, meaning plenty of storage for each patient. For example, if a patient gets delivery every third week, 21 cartons need to be stored at most. Besides from the PD-fluid the patient also needs to store dialysis equipment. The patient makes an order of the necessary need for PD-products to the pharmacy by phone, e-mail or mail. It is a request from the pharmacy not to receive an order by telephone, since it needs to be in writing.

11.9.1 Dialysis treatment

The patient is informed to, before treatment, preheat the fluid to body temperature (37°C). If the fluid is below 37°C the patient will get pain during injection. To secure always having an assessable preheated bag, the patient keeps the bag in turn on a heating plate. Over night, the bag can be kept at heating for up to ten hours, depending on how long the patient sleeps.

11.9.2 Delivery frequency

The most noticeable difference between the patients in Sweden and Italy is the delivery frequency. From the Italian phone interviews it could be concluded that the patients could choose between deliveries once a month or twice a month, according to their storage facilities. It was most common with a delivery once a month. In Sweden the patients receive deliveries more frequent, usually every second or every third week.

The patients always keep a couple of extra bags, to avoid being short of PD-fluid. All the interviewed patients were particular about always using the old PD-fluid before starting on a new delivery.

11.9.3 Storage routines

In Italy the patient receives a visit from a nurse, instructed by Gambro to inspect the storage routines of the PD-fluids. The purpose of the visit is to secure that the patient stores the PD-fluids in a dry and not too cold place. This inspection visit is not preceded in Sweden. Most common in Italy is to store the PD-fluids in the garage or in the cellar. In Sweden it is most common to store the fluids indoors; in a wardrobe or on the floor in one of the rooms.

When asking the Swedish and Italian patients about received storage recommendations, they were always informed about keeping the temperature above the freezing point. No one had been informed to pay attention to temperatures above 25°C. Moreover they all knew, not to keep the fluids in a damp place, for example in the bathroom.

11.9.4 Patient holidays⁴⁵

The patient is not limited from travelling, since Gambro is responsible for the supply of PD-fluids to the travel destination. The patient has to, through his or her hospital counsellor, leave notice to Gambro Global Supply Division a month before the trip. Gambro will with information about the destination, the hotel, the holiday duration etc. make sure that the PD-fluids are in place at arrival.

To make it more convenient for kidney patients to travel and to save supply costs to foreign countries, Gambro Swedish Sales Company once a year organises a joint-holiday. The trip is organised together with a travel company and while the patient pays for the trip, Gambro provides a nurse and the needed medicals.

⁴⁵Lindahl Ulf, Manager of Swedish Sales, Gambro AB, interview 2003-11-03

12 Empirical Study

The chapter describes the purpose of the empirical study, how it was planned and performed, and ending with a presentation of the result.

12.1 Presentation of empirical study

The aim of the empirical study was to monitor transport temperatures between DC Mirandola and DC Lund. The background to the study was to conclude if PD-fluids are subjected to high temperatures and if these temperatures increase the 3,4-DGE concentration, which thereby harm the fluid quality. Moreover the objective was to evaluate the Bioett system for PD-fluids in an ambient temperature chain.

Data was collected by technology provided by Bioett AB and a mechanical device logging temperature continuously over time. Figure 12.1 illustrates an example of a result paper slip from the device logging temperature over time.

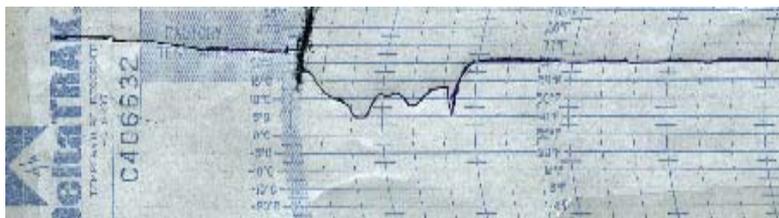


Figure 12.1 Result from a mechanical temperature logger.

At the starting point of the thesis the motive was to, after transport, measure the quota of 3,4-DGE in the conventional PD-fluid. There was an eight-week study containing a two-week trial test period and a six-week final test period.

12.2 Initial trial period

The two-week trial, included three shipments, and was performed to secure that everything worked as expected and to make adjustments for the final test period. Each shipment consisted of two pallets Gambrosol trio (39 boxes) and one single box Gambrosol Standard Solution (conventional PD-fluid). The reason why not only conventional PD-fluid was used was that there was no such order requirements from DC Lund. Instead it was decided that Gambrosol trio should be used, including one box of conventional PD-fluid at each pallet. This alone box was for the 3,4-DGE measurement, when reaching DC Lund.

Twenty TTBs were used for each pallet and four of them were used for the single box. The reason for using as many as 20 TTBs is that they have an uncertainty of 10%. The TTBs were programmed to 30 days, which included both transport and storage, and they were set to an average temperature of 20°C. After production, the TTBs were sent to DC Mirandola in a freeze transport. Once arriving, the TTBs were directly moved into a freezer.

Before the labelling at DC Mirandola, the TTBs were removed from the freezer and thus activated. The TTBs were applied to one or two sides of the pallet's outer plastic film, with a distance of ten centimetres. The single box was labelled with four TTBs, on four different sides. Before leaving DC Mirandola, the mechanical temperature logger was placed on the top of the pallet. View figure 12.2.



Figure 12.2 Two labelled pallets, including one mechanical temperature logger.

When arriving to DC Lund the TTBs were monitored twice with a scanner, directly after incoming and after a couple of days in warehouse's NOC-area. Bioett downloaded the values into a server, where they performed an evaluation of the temperature result.

12.2.1 Result of the trial test period

The purpose of the trial period was to synchronise all involved parts in the distribution chain and secure that everything worked as planned. Furthermore, the trial period gave Bioett time to evaluate, and if necessary modify the final TTBs for more valid results.

There were never any direct problems with the correspondence between DC Mirandola, the authors and DC Lund. Everything worked really well with the arriving shipments. The cargo was labelled and monitored as expected giving the authors temperature data to analyse.

The mechanical temperature logger, delivered with all three shipments, gave information about the actual trailer temperature. It was obvious in the trial period that no extreme temperatures occurred between the destinations. This result was expected since the test was performed in October, when the climate has no critical influence on the transport's inner temperature. The mechanical loggers showed an average temperature of 11°C (appendix 12).

Because the TTBs were set for 30 days and a temperature of 20°C, it became impossible to draw any conclusions from the stored TTB values. The true transport duration was less than three days, which did not give the TTB

enough time to show any identifiable results. Moreover the temperature was less than predicted, which made the enzyme reaction too slow.

12.2.2 Adjustments as a resulting effect

With lack of extreme temperatures, the pallet, which included one box of conventional PD-fluid and 39 boxes of Gambrosol trio, was modified to include 40 boxes of Gambrosol trio. It seemed like a waste of lab resources to measure the concentration of 3,4-GDP, when the result was known to be insignificant.

It was also decided that the boxes should be labelled with TTBs on one short side of the pallet, to simplify labelling and reading.

It was not anymore important to monitor the warehouse temperature in DC Lund, since this part of the distribution chain was temperature controlled. The final TTBs delivered to Mirandola were adjusted to a shorter time interval, from 30 days to 5 days. The temperature of the TTB was changed to 14°C. The reading instructions in Lund were thus simplified to just one reading at arrival. Now the TTBs could be removed from the pallet immediately after reading in Lund, and thereafter become available for order shipments. They no longer had to be stored in the NOC-area, waiting for the second reading.

A further adjustment to the final test period was to ship the PD-fluids from DC Mirandola on Thursdays as well as Mondays and Wednesdays. The reason was that the Thursday shipment was stored during the weekend and not shipped straight to DC Lund warehouse. This was considered a week link in the distribution chain, since it is out of control for Gambro, and thus of importance to be studied.

12.3 Final test period

When the trial period was carried out and adjustments were made, the final test period started. The final test contained 19 shipments during six weeks; each shipment included two pallets of Gambrosol trio. Each pallet was labelled with 20 new produced TTBs. The new TTBs were set to 5 days and 14°C and were delivered to DC Mirandola in a freeze delivery. At arrival, they were immediately moved into a freezer, to pause the TTB reaction. All nineteen shipments included a mechanical device, logging temperature over time.

When arriving in Lund, a warehouse employee read the TTBs. The scanner's stored values were by Bioett transferred to a server and evaluated.

12.3.1 Result of the final test period

Mechanical temperature logger

The climate in north of Europe, was almost the same during the whole test period, which the result shows. According to the mechanical temperature loggers, the temperature on average varied between 3 and 12,5°C. Appendix 12 presents the result of the mechanical temperature loggers from both the initial and trial test period.

In the end of October the climate suddenly changed and became really cold. The mechanical loggers monitored temperatures that had been below the restricted 4°C for 34 hours and exposed to a temperature below 0°C for ten hours. This shipment left DC Mirandola on a Friday and was thereby stored at the Prisma terminal during the weekend.

In total there were 4 shipments out of 22 that did not keep the restricted temperature, where one was exposed to temperatures below zero.

The TTBs

After about four shipments, Bioett discovered that the old TTBs had been used instead of the new ones. The operator in DC Mirandola had misunderstood that the new TTBs were going to be used for the final test period. The TTBs from the first five shipments became unusable.

The values from the following TTBs were evaluated by Bioett and the result is presented in figure 12.3.

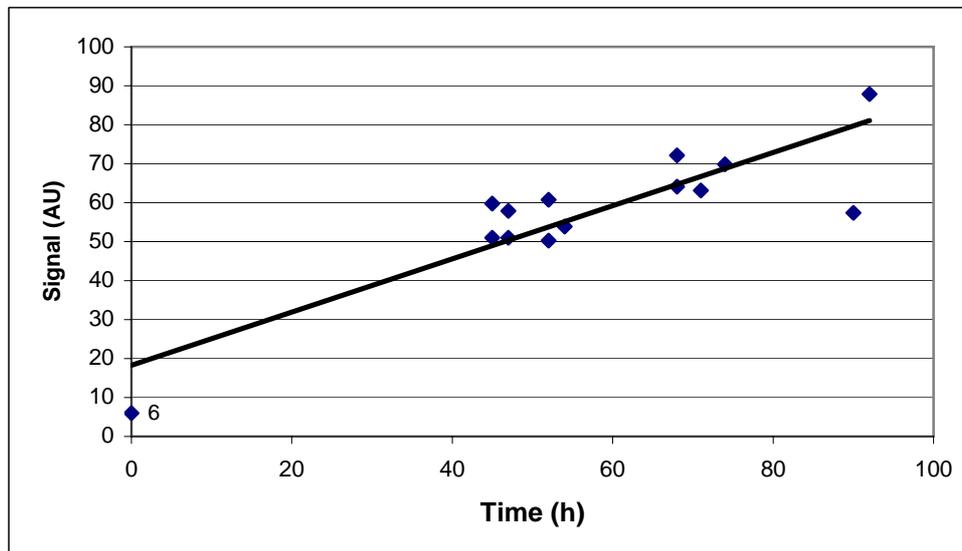


Figure 12.3 Result from the TTBs in the final test period.⁴⁶

⁴⁶ Wehtje Ernst, Research and Development Manager, Bioett AB, 2003-12-17

The graph illustrates the mean values, of the 40 TTBs from each shipment, against time. In this case time is defined as: from when the TTB is activated, i.e. placed onto the pallet, until it is read at DC Lund.

The values plotted in the graph can be understood as: if the value is above the line, it is above the average of all TTBs. If the value is below the line, it is under average. If a value had been far above the line, it would indicate that something unusual has happened during this specific transport. This would be a signal to Gambro that the shipment has been exposed for temperatures above the normal. The plotted values in figure 12.3 are all in the permitted area and indicate that nothing unusual has happened. One disadvantage with the TTBs is that they did not indicate temperatures below zero, which would have been valuable.

The variation in temperature must be higher to be able to draw any conclusions. The limitation to this thesis is that it was performed during autumn and winter, when no high temperatures exist. The TTBs would probably have shown more diverging temperature results, towards the normal regression line if the study was performed during summer.

13 Analysis

This chapter will answer to the problem formulation of the thesis, giving an insight of the distribution chain, existing temperatures and how they will affect the quality of the product. Moreover the system of Bioett will be evaluated, in terms of how it is suitable for an ambient temperature chain. Most important, it will be concluded if the Bioett system is a valuable tool in securing the quality of PD-fluid, and thereby the safety of the patient.

13.1 Distribution of PD-fluid

The focus has been to clarify which temperatures the PD-fluid is exposed to during distribution from production to patient. The centre of attention has been the distribution between Italy and Sweden, where the three-compartment bag (trio) has majority of market shares. It is the conventional PD-fluid, not the trio that is harmed due to high temperatures. All the same, the study of this thesis should be seen as a pilot case and the experience gathered can be applied to any distribution chain, supplying conventional fluid or not.

13.1.1 Transport

In this case study it has been noticed that transport is the weakest link in the distribution chain, in terms of uncontrolled temperature. The Gambro warehouses, evaluated in this thesis, have full control over the products, but as soon as the product gets in the hands of an external actor, the control is lost.

Frozen shipments

The Prisma transports between DC Mirandola and DC Lund, have been observed to use black-cover trucks, not steels-sided that is more protective against the external climate. While logging the temperatures in these particular shipments, temperatures below zero were identified, despite the requirements of keeping 4-30°C. A temperature below zero has no effect on the glucose degradation products (GDPs), but it can cause bag fractures. According to DC Lund operators, the below zero temperature was no surprise, since they long have suspected frozen fluids during transport.

The reason for the freezing was probably the weekend terminal stop, since the low temperatures were identified on a shipment leaving Mirandola on a Friday. When there is a Thursday- or Friday shipment from DC Mirandola, the full-loaded truck will be stored outdoors at the terminal for one or two days. Finding evidence of temperature below zero during winter, there is a big possibility that extremely hot temperatures might have showed up if the season was summer.

According to the Head of Product Development, Solution Division there have been problems with another product, shipped from DC Mirandola. Reclamations due to micro leakages in the over wrapping plastic, unbalancing the product's concentration, have turned up. The reason for this is probably

exposure to cold temperatures, at the Prisma terminal. It should be noted that it takes longer for a fluid to freeze in a moving truck.

To protect the product, the trucks should be steel sided or even better: tempered during winter. There ought to be a restriction, saying not to keep a full-loaded truck outside. The truck should be unloaded, into the terminal's storage area. Today there are only restrictions like this for dialyse machines, since the cold will harm their programmed functions.

Container shipments

The PD-fluid is distributed to markets outside Europe and they are in most cases shipped by sea, in a container. To guaranty keeping a certain load temperature, a reefer container should be used. This is generally not practised by Gambro, only when specific requirements are underlying. The authors have been told that Gambro buys container space under deck, in the centre of the boat, to protect the container from direct sun radiation. However, Gambro employees are saying that this is a false comfort, believing that the container at all times is placed under deck. To come to terms with the real issue, the container temperature should be regularly monitored.

The temperature study in section 8.1.1 showed that container transports, reached temperatures above 30°C several times. If the containers with conventional PD-fluid are transported in the same manner the quality of the fluid will decrease. A reefer container is in this case recommended.

Not using a reefer container can become a real problem when something unexpected turns up in the distribution chain. It might happen that a container is placed at the harbour dock for hours, waiting for a transport or customs. According to section 8.3.2 the container temperature can reach 50°C for more than six hours in a subtropical climate, with outside temperatures around 35°C. Related to figure 4.4, this would give the conventional PD-fluid high levels of 3,4-DGE, risking the safety of patients. Gambro should evaluate when this risk might occur and then use reefer containers when necessary.

13.1.2 Warehouses

The temperature control is good, in the warehouses evaluated in this study. Mirandola has the best-equipped warehouse, with an air conditioning system, cooling down high temperatures. The warehouse in DC Lund and at the pharmacy monitor the temperature, all according to the Good Distribution Practise (chapter 6), but do not have any ability to cool temperatures exceeding 30°C. Results show that there has never been temperatures above 30°C at DC Lund, and this is why an air-conditioning system is not considered.

The warehouse in Canosa, which has no ability to cool extreme temperatures, is the only storage where slightly high temperatures will have no negative effect on the PD-fluid. This is because it is ultimate with a slow temperature decrees, straight after heat sterilisation.

According to figure 4.4 it will take approximately five days to reach a toxic value for conventional PD-fluid, stored in 40 °C. One might wonder if it is possible to reach this temperature in one of the worldwide warehouses. Section 8.1.2 shows the highest monitored warehouse temperature of 38°C. This was an Asian warehouse and although the peak duration was not registered, it can be mentioned that it requires approximately ten days of storage, to harm the fluid at this temperature. Even if the temperature does not keep 38°C for ten days, the high warehouse temperature will increase the content of 3,4-DGE and the PD-fluid becomes more vulnerable for future temperature peaks. Suppose that the PD-fluid has been exposed for temperatures around 35°C for a couple of days, with a gradually increasing 3,4-DGE concentration. When the patient sooner is pre-heating the PD-bag, the concentration of 3,4-DGE will increase even further. In a worst-case manner, the fluid might become directly harmful to the patient.

13.1.3 Temperature awareness

Throughout the whole study, in interviews and conversations, it has been found that there does not exist any awareness about which harming effect high temperatures has to the PD-fluid. It is well known among Gambro employees, doctors, nurses and patients to keep the PD-fluid from temperatures below zero, since the bag might crack. For the patient it is mostly important to keep the fluid as warm as possible, since it is extremely painful to intake cold fluids. The boxes are labelled with temperature restrictions, but according to the authors, they only seem to exist to satisfy medical authority and their restrictions. For example, when a patient is preparing a PD-bag for usage, it can be heated for up to ten hours in 37°C, despite the 4-30°C storage restriction.

The lack of temperature awareness inside Gambro can cause problems throughout the whole distribution chain. If the transport buyer does not require a controlled temperature transport, the risk of falling out of the suggested temperature interval is high. The transport supplier cannot be blamed for bad quality, caused by temperature abuse, when there has not been any requirement from Gambro. It is a bit blue eyed to think that they would take a close look at the boxes, packed under several plastic layers, just to read the small printed temperature restriction, unless there is a written agreement or clause for temperature control.

When making the study it was clear that the employees did not know exactly what happened to the goods after being sent away from the DC. Take for an example the waiting time at the terminal in Austria, which was not clear for the employees in Italy who had ordered the transport. With a better understanding and better control this kind of happenings can be avoided. It has to be remembered that the transport supplier in usage are using several haulage companies to cover different transport routes. The awareness and control will fall behind even further if clear restrictions are not made from the beginning.

Therefore it is important to improve the DC's understanding of the fluid's temperature sensitiveness, so the planning of shipments can be improved. The awareness should start with better demands from the superior in the organisation, which will be dispersed throughout the whole organisation.

An increased awareness would hopefully also avoid careless handling at the hospital pharmacies. Since they do not know better, the PD-fluids were in one case observed next to a window and a radiator. A warm and sunny day would expose the PD-fluid to high temperatures for several hours.

13.2 Temperature studies

The biggest problem is not to control the required temperature range of 4-30°C for the PD-fluid. Providing temperature-controlled transportation can easily do this. The real issue is to come to terms with, if and when the PD-fluid is subjected to extreme temperatures, and if there really is a need for temperature-controlled transportation.

13.2.1 Temperatures harming the PD-fluid

Unfortunately this case study was not performed during the warm summer months, where extreme temperatures could have been monitored in the distribution chain. It is not known if harmful temperatures exist, inside a shipment, between Italy and Sweden during the warmest season. The authors and readers can only speculate in this, but it is important to draw a parallel between previous temperature studies and the conventional PD-fluid. A conclusion can be made that extreme temperatures exist in both trucks and containers, according to section 8.2 and section 8.3.

Keep figure 4.4 and appendix 8-9 in mind when damaging effects of the conventional PD-fluid, is evaluated according to high temperatures. It has to be remembered that Gambro has a worldwide market and therefore the temperature results in section 8.2-8.3 are of interest.

Truck transports

The study in section 8.2 describes the temperature inside a steel-sided truck in the United States' southwest. It is interesting to analyse what would happen to the PD-fluid it was subjected to these specific conditions. Appendix 9 illustrates a one-hour temperature peak of 58°C, at an outside temperature of 38°C. Although there is a difference in the temperature of the fluid and the surrounding air temperature, due to the protective package, it is definite that the concentration of 3,4-DGE would increase rapidly. It would only take minutes to reach a dangerous level of the toxic 3,4-DGE.

Appendix 8 does not show such an extreme temperature peak, but it illustrates much longer high temperature intervals, which can lead to dangerous levels of 3,4-DGE. It has to be remembered that the content of figure 4.4, considers a fluid, with low levels of 3,4-DGE, before exposure to different temperatures.

Appendix 8 is an example of how the quality of the fluid gradually is decreasing with exposure to high temperatures. The effect of one temperature peak cannot be isolated from another, when the influence is analysed. The whole history of temperatures will have an effect, and thereby the influence of one particular peak can be more or less critical. Over time the fluid will become weaker and weaker, and just a slight temperature increase might be the one jeopardizing the quality. A shipment, like the one in appendix 8, will never give the level of 3,4-DGE time to decrease between the peaks, since this takes considerably long time.

Container transports

The study of section 8.3 describes how much higher the temperature is inside a container compared to the outside temperature. There could be temperature differences between 20-25°C in a subtropical climate with more than 12 hours of sunshine a day. The warmer the outside temperature was, the higher was the difference between inner- and outer container temperatures. This means that during a 30°C summer day, it can become 50°C in a container. Although the reliability of the measurements is unsure, the trend is obvious. Extreme outside temperatures, will give even more extreme container temperatures.

13.3 The Bioett system

For this thesis Bioett's TTB has been especially developed to monitor room temperature. The TTB is successful in securing the quality of a frozen or chilled temperature chain, and now the aim is to be as successful in monitoring the ambient temperature chain.

13.3.1 Difficulties in monitoring an ambient chain

The authors have identified a few difficulties in monitoring an ambient chain, which can turn the TTB into a drawback.

First of all it is hard to foresight the surrounding temperature. The climate can differ enormously, country-to-country and season-to-season. It is almost impossible to forecast the weather and also the temperature. The temperature is hard to predict and therefore it is even harder to program the biosensor, since its accuracy depends on the surrounding temperature. A TTB set for 20°C as a normal value, will not be as predictable if the surrounding mean temperature, would turn out to be 14°C. It can be questioned for which mean temperature a TTB, for a shipment between Lund and Australia, should be programmed? In January the mean temperature in Lund might be below 0°C Celsius, while the temperature in Australia can reach a far bit over 30°C.

Another difficulty is that the sensor requires reading in as many parts of the distribution chain as possible, to give a full evaluation of the temperature at critical points. If the reading points are too few and too far from each other it will be hard to identify if and where exposure to extreme temperatures took

place. The only thing that can be monitored is the shipments accumulated temperature. Many reading points require lots of resources in form of time and money.

An example is the container shipment between Italy and Korea, which approximately takes one month. The TTB's value can only be read before and after the shipment. This means that the value can be understood in different ways, either as an average temperature during the whole journey or as an unequal temperature with different temperature peaks. Notice that the TTB only views the accumulated temperature or the average temperature. It can never be known for how long the peak existed or if it really existed at all.

The empirical study of the thesis gave temperature results from the mechanical logger as well. According to the authors this gave a more accurate picture of the temperature in the distribution chain, since it could give more than the accumulated temperature. It showed temperature peaks, when in the distribution they occurred, and their exact duration. This was the source that could make it possible for the authors to identify weak points in the distribution chain. Moreover the mechanical logger gave the authors evidence of temperatures below zero, which the TTB could not.

13.3.2 Early warning system

To solve the problem with temperature peaks, one alternative is to produce a TTB that only monitors temperatures above a certain temperature. For instance, a TTB that would start reacting with temperatures above 40°C and continue its enzyme reaction until the temperature gets below. The TTB can now work as an early warning system, by signalling when a certain transport has been subjected to temperatures above 40°C. To be on the safe side when exceeding 40°C, Gambro would have to quarantine fluids, to reach a no critical 3,4-DGE concentration. The limitation to this system is that it would be hard to know which temperature to set the TTB for, since there is nobody to say which should be the critical signal point. It could be 40°C, but it could also be 38°C or 45°C, depending on the time the transport has been subjected to the certain temperature. Yes, it could be a warning system, but it should first by Gambro be clarified which temperature to warn for. Today there are many speculations, but it ought to be clarified before implementing an early warning system.

13.4 Is the TTB applicable for Gambro?

The aim of the Bioett system is to reveal gaps in the ambient temperature chain. It is clear that temperature variations exist in the distribution chain of PD-fluids, which the Bioett system to some degree can show. The question to be answered is: why there is a need to monitor the ambient temperature chain for Gambro PD-fluid and which gaps that are important to reveal? First of all, as discussed throughout this thesis, the temperature has a negative effect on

the conventional PD-fluid and therefore a controlled temperature distribution would improve the quality of the product. Secondly it has to be clear, how to relate temperature variations to the product quality. It is by now known that the relation exist, and therefore it can be discussed if the TTB, by monitoring the temperature, indirectly can evaluate the quality of the PD-fluid?

Before the discussion, the definition of quality has to be remembered. The quality of PD-fluid in this thesis is: a low 3,4-DGE level, which is time- and temperature dependent.

13.4.1 The true temperature reaction

To make the biosensor a valuable tool for Gambro in monitoring the temperature, and thereby the quality of the PD-fluid, the reaction of the biosensor needs to be as close to the PD-fluid as possible. Today the TTB will react and start ticking according to the speed of the reaction from the big tank, illustrated in figure 4.2. As described in section 4.3.2, this will affect the concentration of the toxic 3,4-DGE, but almost negligible compared to the equilibrium relation between 3-DG and 3,4-DGE. This means that the TTB will only estimate one of the reactions influencing the concentration of 3,4-DGE. It may thus not signal when the toxic concentration of the 3,4-DGE is getting critical.

13.4.2 A reversible TTB reaction

If the TTB was set for the true temperature reaction it would underestimate the quality. To explain it further the authors will make a comparison to how food quality, in terms of durability also is time- and temperature dependent. Time- and temperature reactions seem to be the similarity between the qualities but with a better insight the difference can be identified. Food quality can never be improved, but the quality of PD-fluid can.

A fluid exposed to high temperatures will reach a high concentration of 3,4-DGE, but the level will decrease over time, at room temperature. If you expose a litre of milk to a high temperature, it will reach its expire day much quicker, and thereby loose its quality by becoming sour. It does not matter for how long or at which temperature it is stored afterwards, since it can never retain its quality.

With this background it can now be understood why the TTB can be applicable for the food industry but not for the PD-fluid. The TTB does not consider a backward reaction and this is why the quality can be undervalued. Say that the TTB's value could be adjusted to the transformation speed between 3,4-DGE and 3-DG, at different temperatures. The value would become higher, with rising temperature, adding on to the registered value, which would be constant at a predicted temperature. The downfall is that the value can only be added on, not decreased when the temperature is going back to normal. Since the TTB is showing an accumulated effect over a period of

time, it does not take under consideration that the quality of the PD-fluid can be enhanced.

The PD-fluid needs a TTB with a ticking clock that can be rewound every time the level of 3,4-DGE is decreasing.

13.4.3 The initial value of 3,4-DGE

Say for an instant that the TTB could consider a backward reaction, giving a rewinding clock. Now the difficulty would be to know when and how much to rewind the clock. The TTB value should be reset to zero, when the level of 3,4-DGE is back to the level after production quarantine.

Not knowing the 3,4-DGE concentrations when being released from the production is another issue, making Bioett's TTB or any other temperature indicator unsuccessful. Gambro needs to monitor the initial concentration of 3,4-DGE, after the fifteen-day quarantine, to provide the TTB with an absolute zero value. Today the concentration of 5-HMF is measured, but this is not showing the true concentration of 3,4-DGE. Just as the TTB, it is underestimating the concentration, since it is probably only measuring the flow from the big tank in figure 4.2.

By not knowing the history of the PD-fluid, when being exposed to an extreme temperature for a certain amount of time, it is not known if it will be unsuitable for use or not. Everything is about how high the level of 3,4-DGE is, before a sudden temperature increase is submitted.

13.4.4 A complex distribution chain

If a Bioett system, suited for the 3,4-DGE reaction, was implemented throughout the whole distribution chain, it would create complexity and add big costs. Every time a carton with conventional PD-fluid is labelled with a TTB the labour time increases. In the DCs, the TTBs should be read and labour time for reading is added. If the TTB should be read at the medical retailer, such as the pharmacy in Sweden, all the medical retailers in all markets should be equipped with a Bioett detector. This would mean high costs in equipping the medical retailers with detectors. The medical retailers would also have to be equipped with an Internet access and computer. This will probably not be an issue in the high-developed countries such as Sweden, but in the less developed countries this might be a problem.

It can now be concluded that the TTB is not applicable for the PD-fluid and its reversed reaction. The TTB can monitor the ambient temperature chain, but this cannot be related to the quality of the PD-fluid, since the glucose reaction is far more complicated than the TTB enzyme reaction. Although the TTB is good in monitoring the temperature, and to some degree indicate the glucose degradation, it cannot act as an indicator for good or bad quality. Using the TTB as a tool to secure the quality of the product, by monitoring the

temperature, loses its value to Gambro, since nobody can tell which effect the temperature result will have on the PD-fluid.

13.5 The PD-market

Conventional PD-fluid has today, in total the largest worldwide market, 90%. The conventional fluid is compared to the trio, much more sensitive to high temperatures and is therefore with its high GDP level, not providing the patient with the best quality.

Gambro has only a small part of the total PD-fluid market, where 90% of Gambro's market consists of the trio. The trio is temperature resistant and to reach the critical level of 3,4-DGE, the trio has to be exposed for high temperatures for a long time. This will probably never happen and the trio can therefore be considered to include very high quality.

With this knowledge, Gambro has a good chance of increasing their market shares, by marketing the benefits of the trio. Today Gambro holds the patent of the trio and has to convince patients worldwide, about the advantages. It is probably a good idea to gradually remove the conventional fluid from the product portfolio and increase efforts to the trio.

13.6 Cost savings in the distribution chain

Along the way of the research, evaluating temperatures in the distribution chain and their effect on the quality of the product, it has been impossible to not run into other issues of interest. The authors will in this section present some points of interest, that with further investigation could lead to cost savings for Gambro.

13.6.1 Transport routines

One cost demanding issue is that pallets including PD-fluid are not allowed to be double-stacked, during transport. Today the truck is only half utilized and this could be improved by new developments. For example the carton could be improved or the pallets could include a top collar, which would take the second pallet load of the first. This would provide cost savings by less needed trucks.

Gambro ought to evaluate the advantages of having one single transport supplier, with a closer co-operation. It would lead to advantages in cost, control and coordination for both parties. Having for example Schenker as a worldwide supplier would make it easier to coordinate transport routes between different markets and it would be worthwhile, sharing valuable information by EDI. Many time-consuming routines, like planning shipments, calling up the transport supplier and on could be avoided by EDI.

With one single transport supplier it also become easier for Gambro to control the shipments and evaluate the success of the supplier. Since Gambro, because

of its size would become a more dominating customer, it would facilitate cost reductions and improved performance.

13.6.2 Order routines

The order routines inside and outside Gambro have big potential for improvement. First of all there are no requirements on how much planning in advance the doctor or nurse should have, when transferring an order to the sales company.

Today the orders are changed frequently; they can be changed the same day as being shipped from DC Lund. Of course this can be seen as good service, but it should be questioned, if it is necessary, since it requires a lot of administrative work. This is something the doctor or nurse is unaware of and there is usually no direct reason for the irregular order routine. The best explanation is probably lack of planning and organisation. If nobody demands a regular order routine, why should the hospitals put any energy into it? It is more comfortable to put in a spontaneous order, and then change it a few times if the conditions are changed.

To improve the coordination of the supply chain, it would be a big benefit to make a customer order, visible through the whole chain, all the way back to the production unit. Since the different parts of the supply chain in many cases have different information systems, this is yet today impossible. It would be optimal to share information across the internal borders of Gambro, by a common information system. This would save a lot of administrative work and information being lost or miscalculated. Moreover a common information system facilitates planning in advance.

13.6.3 Stock Keeping Units

The production of PD-fluid year 2003 included 150 Stock Keeping Units (SKUs), giving an ineffective production and labelling process, with many small batches. Today the markets have different PD-bags and cartons with different texts on different languages. With a multi-language PD-bag and carton, the number of SKUs could be reduced, which would lead to more efficiency in the distribution chain.

14 Conclusion

This is the last chapter of the report, where the most important thesis conclusions will be summarised.

The objective of this thesis was to monitor existing temperatures in the distribution chain, between Italy and Sweden, and also through observations and interviews make a fully mapping of the distribution chain. During the research, the authors were furthermore evaluating existing awareness to temperature requirements, among the stakeholders.

Bioett's system together with mechanical temperature loggers, were used in revealing diverging temperatures in the distribution chain. The objective was not only to evaluate the TTB as a tool in monitoring the distribution temperature, but also to see its potential in indicating the quality of the PD-fluid.

14.1 Transport and storage

In the transports between DC Mirandola and DC Lund it was concluded that the PD-fluid was exposed to temperatures below the restricted 4°C and in one case it was exposed to a temperature below zero. To prevent this, the authors suggest that tempered trucks must be used during cold winter months and the transport should be planned without the terminal stop.

Gambro's worldwide container transports have exceeded 30°C several times. These temperatures might not directly harm the quality of the PD-fluid but it is clear that there is little control over the transport temperatures and that the temperature restrictions are not followed. Gambro needs to evaluate when conventional PD-fluid and other temperature sensitive products are transported in a container that might exceed 30°C and in those cases use reefer containers.

The warehouses in Italy and Sweden have good control of the storage temperatures, which also are regularly monitored. A previous study, evaluating existing temperatures in Gambro's Asian warehouses, substantiate that the average temperature has been over the restricted 30°C. One case shows a temperature peak of 38°C. If the conventional PD-fluid is stored under these circumstances the quality will markedly decrease.

14.2 Awareness

To prevent the conventional PD-fluid from being exposed to high temperatures in the worldwide distribution chain, the temperature awareness must be improved. It can be concluded that there is a huge lack of temperature awareness among the stakeholders of Gambro. There is a common knowledge about which negative effect temperatures below zero have, but hardly anybody mentions anything about high temperatures. The lack of temperature

awareness among the Gambro stakeholders is according to the authors, the explanation to why the temperature control is lost during transport. On the whole the warehouse temperature is controlled, but as soon as the product is in the hands of an external actor, the control is lost.

No actor can be blamed, especially not the transport supplier, since there are no clear temperature restrictions. An increased awareness among the Gambro employees would give them the knowledge to become more constructive in their work; giving clear transport restrictions and having handling planes if anything out of the ordinary happens. An increased awareness would avoid most critical handling in the distribution chain, and thereby decrease the need for temperature-controlled transports.

14.3 Quality improvement

Since it is so hard to control which effect the distribution temperature has to the quality, the quality needs to be improved in the beginning of the supply chain. The 3,4-DGE concentration should be at such a level when leaving the production, that the need for quality control can be eliminated. If the 3,4-DGE level is not controlled when leaving the production, it will according to the authors become harder and harder to secure the quality, the further away from the production the product gets. This means that the most critical point in the complex distribution chain will be at the patient.

By controlling the GDP levels and minimizing the 3,4-DGE, with a long and slow temperature decrease after sterilisation, the PD-fluid will become more resistant to damaging effects in the distribution chain.

14.4 The TTB – in securing the quality?

Considering the discussion in the previous chapter, the authors do not believe in the TTB as a tool to secure the quality of the PD-fluid. It might monitor the average transport temperature and reflect the total amount of glucose degraded, but for which purpose? The requirement should be to secure the quality of the product, which the TTB cannot fulfil. If the TTB should be usable it must have the same reaction speed as the reaction between 3-DGE and 3,4-DGE, the TTB reaction must also be reversible. The TTB reaction must additionally consider that the reaction speed of the 3,4-DGE is much faster with an increase in temperature, compared to a decrease in temperature.

The TTB cannot be configured to suit these requirements and maybe no monitor system can. But the question is if it is a temperature monitor system that Gambro needs? It is the authors' believe that Gambro should start working with improving the temperature awareness and in that way optimise transport and storage.

References

Books:

Bell Judith, ”*Introduktion till forskningsmetodik*”, second edition, Studentlitteratur, Lund, 1995

Yin Robert K., ”*Case Study Research: Design and Methods*”, Second Edition, Volume 5, Sage Publications, 1994

Articles:

Axelsson, Jan R C, ”*Quality and Ergonomics - towards successful integration*”, department of mechanical engineering LiTH, Linköping, 2000

Erixon Martin et al, ”*PD fluids may be perilous if used too soon after sterilization*”, Gambro AB, Lund, 2003

Kayum Robert, ”*Temperature-controlled distribution in the health Care industry*”, Business Briefing PharmaTech, Business Briefings Ltd, London, 2002

Kayum Robert, ”*The supply chain is no longer a weak link in the global Pharmaceutical industry*”, Pharmaceutical Manufacturing and Packing Sourcer, Samedan Ltd, London, 2002

Kjellstrand Per et al, ”*Storage may be as detrimental to PD fluids as heat sterilization*”, Gambro AB, Lund 2003

Linden Torbjörn et al, ”*3,4-Dideoxyglucosone-3-ene (3,4-DGE): A cytotoxic glucose degradation product in fluids for peritoneal dialysis*”, Gambro AB, Lund 2002

Taylor John, ”*Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products*”, the Pharmaceutical Journal, vol 267, London, 2001

Tuncer Murat et al, ”*Chemical peritonitis associated with high dialysate acetaldehyde concentrations*”, Nephrol Dial Transplant 15: 2037-2040, Turkey, 2000

Oral sources:

Berggren Claes, Manager Distribution Centre Lund, interview 2003-09-18

Gröndahl Lars, Customer Service Manager, Schenker AB, interview 2003-10-07

Joachimsson, Ingvar, Manager Quality and Control, Gambro AB, interview 2003-11-03

Kjellstrand Per, Senior Scientific Advisor interview, Gambro AB, interview 2003-11-19

Lindahl Ulf, Manager of Swedish Sales, Gambro AB, interview 2003-11-03

Roos Stig, Apoteket AB, the hospital pharmacy in Lund, interview 2003-10-17

Sandberg Per, Manager DC Lund, Gambro AB, interview 2003-09-17

Sjögren Anette, Qualified Person, Gambro AB, interview 2003-10-02

Web Pages:

<http://www.gambro.com>, web page by Gambro AB, 2003-09-09

http://www.ista.org/Knowledge/ISTA_Temperature_Report-2002.pdf, web page by ISTA, 2003-10-21

<http://www.containerhandbuch.de>, web page by the German Insurance Association, 2003-10-14

<http://www.apoteket.se>, web page by Apoteket AB, 2003-10-23

<http://www.bioett.com>, web page by Bioett AB, 2003-10-01

References

Other:

Council Directive 92/25/EEC

Gambro AB, Intranet, 2003-12-09

Gambro Basics, educational material by Gambro AB

Flank Peder, Development Engineer, Gambro AB, Transport Studies, 2003

Joachimsson Ingvar, Manager Quality and Regulatory, Gambro AB, 2001

Olsson Petter, Ousbäck Christoffer, ”Säkerställande av en oavbruten kylkedja”, master thesis, division of packaging logistics at department of design, Lund Institute of Technology, 2003

Wehtje Ernst, Research and Development Manager, Bioett AB, 2003-12-17

Appendix 1

Useful words and definitions:

Ambient temperature – Temperature around 25°C.

Chemical Peritonitis – Inflammation of the peritoneum.

Dialysis – Cleaning of the blood by artificial means.

Glucose Degradation Product (GDP) – During heat sterilisation of the PD-fluid, glucose is degraded to glucose degradation products. For example 3,4-DGE, 5-HMF and 3-DG.

Heat sterilization – During manufacturing, the PD-fluid needs to be sterilized to exterminate bacteria.

Hemodialysis – Purifies the blood outside the body by an artificial kidney.

Kidney failure – Declined kidney function.

Peritoneal dialysis (PD) – The blood is treated without being removed from the body. Instead a cleansing fluid is brought into the patient's abdominal cavity where the peritoneum acts as a dialysis membrane.

Peritoneum – The thin membrane covering all the organs in the peritoneal cavity.

PD-fluid – The cleansing fluid brought to the abdominal cavity.

Quality – In this thesis, the level of 3,4-DGE.

TTB – A programmable biosensor in form of a self adhesive label, which measures the accumulated effect of the temperature, of the product, over a period of time. Developed by Bioett AB.

3,4-DGE – The most reactive and toxic GDP.

Appendix 2

Interview questions: Per Sandberg, 2003-09-17.

Transports

- Which transport supplier does Gambro use?
- Which demands are there on the transport supplier?
- Does the transport supplier manage Gambro's demands?
- Has Gambro changed transport supplier recently?
- Are Gambro able to influence the transport supplier?
- Who is responsible for the agreements to the transport supplier?
- Is the PD-fluid consolidated with other products?
- What kind of packaging is used for the PD-fluid?
- Where are the distribution centres located in Europe and the world?
- How far is the transportation from the distribution centre in Italy to the distribution centre in Lund? How long does it take?
- Are there any hold-ups on the way?
- Are there any restrictions for distribution of medical products?
- Are there any recommendations about how to handle the PD-bag regarding the temperature? Is there a knowledge about that the PD-fluid is temperature sensitive?
- In what temperature is the PD-fluid transported?

DC Lund

- Is there a process description for the activities at the warehouse?
- How often is the goods coming in and going out? How much goods is kept on storage? How high is the safety storage?
- What temperature is kept in the storage?
- How long, in average, is the PD-fluid kept in storage?
- Is there prepared routines about how the PD-fluid should be handled?
- Is there any form of quality control for the PD-fluid?
- How are the customers ordering? After demand or on regular basis?
- How much complaints are there on the PD-fluid?
- How much reclamation does the PD-fluid count for?

Appendix 3

Interview questions: Lars Gröndahl, 2003-10-07.

- How many terminals does Schenker have in Sweden?
- How many of them are used for Gambro's goods?
- How often does Schenker pick up goods from Gastelyckan?
- How many haulage companies are used?
- Are the goods from Gambro going directly to the customer or to a terminal?
- Are there any transport documents for Gambro's PD-fluid? What information does it contain?
- What demands does Gambro have for the handling of the PD-fluid?
- Is temperature controlled transports used for Gambro's products?
- Are the pallets with goods from Gambro piled up on each other?
- Are the goods from Gambro marked as medical products?
- With what kind of goods are Gambro's products consolidated?
- Are there any studies made about how warm a cargo gets in hot climate?
- What kinds of trucks are used for Gambro's goods? Steel sided or covered? If covered, is it black?
- How can Schenker guarantee that the goods are only exposed for room temperature?

Appendix 4

Interview questions: Stig Roos, 2003-10-17.

Incoming goods

- How often is PD-fluid delivered to the pharmacy? What days?
- How much is delivered each time? Is there any variation?
- What time is the PD-fluid delivered?
- Who receives the goods?
- What does the delivery contain except PD-fluid?
- Is the goods directly moved into the storage or is it possible that it will stay on the loading platform for a couple of hours?

Storage

- Where is the PD-fluid stored?
- How much PD-fluid is kept on storage?
- How long is the PD-fluid stored before it goes to the customer?
- How warm can it be in the storage area?
- Is the storage area temperature controlled?

The patient

- How often does the patient meet the nurse?
- Is it the pharmacy that takes care of the distribution of PD-fluids to the patient?
- How many patients is the pharmacy distributing to?
- How often does the patient pick up the PD-fluids by themselves?
- How much PD-fluid is stored in the patient's home?
- What kind of recommendations about storage are the patients provided with?
- Is there awareness about how the patients are storing the PD-fluids?

Appendix 5

Interview questions: Ulf Lindahl, 2003-11-03.

- How many PD-patients are there in Sweden, Norway, Denmark and Finland?
- Is the distribution centralized to a few regional pharmacies?
- Are these distribution pharmacies located to hospitals or clinics?
- Are all the distributing pharmacies having a big storage local as the Lund pharmacy?
- Is the pharmacy in Lund a standard example?
- Is it always the pharmacy or the clinic that orders PD-fluid from Gambro?
- How often do they order?
- Is the PD-fluid always distributed to the patient by a transport service or is the patient picking it up?
- Who pays for the transport service?
- If the patient wants to go on vacation, how and who is planning for the distribution in that case?
- How long before going on vacation must the trip be announced?
- Who pays for the distribution to the destination?
- Is the PD-fluid transported by plane?
- Are there any special handling and storage recommendations when going on vacation to a tourist destination?
- Who is deciding from when thermo trucks should be used?
- How is that decided?

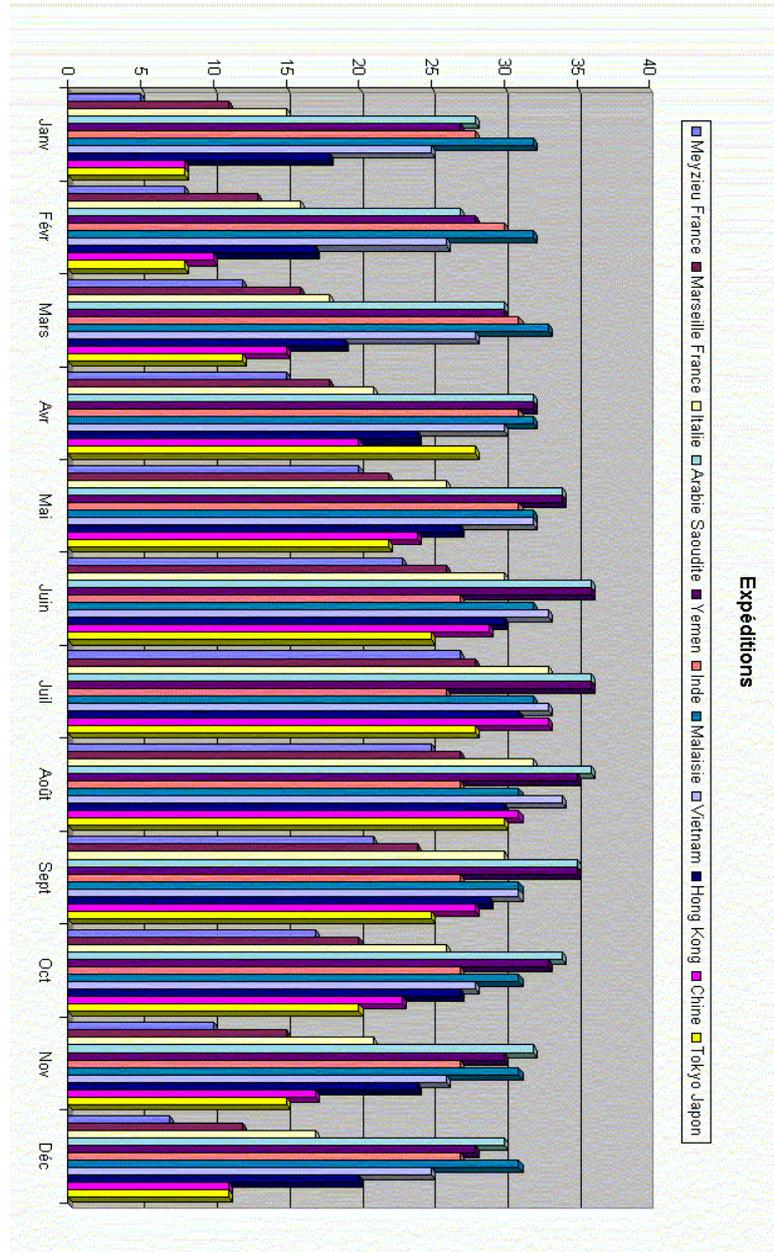
Appendix 6

Patient interview questions:

- Where do you live, which city?
- Are you living in a house or in an apartment?
- How many square meters is your home?
- What kind of PD-fluid do you use?
- How many PD-bags do you use per day?
- Are the PD-fluid delivered to your home? In that case by whom?
- If no on question 6, do you bring them home by yourself and where from?
- How often do you refill your storage of PD-fluids?
- What quantities do you get at each delivery?
- Do you use all the stored PD-fluids before getting a new delivery?
- If not, how many PD-bags have you left?
- Do you use these before you use the bags from the new delivery?
- Where in your home do you store the PD-bags?
- What temperature does this storage area keep?
- What information about storing conditions did you get from the nurse/doctor?
- How many hours is it between your last dialysis in the evening, until the first in the morning?
- Is there always a PD-bag on the heating plate between the dialysis treatments?

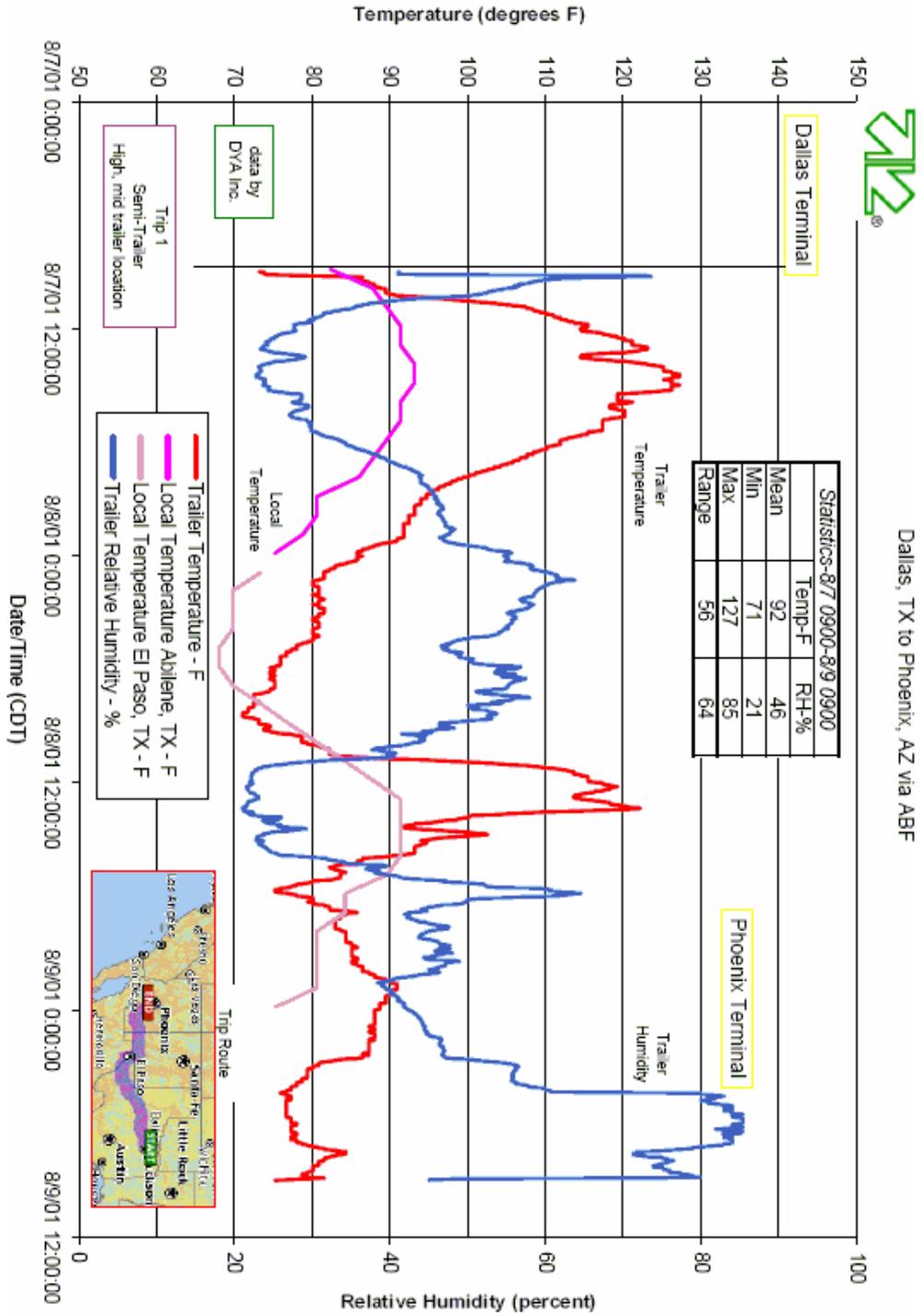
Appendix 7

Graph illustrating Gambro's temperature study results.



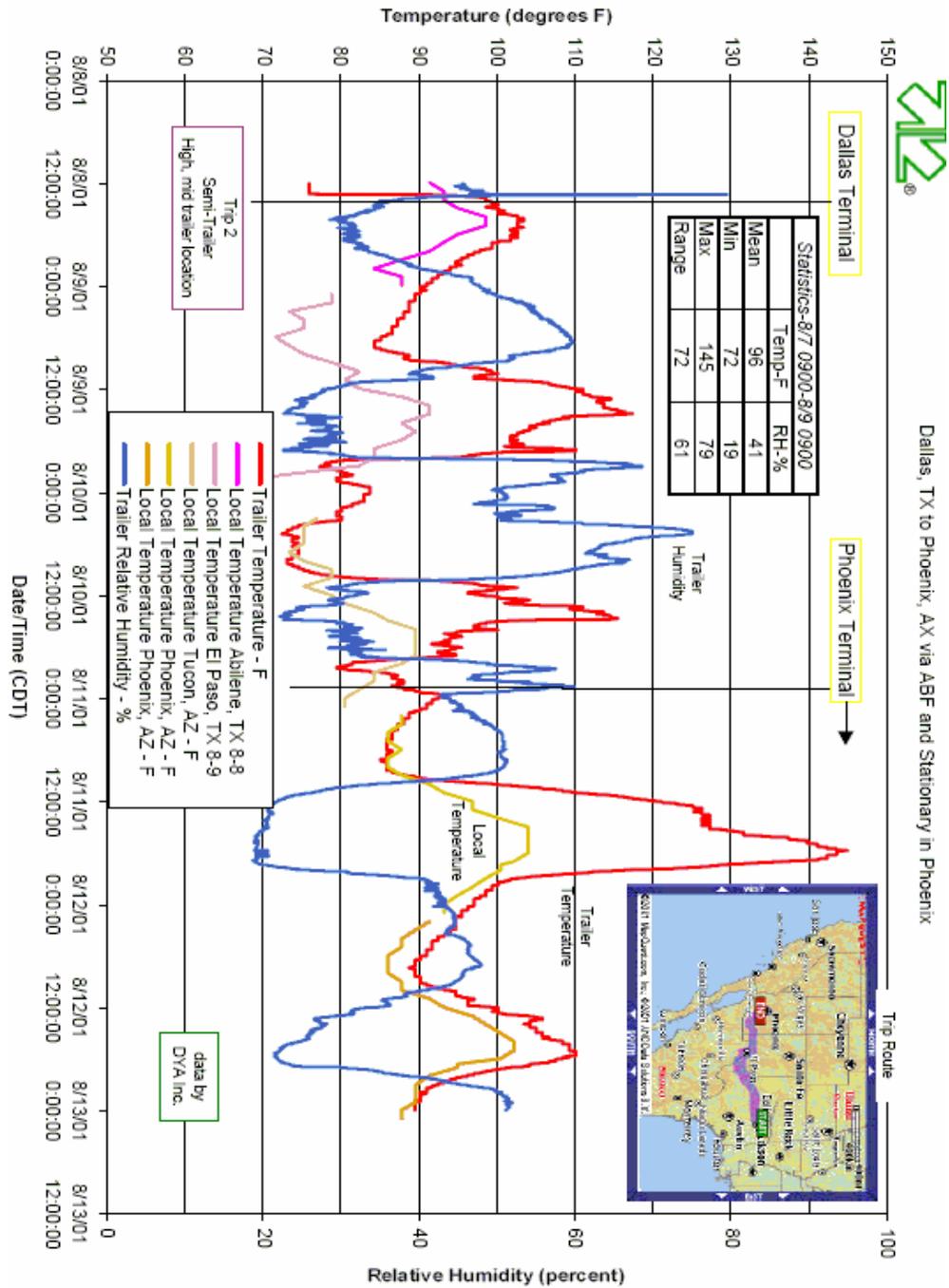
Appendix 8

Graph illustrating the ISTA study result.



Appendix 9

Graph illustrating the ISTA study result.



Appendix 10

Markets for the conventional- respective trio PD-fluid.

Conventional

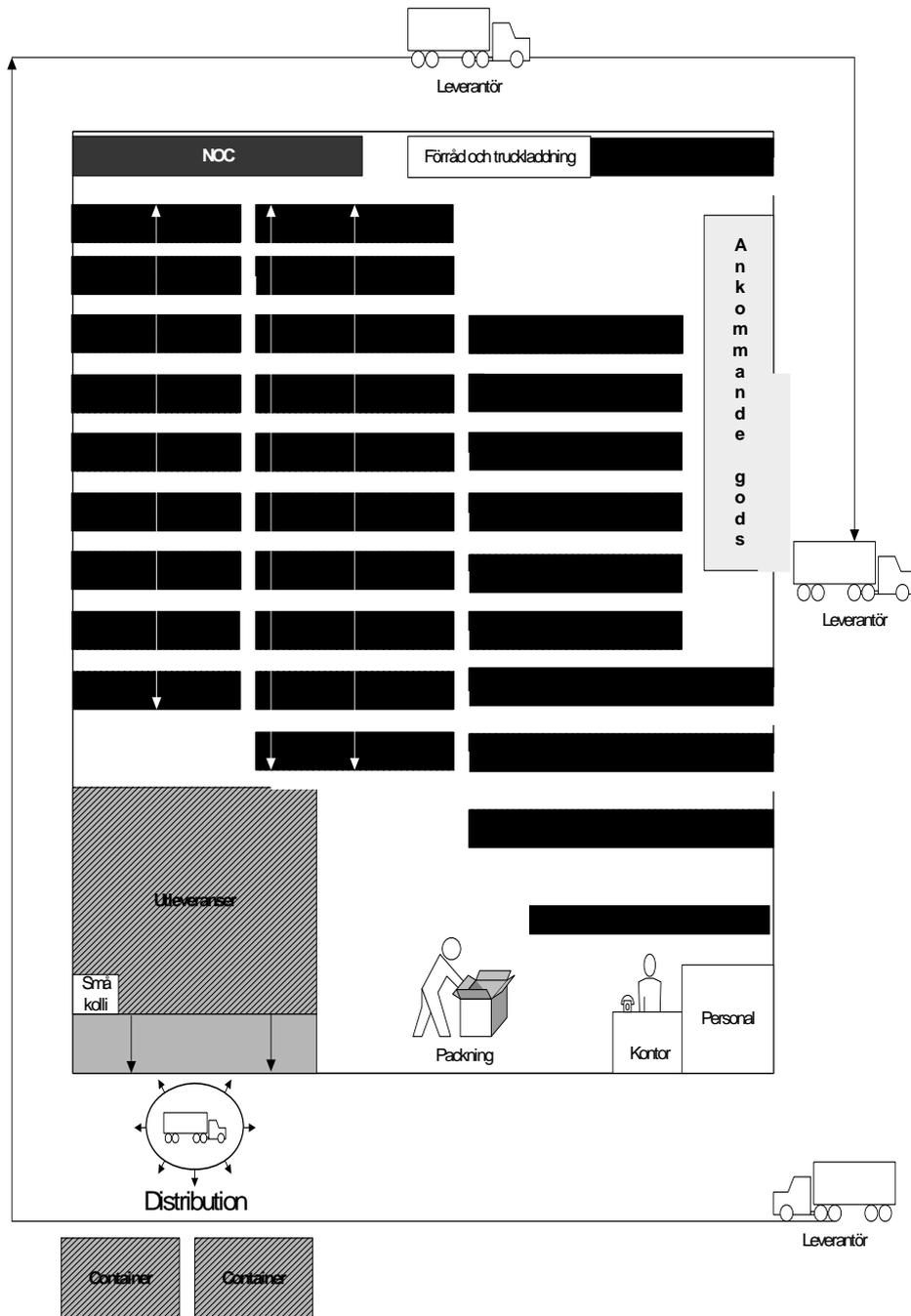
Austria
Belgium
Czech Republic
Estonia
France
Germany
Greece
Hungary
Korea
Kuwait
Latvia
Luxemburg
Poland
Portugal
Slovak Republic
Spain
The Netherlands
United Kingdom

Trio

Australia
Austria
Belgium
Canada
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hong Kong
Korea
Latvia
Lithuania
Norway
Portugal
Slovak Republic
Spain
Sweden
Switzerland
The Netherlands
United Kingdom

Appendix 11

Drawing of the DC Lund warehouse.



Appendix 12

Results from the mechanical temperature loggers.

Period	Transport	Day	Time	Duration	Min temp	Max temp	Average temp	Hours below zero degrees	Hours below 4°C
Initial	1	06-Oct	12.30	2	7.5	15	10		
	2	08-Oct	16.30	2	7.5	15	11		
	3	13-Oct	11.20	2	7	15	11		
Final	1	24-Oct	14.03	3	-2	8	3	10	34
	2	27-Oct	21.00	2	1	10	6		9
	3	29-Oct		2	7	11	8		
	4	31-Oct	14.15	3	7	11	9		
	5	03-Nov	16.50	2	4	14	9		
	6	05-Nov	16.00	2	5	14	10		
	7	07-Nov	15.55	3	4	14	8		
	8	10-Nov	17.03	2	4	10	8		
	9	12-Nov	12.30	2	3	13	7.5		1
	10	14-Nov	16.45	3	4	12.5	7.5		
	11	17-Nov	16.20	2	4	12	7.5		
	12	19-Nov	15.25	2	6	14	11		
	13	21-Nov	16.40	3	6	12	9		
	14	24-Nov	16.45	2	8	14	12.5		
	15	26-Nov	11.15	2	5	12	9		
	16	28-Nov	14.05	3	7.5	12	10		
	17	01-Dec	14.55	2	7.5	14	11		
	18	03-Dec	14.30	2	6	11	9		
	19	05-Dec	15.40	3	0	10	4		27