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PRODUCTION OPTIMISATION AND VALUE CHAIN  
ANALYSIS FOR DECELLULARISED SKIN

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May 09, 2017

THESIS SUBMITTED TO THE DEPARTMENT OF ENGINEERING SCIENCE,  
IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF  
MASTER BY RESEARCH AT THE UNIVERSITY OF OXFORD

## **Abstract**

Due to rapidly advancing developments in tissue engineering, and the depth of its potential for application in the health sector, its involvement in medical therapy have become the focus of pharmaceutical and clinical studies across both academia and industry. Nevertheless, there remains a significant gap between the commercial availability of biomedical technology products and their demand – with high costs and low manufacturing efficiency acting as key contributing factors towards this discrepancy.

For this project, a simple sequential decellularised skin production process was designed based on the available information in the literature. In aiming to minimise the total cost of production, the size and quantity of components – as well as the time-sensitive scheduling of production stages – were optimised. Furthermore, the feasibility of eliminating freeze-drying to reduce the total cost of production was analysed, taking into account the difference between the reduction of operational costs and the additional costs that are incurred due to increased wastage from its reduced shelf life. Finally, this product is examined on a larger scale where all activities – from manufacturing to application – and the total costs incurred throughout the decellularised skin product lifetime is evaluated via the framework of value chain analysis proposed by Porter[1].

# Acknowledgements

Immeasurable gratitude and heartfelt appreciation are extended to the following persons, who in one way or another have contributed towards making this study possible.

First, I would like to express my sincerest gratitude to my advisors, Prof. Zhanfeng Cui and Prof. Aidong Yang, for their continuous support towards my research, and for their patience, motivation and immense knowledge. Prof. Cui's mentorship was invaluable to the research and writing of this thesis, I could not have imagined having a better advisor and mentor.

I would also like to thank my fellow lab mate, Miss Qian Xu, for the stimulating discussions and her company during the numerous sleepless nights where we strove to meet deadlines, and for all the fun and laughter we have shared in the past two years.

Last but definitely not least, I would like to thank my family and my fiancée, Mr. Hang Xu, for supporting me in everything I do, and for being present throughout the writing of this thesis.

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# **CHAPTER 1**

## **INTRODUCTION**

### **1.1 BACKGROUND**

Tissue engineering applies engineering principles and the knowledge of cellular and biological sciences to the creation of live tissue substitutes to improve or compensate for the function of diseased or lost human tissue – an important component of regenerative medicine. The scope and relevance of tissue engineering in regenerative medicine have grown tremendously in the past few decades. It is currently possible to grow viable bone, blood vessels, cartilage and even muscles with the current technology.

The cell is the basic functional unit that forms a tissue and groups of cells create a system known as the extracellular matrix, which act as a scaffold of relay stations where information is transduced through the action of various signaling molecules. At these relay stations, biochemical processes can be controlled and regulated. Researchers have been able to manipulate and control these stations by artificially developing and building these scaffolds with substitute components[2]. With regard to tissue engineering, these scaffolds provide an essential cellular framework for engineered tissue products but can also function in isolation such as in allowing the implantation of functional biomaterials

and are usually made using synthetic polymers or natural biopolymers. There are two methods of creating scaffolds: cells can be allowed to self-assemble or newer tissues can be created by building on existing scaffolds[3]. These are then used in the bioengineering processes of the organ systems.

In general, a combination of engineering, cell technology and material production processes are synergised to improve the production of tissue engineering products. As an example of an emerging technology, 3D printing provides a cost-effective approach for the development of tissue engineering scaffolds. Since the integrity of 3D complexity is critical to establishing multicellular interactions[4], 3D structural considerations must be factored into the development of scaffolds, which can be achieved using this method. In tissue engineering, the greatest challenge remains the need to provide and accommodate multiple cell sources to meet the patient's customised needs. While polymer hydrogels composite and cell aggregate systems can be synthesised by cost-effective 3D manufacturing processes, these accurate developments and heuristic processes need to be considered [5].

In situations where artificial cellular components are inadequate in aiding recovery, the use of pluripotent stem cells serves as an important technology in the development of scaffolds. These progenitor cells can differentiate and develop into multiple cell types, providing potentially diverse solutions to tissue engineering needs for more than two decades. However, the required experimentation and high development costs result in

production expenditures that are so extensive that they act as a barrier to effective commercial utilisation by the masses[6]. Therefore, despite its potential, high production costs remain a major factor that impedes the commercial development and application of tissue engineering. The cost of production can be divided and analysed by examining the direct costs involved in production or indirect costs that differ based on the individual requirements of the patients. Future research that focus on either of these aspects are important so that the potential of tissue engineering as a form of specialised healthcare can be realised and made more accessible to the public.

Decellularised skin is a biomedical product that can be applied to compromised skin, such as burns or skin ulcers. The product is applied as a wound dressing and participates and aids in skin renewal; derived from porcine biological components, the cellular contents are released and only collagen matrices remain and participate as the active recovery agent. Decellularised skin serves three main functions: the first is to act as a physical barrier that prevents bacterial infections which infiltrate the skin; secondly, it prevents moistening of the injured area, which can delay healing and promote secondary infections. The third function supersedes the action of normal bandages, participating in wound healing by supplying biological tissue infrastructure. The porcine-derived skin collagen matrix has a microscopic structure that closely resembles the components human skin, providing a scaffold for the patient's skin cells to integrate and allowing the skin to recover without scar formation.

## 1.2 AIMS AND OBJECTIVES

Focusing on decellularised skin, a relatively simple and well-understood tissue engineering product, this thesis aims to explore systems engineering and apply analytical approaches to the reduction of costs for producing and applying decellularised skin products. The specific objectives are:

1. To apply the model established by Lin and Floudas in describing the whole production process of decellularised skin, based on a State-Task Network (STN).
2. To determine model parameters using a combination of parameters from the literature and from performing market research.
3. To develop and validate a numerical model using the parameters and constraints of an optimisation model found in the literature which uses a General Algebraic Modelling System (GAMS).
4. To optimise the decellularised skin production process by applying the developed model, which consists of all the parameters and constraints that relate to production.
5. To evaluate the feasibility of eliminating the freeze-drying step of the production process by weighing the advantages (reduction in production time and consumption of electricity) and disadvantages (reduced shelf life will lead to greater wastage) of the alternative production method (refrigeration at -80).
6. To perform a value chain analysis that determines how the value of the

decellularised skin product is incremented from the raw material to the final treatment product during production.

### **1.3 OUTLINE OF THE THESIS**

The thesis consists of six chapters. Following the brief introduction in Chapter 1. Chapter 2 presents a concise literature review which focuses on the relevant aspects of tissue engineering, schedule optimisation, production with freeze-drying and value chain analysis. In Chapter 3, the details concerning the optimisation model and the optimisation results are presented. In Chapter 4, the advantages and disadvantages of using a freeze-dryer in the production of decellularised skin are considered. Furthermore, the cost-effectiveness of using hypothermal storage as a replacement for freeze-drying in terms of varying shelf life and waste percentage are examined, to determine how long a shelf life is required for the alternative production method to be more cost effective. In Chapter 5, the value chain analysis for the production of decellularised skin is performed, where each step in the entire production process that leads from the conversion of raw materials to the end product is evaluated, to identify potential avenues that can be fine-tuned to further reduce production costs.

# **CHAPTER 2**

## **LITERATURE REVIEW**

### **2.1 RECENT DEVELOPMENTS IN TISSUE ENGINEERING**

In recent decades, with increasing developments in tissue engineering in biology, stem cell therapies and cell-based treatment have become the focus of pharmaceutical and clinical studies in both academia and industry. Due to the regenerative features of stem cells, stem cell therapies have been mainly developed to handle organ failures and degenerative diseases[7]. For 50 years, since the first hematopoietic cell transplantation (HCT), or bone marrow transplant, was successfully carried out, HCT technology has been exploited in the treatment of diseases, including leukaemia and multiple myeloma[8]. More recently, in addition to their application in HCT, stem cell and cell-based therapies have also been used to treat burns and to regenerate the corneal epithelium[7]. In terms of cell-based therapeutic applications, treatment materials essentially involve mesenchymal stem cells, induced pluripotent stem cells or other derivative cells from these cells. In 2013 in Japan, the first clinical study was carried out which applied induced pluripotent stem cells to the treatment of macular degeneration caused by aging[9]. In fact, research into stem cell therapies has grown rapidly since 2006, although this

technology is associated with certain safety concerns[10]. Indeed, with regard to the genetic instability in culture as well as the possibility of tumour transformation in long-term culture conditions, the clinical application of stem cell therapies is in its preliminary stages[11]. Although stem cell therapy and relevant regenerative pharmacy manufacturing are promising, these technologies are still in the initial stages of testing, and have been applied only in academic centres and in laboratories[8]. As a result, a long route of clinical testing is required, including the performance of large-scale efficacy trials to develop successful cell-based therapies.

While the implementation of cell therapy to daily clinical practice can seem distant and challenging, there has been considerable progress with regard to their clinical application. According to research reports, the cell therapy sector is steadily progressing [12, 13]. More importantly, in order to encourage prospective new therapies for severe diseases, the US government has passed and implemented the Food and Drug Administration (FDA) Safety and Innovation Act which hastens and facilitates the research and development period, and accelerates the time required for their approval for use in pharmaceuticals and medical therapies[14]. Meanwhile, funding offered by the California Institute for Regenerative Medicine for commercial activities has been made available for pharmaceutical organisations, which provides substantial funds towards the research and development of cell-based new drugs[15]. Another stimulus to cell therapy growth is attributed to the funding from the US Defense Department, which supports cell-based

therapeutic research that specialises in supporting the recovery of thermal burns and radiation injuries[15]. Moreover, because regenerative medicines serve both to treat chronic diseases and drive economic growth in the pharmaceutical sector, they are encouraged by governments. Indeed, leading industrialists from the UK and USA have recommended their governments address the regulatory challenges in research and development faced by the cell-based regenerative pharmaceutical industry. Meanwhile, according to the NASDAQ Biotech Index[16], the cell-based pharmaceutical sector generally experienced steady and healthy growth, indicating favourable economic and market conditions for cell-based, regenerative medicine manufacturing. Most importantly, the progress in clinical trials of cell therapies funded by clinicians from academia as well as corporations from the industry essentially indicates healthy growth in the pharmaceutical sector[15].

## **2.2 OPTIMISATION OF PRODUCTION SYSTEMS DESIGN AND SCHEDULING**

### **2.2.1 Classification of batch process scheduling problems**

Scheduling is a crucial issue for improving production performance and discussions to optimise production methods have been ongoing for the past few decades (e.g. [17-20]). However, the capacities of different methods are different in terms of handling variables such as batch size and storage.

In order to develop a scheduling model for batch processes, a systematic characterisation of batch processes must be considered which takes into account the most relevant problematic features. The main features of batch processes include 13 major categories, concerning not only the raw material (feed) and primary equipment, but also consumer demand and time-related constraints, which for example, relate to process topology, equipment assignment, equipment connectivity, inventory storage policies, material transfer, batch size, batch processing time, demand patterns, changeovers, resource constraints, time constraints, costs, and degree of certainty.

First, the complexity of batch process problems is significantly influenced by its topological implications. Most batch processes are sequential, i.e. they follow a chronological order of events that are defined by the product recipe. Sequential processes can be further divided into single or multiple stage processes, and a multiple stage process can either describe a multi-product or a multi-purpose process. The main difference between a multi-product and multi-purpose process is determined by whether the products in the plant are produced within the same production path. In a multi-product process, all the batches follow the same production path, while in a multi-purpose process, the batches can be derived from multiple production paths. However, as the applications become more complex – for instance, when the production recipes include operations such as mixing, splitting and material recycling – networks with an arbitrary topology must be applied. The assignment of equipment can be fixed or variable and the equipment

can be partially or fully connected.

Secondly, inventory policies can be included as another important process flow parameter. These often include factors such as unlimited intermediate storage, non-intermediate storage, finite intermediate storage and zero-wait. The factor of batch size can be fixed or variable. Pharmaceutical plants usually handle fixed batch sizes as the integrity of product needs to be maintained, while polymer plants tend to handle variable batch sizes as the intermediate product can be mixed or split. Similarly, both fixed and variable batch processing time can be found in different plants depending on the product characteristics. Demand patterns can also vary, either with respect to a fixed due date that must be met without fail or a production target within a fixed time frame. Another important factor is the turnover rate, with the transitions being either sequence-dependent or unit-dependent. As with equipment and resource constraints, limitations in utilities and labour are also an important factor that can complicate scheduling matters. In addition, time constraints caused by non-working periods, maintenance periods and shift periods also need to be considered, as they occur in reality and disrupt the production flow. Furthermore, cost is an important issue; and the costs of equipment, utilities, inventory and changeover must be considered. Finally, the issue of data uncertainty should be considered, as they exert a profound impact on production in the long term. Overall, it is clear that a wide range of factors need to be considered when dealing with batch scheduling problems.

### **2.2.2 Batch process scheduling optimisation methods**

A number of researchers have discussed the methods for optimising production (e.g.[17-20]), although not all of them are relevant as their implications apply to a limited range of batch sizes and storage practices. The complexity of multi-purpose/multi-product batch plants is a result of numerous features of batch scheduling issues, including process structure, equipment requirements, materials, batch size and storage policies. These features creates a diverse set of problems that must be individually optimised.

In general, according to the type of representation, the optimisation models can be classified according to four principles[21].The first is time representation, where optimisation methods differ depending on whether events occur randomly in time or within a fixed time frame that can be known in advance - these behaviours are described in the discrete-time and continuous-time model respectively [22].

In terms of the principle of material balances, there are also two types of optimisation methods: the state-task network (STN) and the resource-task network (RTN). A novel feature of the former is that both the individual batch operations (“tasks”) and the feedstocks, intermediate and final products (“states”) are included explicitly as network nodes. Processes involving the sharing of raw materials and intermediates, batch splitting and mixing, and the recycling of materials can be represented unambiguously by such networks[23-26].

The third principle concerns the formulation of the objective function. This classification determines the model computational performance, constraints and speed.

The last principle is event representation, which governs how scheduling models are designed, which are determined by specific events or concepts that are used to allocate resources appropriately.

The discrete-time method is applied when it is feasible to divide the production period into fixed time intervals, where all the events can be chronologically aligned. This method was studied by Bowman[27], and its applicability to chemical processing has been more recently considered, see for example [28-30].

The limitation of the discrete-time method affects its performance in some aspects, and thus the continuous model is attracting more and more attention. There are two types of computational processes that can solve this kind of problem. The first is the sequential process, which arranges the events according to the order of the production process and does not consider the balances of mass. This is more suitable for products with a relatively large, fixed market demand. Pinto and Grossmann[31] used this method and made some improvements to it. Lamba and Karimi[32], and Moon[33] made a significant contribution to this approach in building the continuous-time models. These sequential processes are widely employed to cope with multi-purpose plants which have diverse features, such as different batch size, various intermediates and different storage policies.

The optimisation of multi-purpose plants needs to combine the synthesis, scheduling and design at the same time, otherwise it is easy to over- or under-design[34, 35]. For the purpose of planning a plant production with a given time horizon, the difference between lower-level and higher-level sequencing problems need to be determined. The former specifies the exact time (event time) of each batch of material going through the production process. The latter is meant to specify the number of batches of each product so that the production requirement can be fulfilled. In typical industrial production, the distinction between “scheduling” and “sequencing” is not clear as both of them need to be considered. Egli and Rippin[36] considered this problem and have reported algorithms considering both sequencing and scheduling. This Mixed-Integer Non-Linear Programming (MINLP) problem was solved by various methods with different assumptions. Crooks[37] applied the STN network and a discrete-time method to the process of integrating the synthesis, scheduling and design processes. Then Barbosa-Póvoa and Pantelides[38] utilised the RTN discrete-time modelling to deal with this problem and solved the related MILP problem. However, most of these models are based on certain data and assumption. The uncertainty of the chemical processes, such as the parameters, environmental conditions and potential accidents, still needs to be coped with.

In summary, the existing methods that deal with the multi-purpose batch plants can be classified into different types according to the time representation and several other features. The discrete-time approaches suffer from their inherent limitations, and

therefore more and more attention has been paid to the continuous methods. Various continuous-time models have been established based on time slots or event points. Meanwhile, some other researchers have studied the problems of uncertainty of chemical processes using different methods. However, these optimisation algorithms still need to be improved and the mathematical models need to be enhanced to solve the integrated design and scheduling problems more efficiently.

### **2.2.3 Scheduling constraints captured by alternative optimisation approaches**

Following the classification of batch process scheduling problems and key factors to be considered, this section presents the specific model variables and model equations which are included in the most relevant existing work[39-42]. The main model equations include allocation constraints, capacity limitations, mass balance constraints, batch size constraints, time and sequencing constraints, and resource balances.

An allocation constraint usually imposes the condition that no more than one task can be performed in unit  $j$  during time interval  $t$ . This constraint is usually implemented by a binary variable  $w_{ijt}$  for each task  $i$ , and its expression can be slightly different in different approaches. This variable has a value of 1 when task  $i$  is started in unit  $j$  at time  $t$ . There are also capacity constraints. These usually indicate that the batch size, which is usually represented by the variable  $b_{ijt}$ , should fall between the minimum capacity and

the maximum capacity of the equipment. The variable  $b_{ijt}$  indicates the batch size of task  $i$ , which is processed by equipment  $j$  at time  $t$ . Batch size constraints are similar to capacity constraints; some models use batch size constraints to impose the minimum and maximum batch size at the beginning and the end of each task. Mass balance constraints usually indicate that each state  $s$  of the product at time point  $n$  should be equal to the material (or intermediate product) which is remaining in time point  $n-1$ , plus the material produced at time point  $n$ , minus the material consumed at time point  $n$ . The time and sequencing constraint is usually used to enhance the requirement that the starting time of task  $i$  should be greater than the finishing time of the task. The resource balance is used to describe the relationship that the resources available for time point  $n$  are equal to the excess amount of resources at time point  $n-1$  adjusted by any material produced/consumed by tasks which start/end at time point  $n$ .

#### **2.2.4 Application of batch process scheduling optimisation**

In real-world industrial problems, complexity arises from a combination of a wide range of operational constraints which need to be considered, such as very large-scale production, multiple units available for each task, etc. Literature in the field of scheduling optimisation of biotechnology and biochemical processes is fairly limited. Samsatli and Shah[19] have proposed an optimisation model for the biochemical production process of an intra-cellular enzyme. The production is composed of a fermentation stage (or stages) followed by a number of separation stages; the process involves nine production stages

and four operation units (pieces of equipment). The variables in this model include both continuous variables and binary variables; the problem may be formulated as a mixed-integer programming one. The optimisation of this biochemical process has been divided into two parts. In the first part, the selection and the capacities of the equipment are decided. In the second part, the exact sequence of the process and the timing of the tasks are decided using the results obtained from the first stage. The formulation of the second-stage optimisation is based on a discrete uniform time grid. The second example is from Jennings et al.[43], who tried to apply optimisation to a chromatographic process widely used in the separation and fraction of multicomponent biochemical systems. They optimised the process by maximising the throughput (measured by a minimum operational time) and the resolution (measured by the difference between two successive breakthrough times) for the system. In order to optimise the chromatography systems, the variables are approximated by a piece-wise linear function, so that the problem can be solved without developing a new optimisation algorithm.

A scheduling optimisation problem for the polymer industries was studied by Wang, Loll, Stobbe and Engell[44]. It deals with a multi-product batch plant where two types of expandable polystyrene with different grain fractions are produced following the same process sequence. The scheduling goal is not only to satisfy the customer orders with minimum delay, but also produce the right amount of grain so as to minimise the production of unwanted fractions. The problem is intrinsically non-linear; therefore, it is

represented through a mixed-integer non-linear mathematical problem formulation. Wang, Loll, Stobbe and Engell[44] developed a formulation which includes 1,009 binary variables and 2,656 variables in total. It is impossible to use general purpose algorithms to solve the optimisation problem with such a large number of variables. They took into account particular problem features and used a special scheduling algorithm to get a sub-optimal solution in a reasonable CPU time.

A value chain is defined as a range of activities that starts at the design phase and is followed by the production, marketing and end with distribution of the product[45]. In other words, it is the process deployed by industries from the very start to the final delivery of the products. The value chain begins with the procurement of the raw material and how it is sold to the consumers. This is different from supply chain management. The primary goal of the value chain is to ensure that each stakeholder in the value chain effectively communicates with all others[46]. Logistics management is a part of the value chain that is used to meet the requirements of the process by the efficient transporting and storage of the products. Effective logistics management aids in the reduction of expenses and enhances the product quality while meeting consumer demands. To achieve this, there should be an appropriate selection of vendors with the capacity to provide transport, which should be achieved by choosing the most effective route. There should be a competent delivery method for the products to reach the consumers[46]. The introduction of the required software and information technology resources are needed to handle the

processes. Businesses are continually looking for ways to improve the business design to improve productivity and reduce the costs involved while ensuring that the quality and safety of the products[46]. This requires complex heuristics and efficient management.

## **2.3 PRODUCT PRESERVATION AND THE FREEZE-DRYING PROCESS**

Two frequently used methods for preserving biomedical products are freeze-drying and freezing (the product is preserved at  $-80$  degrees Celsius)[47]. Both of the methods are expensive. However, these methods have the advantage that they can give the biomedical product a long shelf life (usually around two years)[48]. Freeze-drying prolongs the shelf-life of specimen by dehydration – it works by freezing the specimen to an extremely low temperature, ultimately reducing the surrounding pressure and causing the water content to sublime. This process is used by the pharmaceutical companies to increase the shelf life of vaccines or other medicines. Since freeze drying results in the desiccation of the material, it becomes more feasible for them to be transported in glass vials, or in the form of lyophilised or dry powders. Due to the latter advantages, freeze-drying widely used in the food industry, and also in the preparation of biological samples for microscopy [49].

At the industrial level, freeze-drying is a slow process as each stage is time consuming, resulting in high operation costs that evolve from the high energy and electrical requirements[50]. Therefore, the expense of time and financial capital in the production

of decellularised skin can be dramatically reduced by omitting the freeze-drying process. Given the above limitations, more efforts are needed to improve the storage for organic perishable products. While storage and transport are stages beyond production, these are fuel into the overall cost of the value chain for producing tissue engineering products.

## **2.4 VALUE CHAIN ANALYSIS**

A value chain analysis allows one to achieve an intricate understanding of all the different activities and processes that are involved in a supply chain, from the procurement of raw materials to the application of the completed product. Here, value is defined as the economic value created during each step of the process or activity. Value chain analysis is widely applied as a support tool to aid industrial decision making. The activities concerning inbound logistics, operations, outbound logistics, marketing and services are all important primary elements of the value chain[51]; secondary activities concerning the procurement of products, management of people, provision of infrastructure and technological needs are also integrated into the value chain analysis[51].

The volatility of consumer and market demands motivate businesses to perform value chain analyses, since it yields critical information that allows one to negotiate the difficult task of inventory management. The most helpful outcome of a value chain analysis is the development and optimisation of processes that address the issues of storage and logistics to adapt to varying market demands. Market erraticism creates a need for continual re-

evaluation and re-design of business processes to maintain healthy supplier/customer relationships. Thus, the performance of value chain analysis helps companies to address efficiency issues that are introduced by the unpredictability of market demands.

For companies that handle perishables such as food and other bio-products, contamination due to improper management can result in additional wastage and contribute to disease-spreading. During transport and storage, measures should be taken to safeguard against any interaction with microbial pathogens or contaminants that can compromise or degrade the quality of the products. These measures will inevitably incur additional costs to the companies, which can be rather significant in certain cases[52]. Recent research supports the idea that value chain analysis helps to address most of the latter issues by revealing steps in the production chain that can be modified to reduce costs and maintain product quality.

#### **2.4.1 Important considerations of value chain analysis for biomedical and pharmaceutical products**

The first step that is required to begin the value chain analysis process is to define the inbound and outbound logistics that are involved. In the case of biomedical and pharmaceutical industries, where goods are highly sensitive to changing temperatures and have a relatively short shelf life, the cost of incubation become important to the value chain analysis. These goods include serum, bacterial cultures and stocks, microbes,

antibiotic and culture plates, which must be stored at specific temperatures[51] [53].

In the biotechnology industry, manufacturing activities are distributed into three phases: the discovery phase, the testing phase and the manufacturing phase [54]. The discovery and clinical testing phases typically require a large amount of capital[54] [55], which have to be carefully considered during cost analysis. Once the product has been developed and approved, protocols concerning patenting and manufacturing become relevant. Biotech companies are required to possess the relevant equipment to allow that to adopt the required procedures and quality control measures to ensure that their product meets the stringent manufacturing standards that are often set by regulators [53].

#### **2.4.2 Example applications of value chain analysis in other sectors**

Due to concerns about climate change, local governments have introduced incentives to motivate companies to adopt greener practices in their production. A green innovation value chain, which provides a schematic framework that indicates where greener technologies can be used as alternatives to increase the value of the product in production and distribution, is useful for this purpose[56]. Energy and resource savings in the various activities and processes that contribute to the value chain improve the financial yield. For example, the successful utilisation of photovoltaic solar power chains to deliver products that also meet safety and the quality checks have been described[57]. However, the increased infrastructure costs can serve as an impediment to the implementation of

photovoltaic systems. Overall, the incorporation of more green value chains will act to promote mass-market acceptance while yielding higher financial returns[57]. Although the technology is available to aid the transition, future research should focus on reducing infrastructure costs to make this approach more attractive. This greener approach holds promise as it can be adapted to meet commercial requirements while also acting to safeguard the environment[58].

In the food industry, value chain analyses highlight the value of blanching, a process of scalding food products such as vegetables in boiling water or steam for a short period of time [59]. Blanching can be used as a sterilisation process that removes any microbial pathogens or contaminants; the procedure also aids in preventing the loss of vitamins and minerals while brightening the colour of food. The benefits of this system are that it enables increasing the shelf life of products across the whole value chain[60]; research have also found that the drying time can be reduced by blanching. Although blanching is predominantly used in the food industry, it may serve biomedical applications at a larger scale.

Another industry that highlight the importance of value chain studies is reflected in the practices adopted to facilitate fish- and marine-related sales on the Pantar Island in Indonesia, which rely heavily on their maritime industry. The fish products and marine products are collected, processed and traded with an intermediary before the wholesale trading and consumption of the products. During a value chain study, it was found in this

analysis that the involvement of the local communities and individual households in the supply chain led to improvements in the production and maintenance of quality standards[61]. Here the value added is from the local community support. The results indicate that increasing individual household engagement led to a corresponding increase in fish trade and enhances household food security. Hence, apart from scientific advancements, increased stakeholder involvement can also be beneficial to the valuation of the supply chain[62].

## **2.5 SUMMARY**

In the literature review, the recent developments in tissue engineering were briefly discussed. In order to support the understanding of concepts relating to batch scheduling optimisation, production systems design and scheduling factors including the classifications of batch process scheduling problems, batch process scheduling optimization methods, scheduling constraints captured by alternative optimisation approach and the application of batch process scheduling are described and discussed. Secondly, the benefits and the limitations of freeze-drying in production are briefly examined. Finally, the concepts and principles of value chain analysis are discussed.

This thesis is innovative in these three areas: (1) the optimisation of production scheduling, which has hitherto not been applied to tissue engineering products; (2) the consideration of an alternative preservation method (other than freeze drying) in the production of decellularised skin and an assessment of its feasibility; (3) the performance

of value chain analysis on a tissue engineering product, which has also not been reported in the literature.

# **CHAPTER 3**

## **OPTIMISATION OF PROCESS DESIGN AND SCHEDULING FOR PRODUCING DECELLULARISED SKIN**

### **3.1 INTRODUCTION**

In recent decades, with increasing developments in tissue engineering, stem cell therapies and cell-based treatment have become the focus of pharmaceutical and clinical studies in both academia and industry. There is a big gap between commercialised biomedical technology products and demand for them. Supply chain optimisation seems to be a crucial factor being considered in recent years. The aim of this chapter is to apply a detailed scheduling optimisation mathematical formulation to a production plant for decellularised skin.

During the second and third quarter of 2012, favourable changes in regulation of the USA FDA, stock market activity and business promotional news played a positive role as external forces in driving forward the development of the cell therapy industry[15]. In particular, research into the application of a decellularised extracellular matrix for the

induction of other target tissues and the transplantation of skins for burn recovery has been a strong focus in recent years in the cell therapy industry[63].

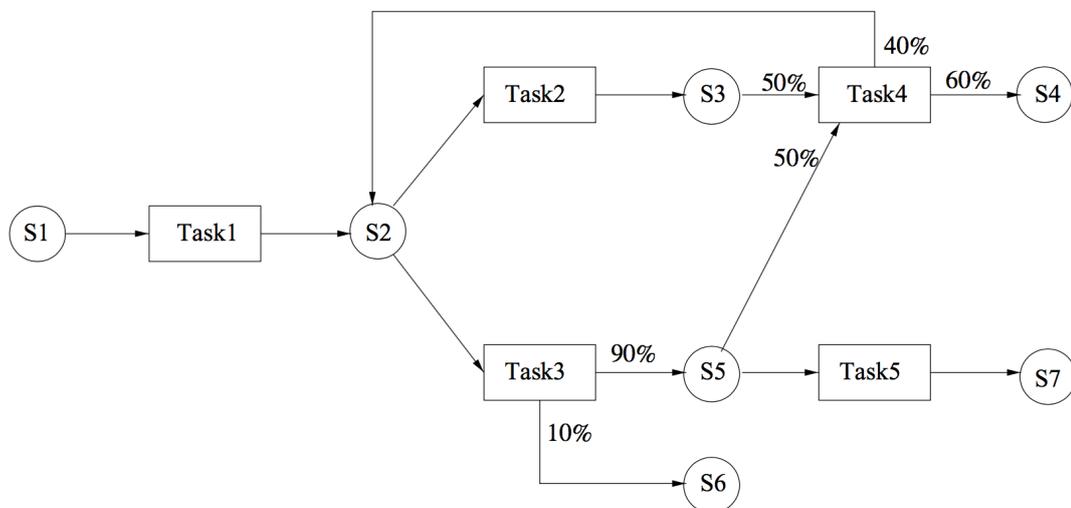
However, production and commercialisation of the therapeutic products is essential for ultimately providing consumers with affordable, accessible and high-quality therapeutic solutions to burned skin transplantation and induced regeneration of skin tissues[64]. Currently, the limited scale of production is still a problem, one which fundamentally affects players throughout the supply chain in the medical industry. In particular, the small quantity procurement of raw materials and components will inevitably raise costs for manufacturers, followed by an increase in logistics costs (inventory and transport) due to small batch size production. All these will ultimately lead to comparatively low profit margin for retailers (clinics, pharmacies and hospitals) and/or high purchase price for consumers (patients). Therefore, the issue of small-scale production is causing problems for the competitiveness of the participants in the whole supply chain, which necessitates the optimisation of the production process in the batch plants in order to reduce costs and increase the affordability of the products[29].

For batch processes, existing work [23] on conventional chemical production shows that it is necessary to take design, synthesis and scheduling processes into account holistically. Specifically, in order to represent the processing requirements effectively for scheduling and coordinating the materials and equipment during the process of production, the

STN[23, 65] can be applied to facilitate establishing the MILP model for the production of therapeutics and medicines.

*STN model: representation of production process*

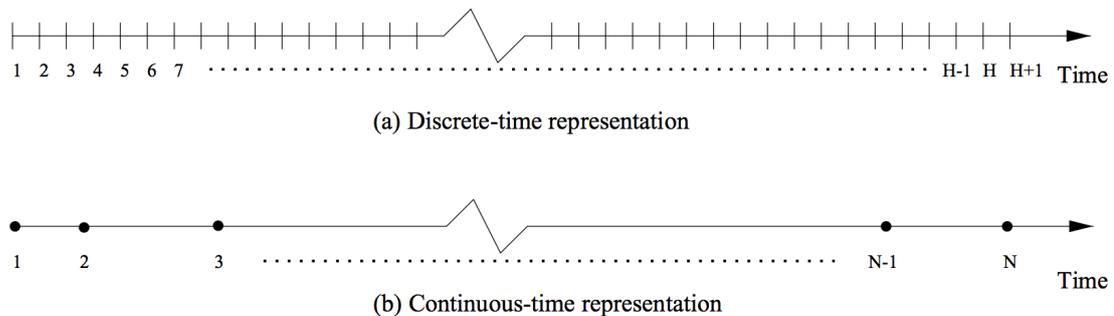
The model presentation of the process of producing biotherapeutics in different batch sizes can be complex. Therefore, aiming at effectively representing the process with clarity and conciseness, the STN model has been proposed by Kondili[23] and applied to resolve this problem. The STN model (see Figure 3.1) is a framework characterised by two types of nodes to indicate the complex process of bio-production: the circular state nodes are used to represent production materials, intermediate products or final products, while the rectangular task nodes are used to represent chemical or physical processes such as heating, cooling, reacting, washing or other types of unit operation. The fractions represented above the process arch correspond to the proportion of consumption or production of a task event.



**Figure 3.1** Example of a production process represented by the STN model[66]

STN model: representation of favourable time horizon

With respect to the production practice in the real world, variable time intervals between fixed-task events are crucial to the optimisation of the processing time of the target product. Therefore, a continuous-time model approach (see Figure 3.2) characterised by time interval variables in the whole processing time horizon is usually preferred over a discrete-time model approach[66]. In fact, managing float variables in the time horizon of the programme (i.e., the biochemical production process) gives the STN model greater flexibility[67]. For example, effective arrangements of the time intervals between task events, such as changeovers, storage of intermediates, batch operation and resource restrictions, can be taken advantage of, thereby allowing for greater accuracy and flexibility in the production process of the target therapeutic product.



**Figure 3.2** Representation of time in STN model: discrete and continuous[66]

Based on the STN model and its successful application in batch production processes, it is proposed to develop the optimisation method for the production process of decellularised skin based on the STN model and the MILP framework.

Both the STN and MILP models have been used quite extensively in solving problems in other areas; however, they have rarely been used in the area of scheduling optimisation for the cells-based product industry. For example, multi-purpose batch plants have been studied by Barbosa-Póvoa and Macchietto[38] to design a detailed formulated multi-purpose batch plant based on the STN description, by solving an MINLP model. The current work aims to find a mathematical model which is suitable for the simultaneous design and scheduling of the production process of decellularised skin. The simplified decellularised skin production process is designed according to literature information in this area[65].

In this work, the optimisation of the production process will be solved using the GAMS (General Algebraic Modeling System), which is a high-level modelling system for mathematical programming and optimisation. The objective of the optimisation is to minimise the total cost by choosing the proper size of the equipment, the quantity of the equipment with same function to be employed, and the proper scheduling of production.

### **3.2 MODELLING METHODOLOGY**

There are some scheduling properties which need to be addressed in the production process of decellularised skin:

- Production process: representing the manufacturing sequences of target products;
- Equipment/units: availability and capacity;

- Favourable time horizon based on continuous-time model: specifying timing for the individual task events; variable time intervals; batch size (including both the consumption of materials and the production of the target products).

A model-based optimisation approach is adopted in this work to optimally determine the attributes above. In the rest of this section, a detailed mathematical model derived from the literature is presented, with previously reported results replicated. This model is then customised to the skin decellularisation process.

### 3.2.1 The model by Lin and Floudas[65]

Lin and Floudas[65] have presented a detailed mathematical model for the optimal design and scheduling of batch processes. The model is based on STN representation.

The main decision variables are:

$e(j)$	binary variables that determine if unit ( $j$ ) exists;
$b(i,j,n)$	the batch size, which determines the amount of material undergoing task ( $i$ ) in unit ( $j$ ) at event point ( $n$ );
$s(j)$	variable that determines the size of unit ( $j$ );
$wv(i,n)$	binary variable that assigns if task ( $i$ ) is undertaken at the beginning of event point ( $n$ );
$yv(j,n)$	binary variable that assigns if unit ( $j$ ) is being used at event point ( $n$ );
$d(s,n)$	variable that determines the amount of product needed to be delivered to market at event point ( $n$ );
$st(s,n)$	variable that determines the amount of state ( $s$ ) at event point ( $n$ );
$t^s(i,j,n)$	variable that determines the time that task ( $i$ ) starts in unit ( $j$ ) at event

point ( $n$ );  
 $t^f(i, j, n)$  variable that determines the time that task ( $i$ ) finishes in unit ( $j$ ) at event point ( $n$ ).

### Indices

$i$  task;  
 $j$  units;  
 $s$  states;  
 $n$  event points representing the beginning of a task or utilisation of a unit.

### Sets

$I$  tasks;  
 $I_j$  tasks that can be performed in unit ( $j$ );  
 $I_s$  tasks that either produce or consume state ( $s$ );  
 $I_p$  processing tasks;  
 $I_t$  storage tasks;  
 $J$  units;  
 $J_i$  units that can perform task ( $i$ );  
 $J_t$  storage units;  
 $S$  all involved states;  
 $S_t$  states that can only be stored in dedicated storage units;  
 $N$  event points within the time horizon.

### Parameters

$\rho_{si}^p, \rho_{si}^c$	proportions of state ( $s$ ) produced and consumed by task ( $i$ );
$\alpha_{ij}, \beta_{ij}, \gamma_{ij}$	constant term, coefficient and exponent of variable term of processing time of task ( $i$ ) in unit ( $j$ );
$H$	time horizon;
$p_s$	$\rho$ price of state ( $s$ );
$r_s$	market requirement for state ( $s$ ) at the end of time horizon;
$V_j^{min}, V_j^{max}$	minimum and maximum possible sizes of unit ( $j$ ).
$d(s, n)$	variable that determines the amount of the product that needs to be delivered to market at event ( $n$ );

### Variables

$e(j)$	binary variables that determine if unit ( $j$ ) exists;
$b(i, j, n)$	the batch size, which determine the amount of material undertaking task ( $i$ ) in unit ( $j$ ) at event point ( $n$ );
$s(j)$	variable that determine the size of unit ( $j$ );
$wv(i, n)$	binary variable that assigns if task ( $i$ ) is being undertaken at the beginning of event point ( $n$ );
$yv(j, n)$	binary variable that assigns if unit ( $j$ ) is being used at event point ( $n$ );
$st(s, n)$	variable that determines the amount of state ( $s$ ) at event point ( $n$ );
$t^s(i, j, n)$	variable that determines the time that task ( $i$ ) starts in unit ( $j$ ) at event point ( $n$ );
$t^f(i, j, n)$	variable that determines the time that task ( $i$ ) finishes in unit ( $j$ ) at event point ( $n$ );

## Constraints

### 1. Existence constraints

$$y_{\nu}(j, n) \leq e(j), j \in J, n \in N \quad (3.1)$$

These constraints express the requirement that a unit can be utilised only if it exists.

### 2. Unit size constraints

$$V_j^{\min} e(j) \leq s(j) \leq V_j^{\max} e(j), j \in J \quad (3.2)$$

These constraints determine the range of the size of each unit. If  $e(j)$  equals 1, that is, if a unit exists, then constraint (3.2) corresponds to the lower and upper bounds on the size of the unit,  $s(j)$ . If  $e(j)$  equals zero, then  $s(j)$  becomes 0.

### 3. Allocation constraints

$$\sum_{i \in I_j} w_{\nu}(i, n) = y_{\nu}(j, n), j \in J, n \in N \quad (3.3)$$

These constraints express that in each unit ( $j$ ) and at any event point ( $n$ ) at most one of the tasks that can be performed in this unit (i.e.  $i \in I_j$ ) should be taking place. If unit ( $j$ ) is utilised at event point ( $n$ ), that is, if  $y_{\nu}(j, n)$  equals 1, then one of the  $w_{\nu}(i, n)$  variables should be activated. If unit ( $j$ ) is not utilised at event point ( $n$ ), then all corresponding  $w_{\nu}(i, n)$  variables take zero values, that is, no assignments of tasks are made.

#### 4. Capacity constraints

$$b(i, j, n) \leq V_j^{max} \cdot wv(i, n), \quad i \in I, j \in J_i, n \in N \quad (3.4)$$

$$b(i, j, n) \leq s(j), \quad i \in I, j \in J_i, n \in N \quad (3.5)$$

These constraints express the requirement that the batch size should be within the maximum capacity of a unit ( $j$ ). If  $wv(i, n)$  equals 0, that is, if a task ( $i$ ) is not taking place at event point ( $n$ ), then the first constraint enforces  $b(i, j, n)$  as 0. If  $wv(i, n)$  equals 1, then the second constraint restricts  $b(i, j, n)$  to within the available capacity of unit ( $j$ ),  $s(j)$ .

#### 5. Material balances

$$st(s, n) = st(s, n-1) - d(s, n) + \sum_{i \in I_s} \rho_{si}^p \cdot \sum_{j \in J_i} b(i, j, n-1) - \sum_{i \in I_s} \rho_{si}^c \cdot \sum_{j \in J_j} b(i, j, n) \quad (3.6)$$

$s \in S, n \in N$

Where  $\sum_{i \in I_s} \rho_{si}^c \leq 0$ ,  $\rho_{si}^p \geq 0$  represents the proportion of state ( $s$ ) consumed or produced by task ( $i$ ). According to these constraints, the amount of material of state ( $s$ ) at event point ( $n$ ) is equal to that at event point ( $n-1$ ), adjusted by any amounts produced or consumed between the event points ( $n-1$ ) and ( $n$ ), and the amount required by the market at event point ( $n$ ) within the time horizon.

#### 6. Storage constraints

$$st(s, n) = 0, \quad s \in S2, S4, S6, n \in N \quad (3.7)$$

These constraints ensure that those states that can only be stored in dedicated storage units

have to be consumed by some processing task or storage task immediately after they are produced. These states are state 2, state 4 and s6 in the third case study in the chapter.

#### 7. Demand constraints

$$\sum_{n \in N} d(s, n) \geq r_s, s \in S \quad (3.8)$$

These constraints represent the requirement to produce at least as much as required by the market.

#### 8. Duration constraints: processing task

$$t^f(i, j, n) = t^s(i, j, n) + a_{ij} wv(i, j) + \beta_{ij} b(i, j, n)^{\gamma_{ij}}, i \in I_p, j \in J_i, n \in N \quad (3.9)$$

In Constraints Eq. (3.9), the processing time takes a generally non-linear form, consisting of a fixed term and a variable term depending on the batch size. When  $\gamma_{ij}$  equal 1, these constraints become linear as a special case.

#### 9. Duration constraints: storage task

$$t^f(i, j, n) \geq t^s(i, j, n), i \in I_t, j \in J_i, n \in N \quad (3.10)$$

$$t^f(i, j, n_{last}) = H, i \in I_t, j \in J_i \quad (3.11)$$

These constraints express that the duration of storage tasks can take any positive value as long as they end at the end of the time horizon. The concept of storage task is introduced to make it possible to treat dedicated storage constraints and processing constraints in a

general, unified way.

10. *Same task in the same unit*

$$t^s(i, j, n+1) \geq t^f(i, j, n), i \in I, j \in J_i, n \in N, n \neq n_{last} \quad (3.12)$$

These constraints state that task ( $i$ ) starting at event point ( $n + 1$ ) should start after the end of the same task performed in the same unit ( $j$ ), which has already started at event point ( $n$ ).

11. *Different tasks in the same unit*

$$t^s(i, j, n+1) \geq t^f(i', j, n) - H(1 - wv(i', n)) j \in J, i \in I_j, i' \in I_j, i \neq i', n \in N, n \neq n_{last} \quad (3.13)$$

These constraints are written for tasks ( $i, i'$ ), which are performed in the same unit ( $j$ ). If both tasks are performed in the same unit, they should be at most consecutive. This is expressed by Constraints Eq. (3.13) because if  $wv(i', n) = 1$ , which means that task ( $i'$ ) takes place at unit ( $j$ ) at event point ( $n$ ), then the second term of the right-hand side of Eq. (3.13) becomes 0, forcing the starting time of task ( $i$ ) at event point ( $n+1$ ) to be greater than the end time of task ( $i'$ ) at event point ( $n$ ); otherwise, the right-hand side of Eq. (3.13) becomes negative and the constraint is trivially satisfied.

### 12. Different tasks in different units

$$t^s(i, j, n+1) \geq t^f(i', j', n) - H(1 - wv(i', n)) \quad i, i' \in I, j \in J_i, j' \in J_{i'} \quad (3.14)$$

$$j \neq j', n \in \mathbb{N}, n \neq n_{last}$$

Constraints Eq. (3.14) are written for different tasks  $(i, i')$ , which are performed in different units  $(j, j')$  but take place consecutively according to the production recipe. Note that if task  $(i')$  takes place in unit  $(j')$  at event point  $(n)$  (i.e.  $wv(i', n) = 1$ ), then we have  $t^s(i, j, n+1) \geq t^f(i', j', n)$  and hence task  $(i)$  in unit  $(j)$  has to start after the end of task  $(i')$  in unit  $(j')$ .

### 13. 'Zero-wait' condition

$$t^s(i, j, n+1) \leq t^f(i', j', n) - H(2 - wv(i, n+1) - wv(i', n)) \quad i, i' \in I, j \in J_i, \quad (3.15)$$

$$j' \in J_{i'}, n \in \mathbb{N}, n \neq n_{last}$$

Constraints Eq. (3.15) are written for different tasks  $(i, i')$  that take place consecutively with a 'zero-wait' condition due to storage restrictions on the intermediate material. Combined with Constraints Eqs. (3.13) and (3.14), these constraints ensure that task  $(i)$  in unit  $(j)$  at event point  $(n+1)$  starts immediately after the end of task  $(i')$  in unit  $(j')$  at event point  $(n)$  if both of them are activated.

#### 14. Time horizon constraints

$$t^f(i, j, n) \leq H, i \in I, j \in J_i, n \in N \quad (3.16)$$

$$t^s(i, j, n) \leq H, i \in I, j \in J_i, n \in N \quad (3.17)$$

The time horizon constraints represent the requirement that every task should start and end within the time horizon ( $H$ ).

Both short-term (day-to-day) and long-term (monthly, quarterly or annual) operations must be separately considered in the production plan, as they involve different processes which favour a more compartmentalised strategic approach. Long-term strategies afford a company the flexibility of increasing production capacity through purchasing new equipment, allocating new production plants, acquiring new technology, or to improve expertise through retraining or new hires. These considerations are neglected when making a short-term plan, where decisions concerning the procurement of new plants and machinery or the acquisition of technology and expertise are bypassed. For short-term plans, much of the emphasis is on assigning different jobs to the available manpower and machinery. Since the range of strategic or tactical options differ between short-term and long-term strategies, they must be approached differently to achieve the desired results.

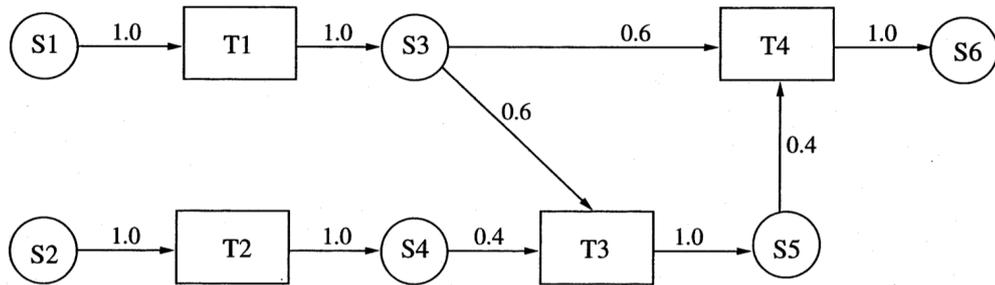
15. *Objective: minimise*

$$\sum_j \alpha \cdot e(j) + \beta \cdot s(j) - \sum_s \sum_n p_s \cdot d(s, n) \quad (3.18)$$

The objective is to minimise the capital costs of units, which consist of a fixed term and a generally non-linear term, depending on the sizes of the units, minus profits due to product sales. Other performance criteria can also be incorporated.

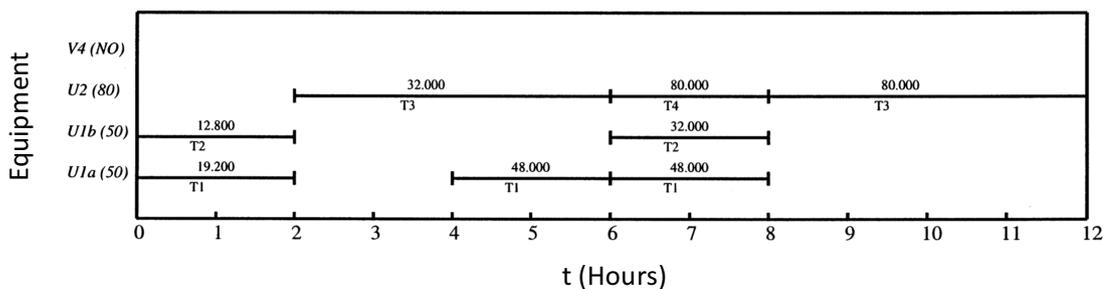
It should be pointed out that the case where different units share the same tasks can be accommodated in the above formulation by considering each task in each unit as a different task with the same features. We should also note that due to the non-linear models of processing time and capital cost, the resulting mathematical programming model is a non-convex MINLP problem. Therefore, deterministic global optimisation methods are needed to determine the global optimal solution.

This model was considered as a suitable starting-point for the present work due to its ability to co-optimize the selection and sizing of equipment as well as the scheduling of the production process. It was implemented in GAMS and solved with the parameters of one of the examples given in reference[65]. The STN of this process (termed BMFIX in[65]) is shown in Figure 3.3.



**Figure 3.3** STN representation for BMFIX process[65]

(S) is the state of the product; the number on the arrow is the fraction of the material consumed by the task from the previous state. Therefore, the total inflow to a task (T) should be 1 in total. The MILP problem of the BMFIX process, which includes 59 binary variables, 175 continuous variables and 332 constraints, was studied and replicated using GAMS in this work; a result identical to that of Lin and Floudas[65], shown in Figure 3.4, was obtained. Thus, it is reasonable to use this model as a validated base model to study the decellularised skin production process.



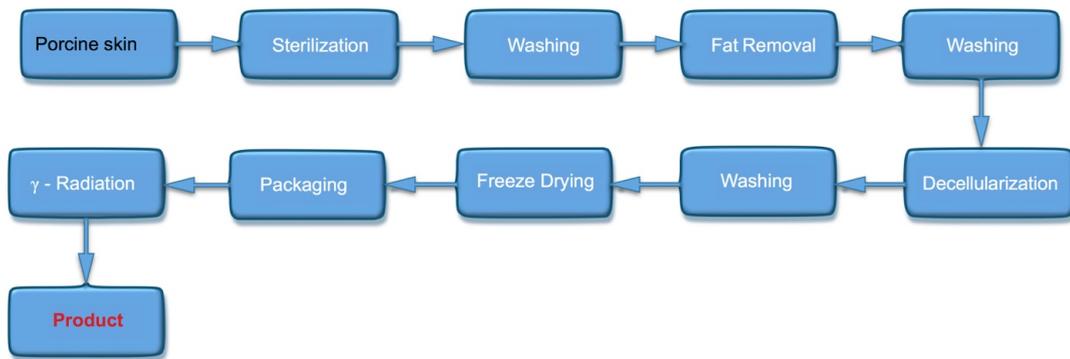
**Figure 3.4** Gantt chart for BMFIX[65]

### 3.2.2 The STN model for the skin decellularisation process

A simple sequential decellularised skin production process is designed, based on the information from the literature. Two case studies (DS48 and DS55) with the same

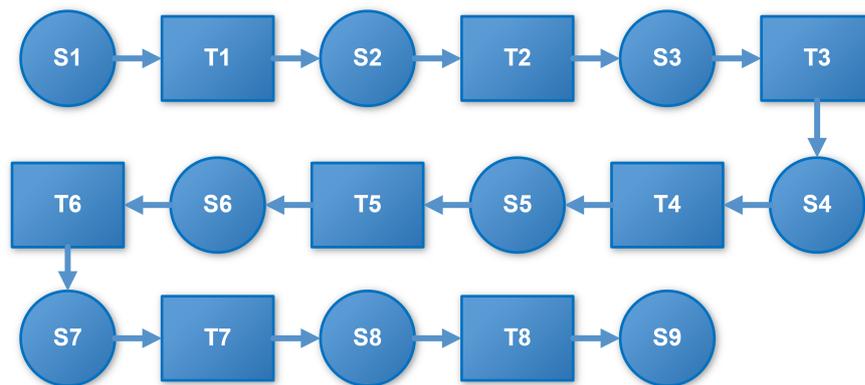
production process but a different production time horizon and market demand are carried out, based on the work of Lin and Floudas[65]. The production time horizons considered for the case studies DS48 and DS55 are 48 hours and 55 hours, respectively. The validity of the model from[65] is checked by carrying out the first case study DS48, and the model is then applied to optimise the target process by carrying out the case study 3, DS168, which has a production time horizon of 168 hours. The model is solved as a mixed-integer linear programming problem with GAMS. The optimal size and amount of equipment as well as the optimal scheduling are identified with the purpose of minimising the total costs.

In this work, the production process of decellularised skin is represented initially as a sequential and linear process, which can be extended to form more complex scenarios in a future study. The current process takes 31 hours in one round of complete operations in DS48 and DS55; the gamma radiation process is not considered in the optimisation as it is assumed to be performed separately. There is currently no storage considered through the entire production process, which means that all materials in the previous step are consumed in the following task. Figure 3.5 presents the sequence of the processing steps involved in the production, which is mapped to a process recipe represented in STN, shown in Figure 3.6.



**Figure 3.5** Production recipe for decellularised skin scaffold

The raw material in this case is assumed to be the porcine skin cut. The full production process that converts the raw material to the product has nine steps.



**Figure 3.6** STN representation for DS48, DS55 process

The raw material is the first stage of the product; therefore, it is called state 1 (S1), which will be consumed by task 1 (T1); after that, the product is in its second stage, (S2), and so on. (S9) is the final stage of the product (decellularised skin). The aim of this initial model is to choose the best size of each piece of equipment (called a unit in STN) and the best production schedule, satisfying the demand with the lowest net capital and operating costs.

Table 3.1 presents the type of equipment required by each task and operational information. Note that the information about chemicals and labour consumption is included here to reflect the information collected so far; this, however, has not yet been used in the work reported here but will be used in the final version of the work.

**Table 3.1** Process requirement based on 100L skin cut

<b>Task</b>	<b>Production process</b>	<b>Equipment</b>	<b>Chemical</b>	<b>Utility</b>	<b>Labour</b>	<b>Operating hour</b>
Task 1	Sterilisation	Tank bioreactor	-Alcohol ethoxylate (AEO) -Salt	Electricity	2	1
Task 2	Washing	Tank bioreactor	–	Electricity	2	1
Task 3	Fat removal	Tank bioreactor	-AEO -Sodium hydroxide -Sodium carbonate	Electricity	2	1
Task 4	Washing	Tank bioreactor	–	Electricity	2	1
Task 5	Decellularisation	Tank bioreactor	-Enzyme -AEO -Aluminium sulphate	Electricity	2	1
Task 6	Washing	Tank bioreactor	–	Electricity	2	1
Task 7	Freeze-drying	Freeze-dryer	–	Electricity	2	24
Task 8	Packaging	Packaging machine	–	Electricity	2	3
Task 9	Gamma radiation	Gamma radiation	–	Electricity	1	–

Table 3.1 also lists the processing tasks involved in the decellularised skin production process assumed in this work. Task 9 (Gamma radiation) is a process in which many batches of products are carried out together after packaging as the very last step before they are transported away from the factory; therefore, this task is not included in the optimisation process.

**Table 3.2** Unit suitability for the tasks

Unit	Suitability
Units $u1a, u1b, u1c, u1d, u1e, u1f$ (Bioreactor)	Tasks 1–6
Unit 2 (Freeze-dryer)	Task 7
Unit 3 (Packaging machine)	Task 8

Table 3.2 lists the unit suitability for the tasks for the designed decellularised skin production process. The model, including the costs of the chemicals and labour, is not reported in this current stage.

### **3.2.3 The adapted model and parameters for the two simple test cases**

The objective function in this work is to minimise the production cost for meeting a given demand. In slight contrast to the Lin and Floudas model, where only the capital cost was considered, the operating cost is included in the objective function:

$$F = [(\sum_j \alpha \cdot e(j) + \beta \cdot s(j)) \cdot \sigma + \sum_j \theta \cdot k(j) \cdot h] - \sum_s \sum_n p_s \cdot d(s, n) \quad (3.19)$$

The objective function consists of two main parts: total costs and revenue. The objective value, which needs to be minimised, has the function: total cost minus total revenue. The first term of the right-hand side of (3.19)  $\Sigma_j$  represents the total costs, which consist of electricity costs and capital costs. The  $\alpha$  and  $\beta$  represent the capital cost constant and the capital cost coefficient. The additional part  $(\Sigma_j \theta \cdot k(j) \cdot h)$  states that the operating cost is derived by multiplying the electricity cost for 1 kWh of electricity ( $\theta$ ) by the power (kW) of the equipment  $k(j)$ , then multiplied by the working hours ( $h$ ) of the equipment, where  $\theta$  and  $h$  are parameters and  $k(j)$  is a variable which has a linear relationship with the size of the equipment. In order to calculate the total cost by adding the operating cost and capital cost together, the capital cost will be broken down to the portion allocated to the operating time horizon by multiplying by a fraction ( $\sigma$ ). The revenue part is represented as  $\Sigma_s \Sigma_n p_s \cdot d(s, n)$ , which has the meaning that the revenue is calculated by total demand multiplied by the unit price.

### **3.2.4 Determination of parameters**

The operating times of the tasks considered within the production process of decellularised skin and the parameters are listed in Tables 3.3–3.5, which are determined based on several published sources[68-75].

Table 3.3 shows the equipment considered in the production process of decellularised skin. The parameters are all collected from researching the relevant sources on the

Internet[68-73]. The price of the equipment is shown as forming a linear relationship with the capacity of the equipment. The equipment with a suitable capacity and the best price is selected by running the model.

**Table 3.3** Parameters in optimisation model

<b>Unit</b>	<b>Capital cost constant (<math>\alpha</math>)</b>	<b>Capital cost coefficient (<math>\beta</math>)</b>	<b>Range of capacity (L)</b>
Tank bioreactor ( <i>u1a-u1f</i> )	2,508	1	1,000–10,000
Freeze-dryer ( <i>u2</i> )	3,410	0.09	1.1–274
Packaging machine ( <i>u3</i> )	2,528	282	1–10,000
Storage fridge ( <i>v1-b4</i> )	300	2.80	36–335

*Note: the constant and coefficient for capital cost of the equipment is derived according to the linear price equation:  $price = \alpha + \beta \times L$*

The price equation is the regression (the best fit line) for several sets of price and size of the equipment. The unit of the capacity of equipment is the litre and the unit for capital cost of the equipment is GBP.

**Table 3.4** Determined parameters

<b>State</b>	<b>Selected value</b>
Skin sheet size	10 cm × 20 cm × 0.2 cm
Unit cost of electricity	0.3 GBP/kWh

*Note: the size (capacity) of all the equipment and the market demand for the product in this model are represented in litres*

**Table 3.5** Determined parameters: power consumption

<b>Unit</b>	<b>Power consumption (Kw)</b>
Bioreactor	$22.519 + 0.007 \times \text{unit size}$
Freeze-dryer	$4.044 + 0.805 \times \text{unit size}$
Storage	$0.518 + 0.001 \times \text{unit size}$
Packaging machine	$1.335 + 0.087 \times \text{unit size}$

The linear equations for power consumption in Table 3.5 are regressions (best fit lines) for several sets of equipment size and the power consumption needed by the equipment[70-73]. The unit for the power consumption is the kilowatt (kW).

### **3.2.5 The adapted model and parameters for the one-week decellularisation scheduling case**

For a factory or a firm, an appropriate production time horizon considered in the production scheduling optimisation model should be longer than that of the two case studies above. However, it should also not be too long, as the optimisation plan should be flexible if there is a change in forecast demand. Therefore, one week should be an appropriate time horizon to consider for real production optimisation. Furthermore, in practical terms, the inter-stage storage should be allowed during the middle of production, and the important operating costs should include not only the electricity costs of the equipment, but also the chemical costs incurred in the sterilisation, fat removal and decellularisation processes. In the final version of the optimisation model for production scheduling, which covers a period of one week, the costs of medical storage and

chemicals are simulated, and the limitation of floor size is also included in the model. The reason for adding the floor size limitation is that all biomedical technology products need to be produced in compliance with good manufacturing practice (GMP), which needs to satisfy the regulations and be approved before it is used for the production. Therefore, GMP is costly. In addition, the packaging process has been extended to three hours instead of one hour, since this is closer to expectations in reality..

The objective in this case study is also to minimise the production cost for meeting a given demand. This is in slight contrast with previous two case studies, where the chemical cost and the inter-stage storage cost were also considered beside the capital cost and the operating cost:

$$F = [(\sum_j \alpha \cdot e(j) + \beta \cdot s(j)) \cdot \sigma + \sum_j \theta \cdot k(j) \cdot h + c] - \sum_s \sum_n p_s \cdot d(s, n) \quad (3.20)$$

The capital cost and electricity cost of inter-stage storage is included in the total cost. The parameters of the capital cost constant ( $\alpha$ ) and capital cost coefficient ( $\beta$ ) of inter-stage storage will be included. In addition, the chemical cost (denoted by  $c$ ) is included.

As the inter-stage storage is considered in the final version of the model, the storage is added as a storage task in this case. The zero-wait constraint in Floudas and Lin's model and adopted in DS48 and DS55 is applied between the storage and the tasks in our model. The time constraints which restrict the starting time and finishing time of each storage are introduced. In addition to the indices, sets, variables, parameters and constraints for

DS168, as new issues such as chemical cost, inter-stage storage and site limitation are considered, the new parameters are listed in the Table 3.6 to Table 3.8. All the parameters presented earlier continue to apply to this case as well.

**Table 3.6** The parameters of floor size of the equipment

<b>Equipment</b>	<b>Floor size (m<sup>2</sup>)</b>
Tank bioreactor	$0.00144 \times \text{capacity}$
Storage fridge	$0.003 \times \text{capacity}$
Freeze-dryer	$0.1 \times \text{capacity}$
Packaging machine	$0.35 \times \text{power consumption}$

The quantity of chemicals used in the production process is according to the weight percentage needed to provide the solution and the batch size of the product. In this work, the amount of solution and the skin should stand in a ratio of 7:1. This means that one litre of skin needs seven litres or seven kilograms of solution, so we can know how many kilograms of chemicals are needed for one litre of skin according to the weight percentage needed for each kind of chemical in the solution. The price per gram of each chemical was found on the laboratory website[76-82].

**Table 3.7** Chemical costs per piece of skin

<b>Chemical</b>	<b>Price (GBP) per piece of skin</b>
Peracetic acid	2.52
NaCl	0.24108
Sodium hydroxide	0.77056
Peregal	0.4956
Sodium carbonate	0.79632
Trypsin	2.1812
Ammonium sulphate	0.00011
Peregal	0.2478

**Table 3.8** Parameters in GAMS

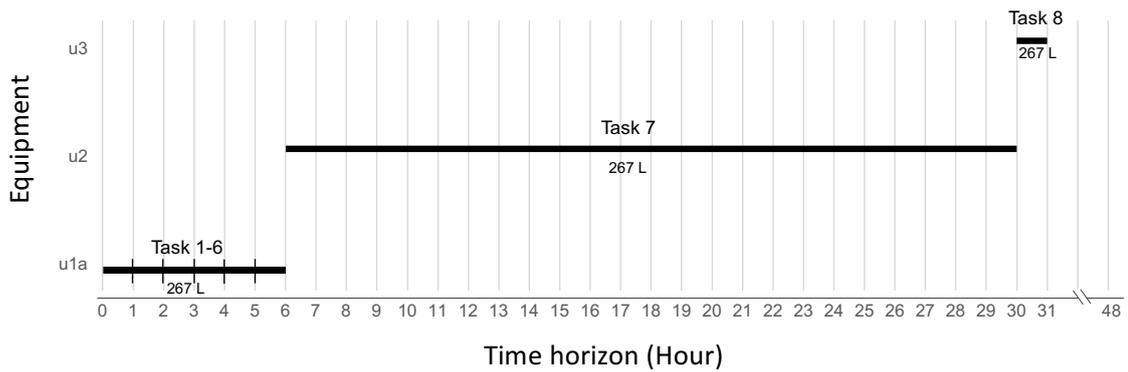
<b>Task name</b>	<b>Cost of chemical (GBP)</b>
Sterilisation	$69.027 \times \text{batch size}$
Fat removal	$51.165 \times \text{batch size}$
Decellularisation	$60.755 \times \text{batch size}$

### **3.3 RESULTS AND DISCUSSION**

#### **3.3.1 Case study I: optimisation scheduling within a production time horizon of 48 hours**

This case study, referred to as DS48, considers the production to meet a demand of 6,675 sheets of decellularised skin (2671) within a time horizon of 48 hours. Figure 3.7 shows the optimal design and scheduling for this case. The application of the formulation

described in this paper to this problem results in a MILP. This was solved using the CPLEX solver on GAMS. The optimal solution has a unit cost (cost per litre of skin) value of 7.3 GBP and involves the equipment capacities listed in Table 3.9 and the capital costs of equipment given in Table 3.10.



**Figure 3.7** Gantt chart for production scheduling of case DS48

It can be seen that the batch size chosen by the model for each task is 267L (6,675 sheets of skin) for tasks 1–8; this is identical to the amount of the product needed for 48 hours, meaning that the optimiser did not recommend running multiple batches of smaller sizes. Note that for bioreactors the equipment size is eight times the volume of processed skin, taking into account the liquid present in the vessels. Storage is not considered at the present stage; therefore, all the materials in the previous stage are consumed by the following task, which starts immediately after the previous task has finished.

**Table 3.9** Optimal equipment capacities for DS48

<b>Unit</b>	<b>Capacity chosen (L)</b>
(U1) Bioreactor	2,136
(U2) Freeze-dryer	267
(U3) Packaging machine	267

Comparing the chosen capacity with the capacity range of the equipment given by the previous section, it can be seen that the chosen capacities are all within the range given and are also equal to the working capacity needed to produce the market demand (with the exception of the tank bioreactor). This is reasonable as the price of the equipment is positively related to the capacity of the equipment. The capital cost is minimised by choosing equipment with a capacity that is exactly equal to the market demand and has no unutilised margin. The minimum capacity of a tank bioreactor needed to produce 267L skin is eight times the skin volume; therefore, the lowest capacity is chosen to minimise the capital cost. In addition, following the model, only one tank bioreactor is employed to complete six tasks. The capacities of the freeze-dryer and gamma radiators are both the same as the corresponding batch sizes. Therefore, the capacities of the bioreactor, freeze-dryer and gamma radiator are 2,136L, 267L and 267L, respectively.

The results for the total cost for the equipment are shown in the two tables below. The total cost, including capital cost and electricity cost, for the 48-hour operating time horizon in this designed plant should be the sum of these costs listed in Table 3.10 and Table 3.11 – the amount is 2,019 GBP. Therefore, the total production cost per litre of

skin is 7.5 GBP, and 0.3 GBP per sheet of skin.

**Table 3.10** Capital cost of the equipment per 48 hours

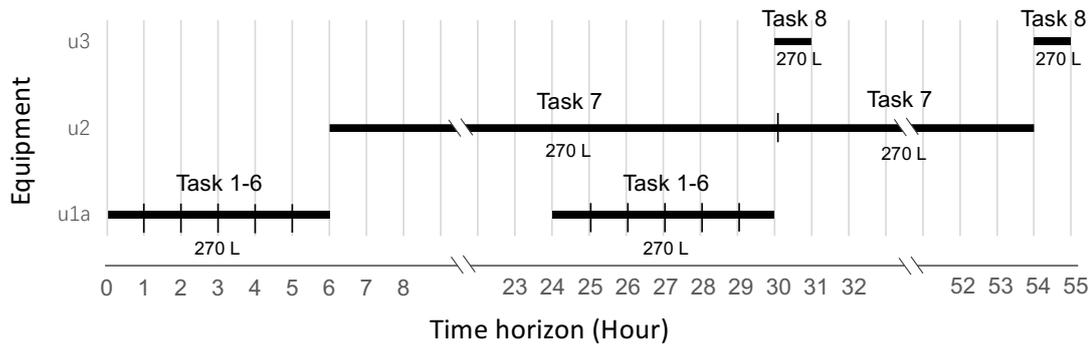
<b>Unit</b>	<b>Capital cost decided by model (GBP)</b>
Bioreactor	3
Freeze-dryer	322
Packaging machine	43

**Table 3.11** Electricity bill for the equipment per 48 hours

<b>Unit</b>	<b>Electricity cost decided by model (GBP)</b>
Bioreactor	67
Freeze-dryer	1,577
Packaging machine	7

### **3.3.2 Case study II: optimisation scheduling within a production time horizon of 55 hours**

As previously mentioned, the total processing time for the entire production of decellularised skin is 31 hours. In the second case study, referred to as DS55, a demand for 13,500 sheets of decellularised skin is to be met within a time horizon of 55 hours. In this case, the total demand exceeds the maximum capacity of one of the units. Therefore, it will lead to more than one round of production in order to meet the market demand. This change increased the complexity of the possible solution and brought the designed production process closer to a realistic production process.



**Figure 3.8** Gantt chart for production scheduling of case DS55

From the Gantt chart in Figure 3.8, the optimal batch size selected by GAMS is 270L (6,750 sheets of skin), which is half the total market demand; two rounds of production are undertaken. In addition, the second round of production is started before the completion of the first. The optimal capacities and the total costs of equipment are shown in Table 3.12, Table 3.13 and Table 3.14.

**Table 3.12** Optimal equipment capacities for DS55

Unit	Capital chosen (L)
Bioreactor	2,160
Freeze-dryer	270
Packaging machine	270

The capacity of the bioreactor chosen by the model is also equal to eight times the batch size ( $8 \times 270$ ) L; the capacity for other equipment is also just equal to the batch size in order to minimise the total costs.

**Table 3.13** Capital cost of the equipment per 55 hours

<b>Unit</b>	<b>Capital cost decided by model (GBP)</b>
U1 (Bioreactor)	3
U2 (Freeze-dryer)	355
U3 (Packaging machine)	47

**Table 3.14** Electricity cost of the equipment per 55 hours

<b>Unit</b>	<b>Electricity bill decided by model (GBP)</b>
U1 (Bioreactor)	135
U2 (Freeze-dryer)	3,188
U3 (Packaging machine)	15

Three types of equipment are employed once in DS55; the capital cost is also minimised by choosing the equipment with a capacity that is exactly equal to the market demand, and therefore with no unutilised margin. The total cost is 3,743 GBP.

In the solution of DS55, the cost of one litre of product is 6.93 GBP; therefore, the unit cost per sheet of skin is 0.28 GBP, compared with the unit cost in DS48, which is 0.30 GBP.

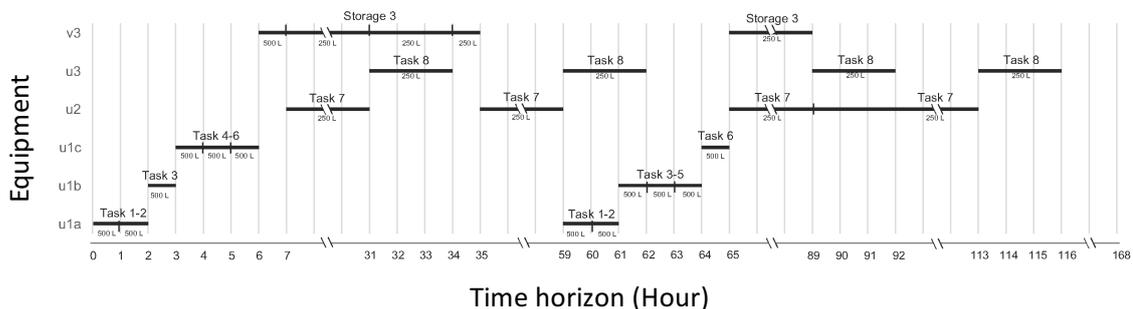
For the case studies outlined in the previous section, the operation time horizons considered are 48 hours and 55 hours. The primary objective of the first case study is to test the validity of applying Floudas and Lin's model as the base model in the decellularisation of skin production. Thus, the first-time horizon is a whole-day time horizon. This accounts for one round of production, which is 48 hours. However, it is

important to note that, in practice, factories do not usually run a single round of production at any one time. They normally carry out several rounds of production with some degree of overlap. They do this to save time and so that the equipment is not left sitting unused for too long. Therefore, the time horizon employed in the second case study is 55 hours. This accounts for two rounds of production, with a degree of overlap. The case study aims to investigate whether the developed model can handle a relatively complex schedule of production, one which is closer to what would in fact happen in a factory.

### 3.3.3 Final version of the scheduled production optimisation model

#### DS168

The optimal production scheduling is shown in Gantt chart below, Figure 3.9. For this case, with the demand for 25,000 sheet of skin, the batch size chosen by the optimisation model is 500L, and two rounds of production processes are undertaken.



**Figure 3.9** Gantt chart for production scheduling of case DS168

The results of the cost breakdown for the final version of the scheduled production optimisation model for decellularised skin production are outlined in Tables 3.15, 3.16

and 3.17. The tables also list equipment capacities, capital cost, and the electricity costs of the equipment, respectively. Table 3.18 outlines the chemical cost for 25,000 sheets of skin.

**Table 3.15** Optimal equipment capacities for DS168

<b>Unit</b>	<b>Capacity chosen (L)</b>
Bioreactor	4,000
Freeze-dryer	250
Packaging machine	250

For this model, the capacity of the bioreactor is equal to eight times the batch size ( $8 \times 500$ ) L. The capacity of the other equipment is, similarly, equal to the batch size, as a way of minimising total costs.

**Table 3.16** Capital cost of the equipment per 168 hours

<b>Unit</b>	<b>Capital cost decided by model (GBP)</b>
U1a (Bioreactor)	32.5
U1b (Bioreactor)	32.5
U1c (Bioreactor)	32.5
U2 (Freeze-dryer)	2,743.3
U3 (Packaging machine)	365
S3 (Interstate storage)	8.5
<b>Total</b>	<b>3,214.3</b>

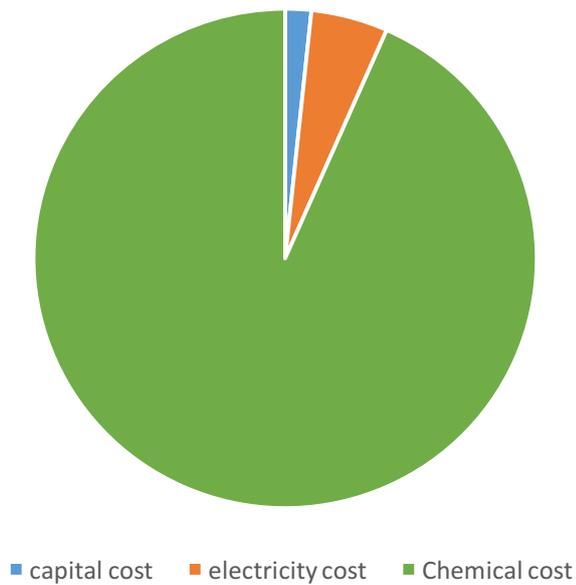
**Table 3.17** Electricity cost of the equipment per 168 hours

<b>Unit</b>	<b>Electricity bill decided by model (GBP)</b>
U1 (Bioreactor)	530.4
U2 (Freeze-dryer)	8,868.7
U3 (Packaging machine)	166.2
S3 (Interstate storage)	33
<b>Total</b>	<b>9,598.3</b>

**Table 3.18** Chemical cost of the production per 168 hours

<b>Task</b>	<b>Chemical cost decided by model (GBP)</b>
Sterilisation	69,027
Fat removal	51,165
Decellularisation	60,755
<b>Total</b>	<b>180,947</b>

According to the results in the tables, the total production cost of the optimised model, for a one-week production time horizon and a demand of 25,000 sheets of skin, is 193,759.6 GBP. The unit cost per sheet of skin is 7.75 GBP.



**Figure 3.10** Pie chart of production costs

Figure 3.10 shows the proportions of capital cost, electricity cost and chemical cost that make up the total production cost. It shows that the largest proportion of the production cost is made up by the chemical cost. The chemicals include the chemicals used in task sterilisation, fat removal and decellularisation. The chemicals used in sterilisation and decellularisation are relatively expensive, which leads to a high unit cost for the product. In addition, the total chemical can be rather expensive due to the large volume of skin. Capital cost and electricity cost occupy only a very small percentage of the total production cost. Therefore, it is reasonable to assume that altering their parameters, in regard to the equipment, will have little impact on scheduling. The quantity of chemicals used is determined by the demand for the product. Consequently, the quantity of chemical cannot change if the demand is fixed, no matter what its associated price.

Although the greatest expenditure was incurred due to the cost of chemicals, it is neither possible nor feasible – depending on the circumstances – to recycle the latter. If a chemical is consumed during the production process (i.e. it does not exist anymore after production), it cannot be recycled. However, even if the chemical remains, it is not economical to recycle it as the cost of separation and purification is often more expensive than their actual cost price.

### **3.4 SUMMARY**

A simple sequential decellularised skin production process has been designed for the study. It is based on the scheduling optimisation model proposed by Floudas and Lin[65]. This model is an adaptation of a previous study, and so requires validation by GAMS. Following this is a two-test case study: where DS48 and DS55 are introduced to examine whether the proposed model can be successfully applied to the decellularised skin production process and whether the proposed model can handle a multiple complex problem. Finally, the concluding test is investigated in version DS168, in line with a number of important issues and in respect to an appropriate time horizon.

The key observation from this work is that the significant cost in decellularised skin production process is chemical cost. However, this is affected only by the amount of skin

produced. The second largest cost is the energy and capital cost of the freeze-dryer, which can be optimised by choosing an optimal size for the freeze-dryer.

# **CHAPTER 4**

## **FREEZE-DRYING PROCESS**

### **REPLACEMENT**

#### **4.1 INTRODUCTION**

Decellularised skin products have become safer and more useful when applied to burn wound and foot ulcer. For safety, it is necessary to store the decellularised skin products such that they could function when needed. The freeze-drying method is used to preserve decellularised skin and prolong shelf life, however, freeze-drying is a slow and expensive process. We critically examine the advantages of using a hypothermal storage replacement here and explore its potential as an alternative preservation method. Hypothermal storage refers to the use of a refrigerator in the medical, scientific, and pharmaceutical fields. Although the use of hypothermal storage enables cheaper and more efficient manufacturing, it results in a significant decline in shelf life which subsequently contributes to an increased rate of waste accumulation – therefore the savings from the reduction of manufacturing costs must be balanced with the cost of its reduced shelf life to make the substitution of freeze-drying viable[50],[83].

### **4.1.1 Objective of this chapter**

From the modelling and analysis of the decellularised skin production process (Chapter 3), it was found that most of the production time and the power consumption (or electricity cost) required for producing the product was incurred during the freeze-drying process. If we replace freeze-drying with 4°C hypothermal storage to preserve the biomedical product, the production and storage costs are expected to be reduced; however, it will lead to the disadvantage of a much shorter shelf life[83]. Therefore, there is a trade-off between cheaper production costs and a shorter shelf life and the challenge lies in determining that this trade-off is economically beneficial. To accomplish this, the total cost of the alternative preservation method is compared to the conventional approach of employing freeze-drying in the production of decellularised skin, taking into account the trade-off between: (1) savings of capital and operation costs by eliminating freeze-drying; and (2) costs incurred due to the increased wastage that is associated with the shortened shelf life of the product.

## **4.2 METHODOLOGY**

First, we optimised the design and scheduling of the alternative method of producing decellularised skin without freeze-drying. This was achieved by adjusting the model that was presented in Chapter 3. The results of the optimisation will determine the viability of this alternative process, i.e. its total production cost, represented as  $c_0$ . The additional

costs incurred by the replacement option (such as the cost of hypothermal storage) will be represented as  $c_1$ . The parameters involved in the cost of hypothermal storage have already been presented in Chapter 3. This chapter will calculate the cost of hypothermal storage on its own, as a function of the shelf life of the stored product.

The effective cost refers to the unit cost of viable product, calculated by spreading the original cost of manufacturing without freeze-drying and incorporating hypothermal storage (i.e.  $c_0 + c_1$ ) distributed within the duration where the product remains viable, which will be influenced by the shelf life. Thus, a comparison between the effective production cost without freeze-drying and the production cost with freeze-drying was carried out, enabling us to arrive a conclusion as to whether the alternative production process that excludes freeze drying provides an economically superior option within a given period of time.

#### 4.2.1 Optimisation of process design and scheduling without freeze-drying

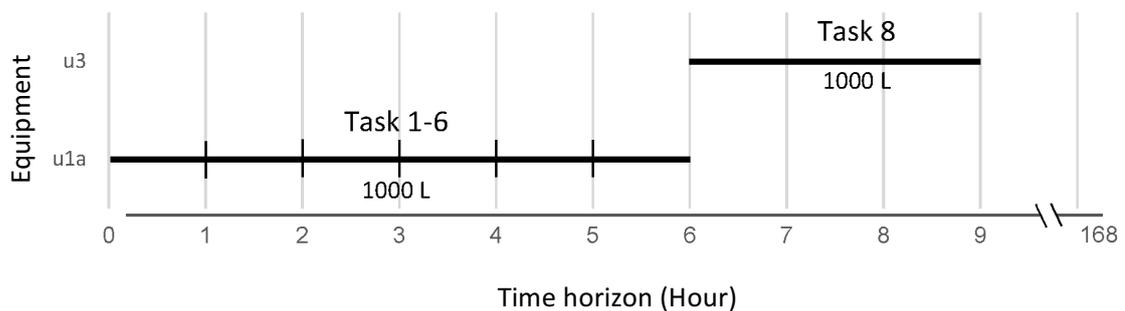


**Figure 4.1** Production process of decellularised skin without freeze-dryer

First, the production process was slightly altered to replace the freeze-dryer with 4°C

hypothermal storage; this change was incorporated into the scheduling optimisation model that was originally presented in Chapter 3, but with the freeze-drying process completely omitted from the production process. The unit production cost without freeze-drying process is referred to as  $c_0$ ; it will be added to the cost of hypothermal storage, which is referred as  $c_1$ . Thus, the unit production cost of a system where the freeze-dryer is replaced by hypothermal storage is  $c_0 + c_1$ .

After removing the freeze-drying process, the optimisation model provides a new schedule for the production of decellularised skin where the production time period is 168 hours. This is outlined in the Gantt chart below.



**Figure 4.2** Production scheduling of decellularised skin without freeze-dryer for 168 hours (one week)

The total production cost for 25,000 sheets of skin (1,000L) is 181,846.8 GBP. Therefore, the unit production cost  $c_0$  is 7.27 GBP, while the unit production cost with the freeze-dryer was 7.75 GBP. Note that  $c_0$  is used as a constant that was added to the hypothermal storage cost; the latter is a function of shelf life and will be studied next.

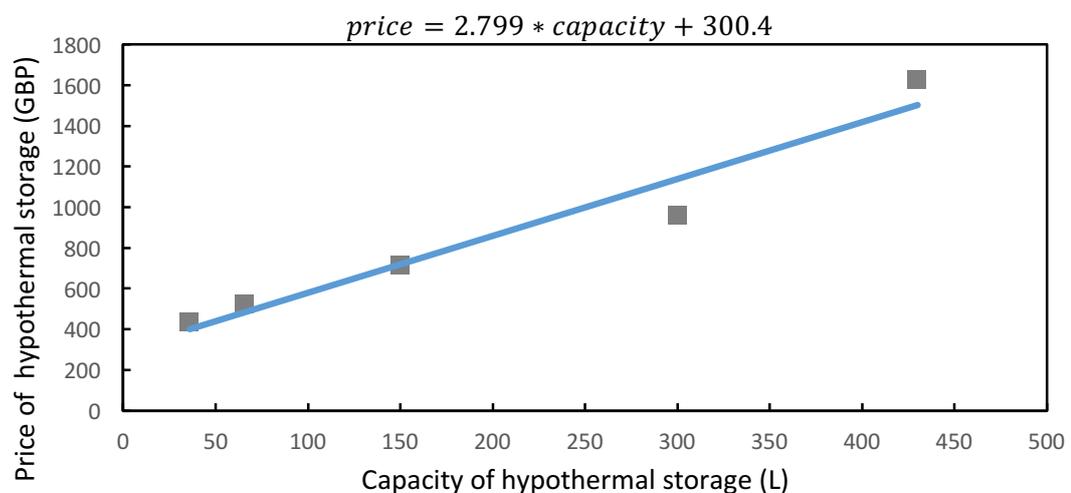
## 4.2.2 Assessing the economics under different assumptions on shelf life and waste product

### Capital cost of hypothermal storage

Table 4.1 outlines the different prices and power consumption values for hypothermal storage, within a range of potential capacities. This data was sourced from the official website of a medical hypothermal storage unit provider[74, 75]. This establishes the relationship between the price and the capacity (or size) of the storage.

**Table 4.1** Parameters of medical fridge (hypothermal storage)

Capacity(L)	Power consumption (kW)	Price (GBP/unit)
36	0.59	436
66	0.63	519
150	0.66	711
300	0.67	960
430	1.1	1625



**Figure 4.3** The relationship between the capacity and the price of the hypothermal storage

The relationship between the price and capacity of the hypothermal storage unit is modelled as follows (cf. Figure 4.3):

$$Y = \alpha + \beta \cdot X \quad (4.1)$$

where  $Y$  is the price of the hypothermal storage, in GBP

$X$  is the capacity of the hypothermal storage

$$\alpha = 300.4$$

$$\beta = 2.799$$

Assuming the life of the storage unit to be ten years, the capital cost of hypothermal storage attributed to a one week period, denoted as  $CC$  (£/week) is converted from equation 4.1 as follows:

$$CC = A + B \cdot X \quad (4.2)$$

where  $A = 0.567$ ,  $B = 0.00537$

The storage capacity required is dependent on the quantity by volume of the product (decellularised skin). In turn, the quantity of skin that requires preservation is directly correlated to its shelf life: it will be stored using hypothermally and may be either used or discarded before its shelf life has expired. As such, the capacity of hypothermal storage needed, denoted as  $X$ , is a function of the shelf life of the skin product.

$$X = \beta \cdot F \cdot t \quad (4.3)$$

where  $\beta$  is the parameter describing the relationship between volume of the skin and the actual capacity of storage required; here, it is set to 1.2;

$F$  is the production rate, in L/day;

$t$  is the shelf life, in days, which is taken as the storage time.

The production rate assumed by this study is 25,000 sheets (1,000 litres) of skin per week.

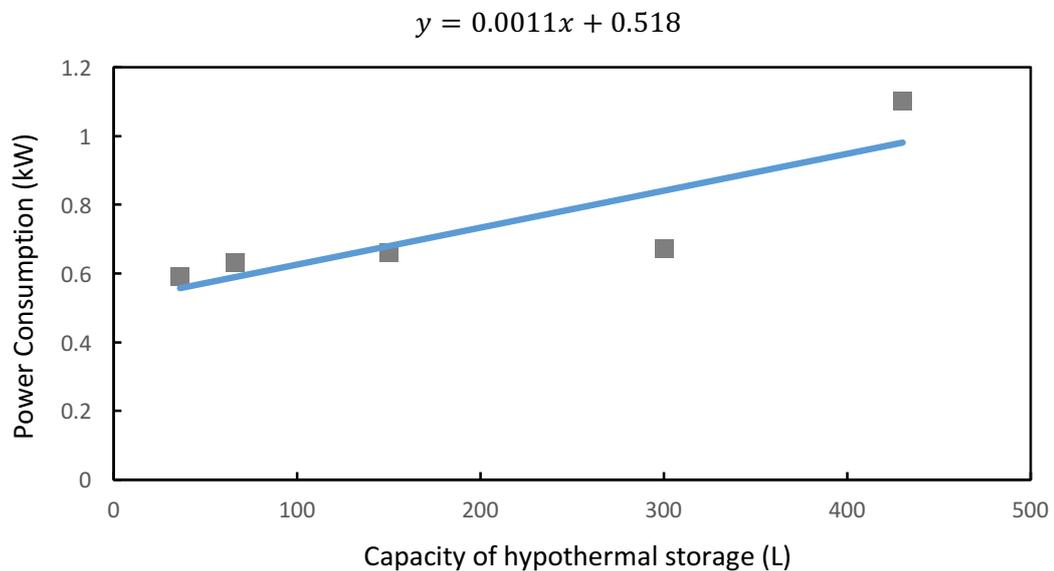
Therefore, the production rate  $F$  is 1,000/7 L/day here. Combining equations 4.2 and 4.3 gives,

$$CC = [A + B \times (\beta \cdot F \cdot t)] = A + C \times t \quad (4.4)$$

where  $A = 0.567$ ,  $C = 0.921$ .

#### Electricity cost of hypothermal storage

Figure 4.4 below outlines the relationship between power consumption and the capacity of the hypothermal storage equipment, which is based on the data from [74, 75].



**Figure 4.4** The relationship between the capacity and the power consumption of the hypothermal storage

The relationship between power consumption and capacity of the hypothermal storage is

as follows:

$$Y = D + E \cdot X \quad (4.5)$$

where  $Y$  is the power consumption of the hypothermal storage (in kW);

$X$  is the capacity of the hypothermal storage, which can be calculated by

Equation 4.3;

$$D = 0.518, E = 0.0011.$$

Therefore,

$$Y = D + F \cdot t \quad (4.6)$$

$$\text{where } D = 0.518, F = 0.1886$$

The electricity cost (EC, in £) is calculated by multiplying the total power consumption (in kW) over the operating period (OP) of concern (in hours) by the price (P) of electricity (in £/kWh).

$$EC = Y \cdot OP \cdot P \quad (4.7)$$

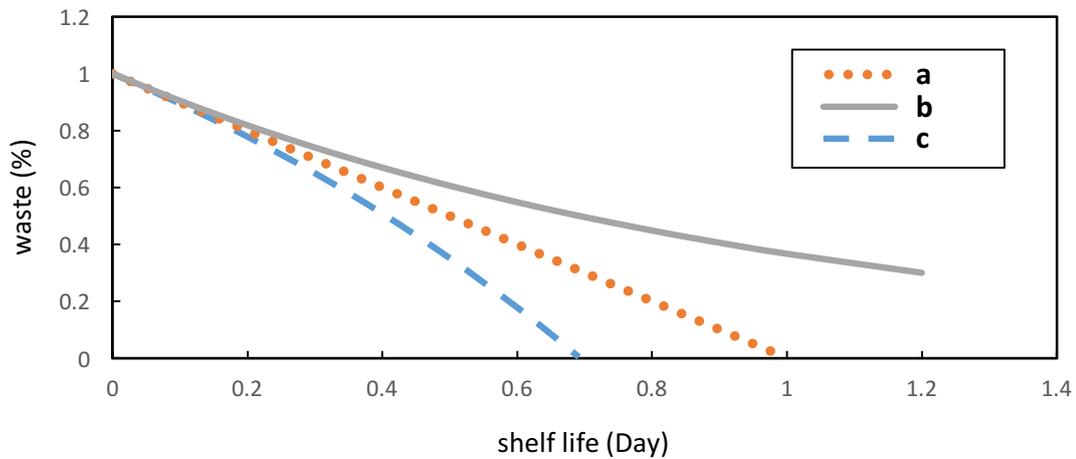
$$\text{where } G = 13.42, H = 4.886.$$

The total cost of hypothermal storage over one week (TC, in £), therefore, is calculated by adding the capital cost (from equation 4.4) to the power consumption cost (from equation 4.7).

$$TC = CC + EC \text{ (for } OP = 168 \text{ hours)}. \quad (4.8)$$

To obtain the unit cost for hypothermal storage, the above (weekly) cost is divided by the amount of product produced over one week.

### 4.2.3 Possible relations between shelf life and product wastage



**Figure 4.5** Three possible (negative) relations between shelf life and waste percentage

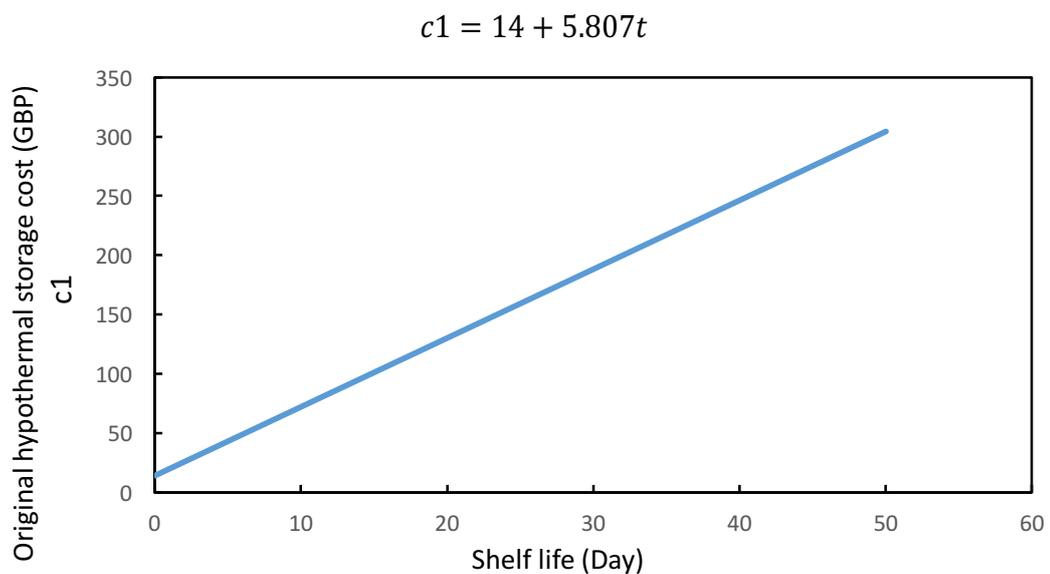
The exact relationship between a product's shelf life and the percentage that is wasted is currently unknown. Intuitively, we expect a negative correlation between these two factors as a longer shelf life would lead to reduced wastage, since a longer shelf life allows a product to be stored for a longer time, and reduces the probability of wastage caused by the uncertainty in demand. Mathematically, there are three possible relationships between shelf life and waste percentage, as shown in Figure 4.5. These are labelled a, b and c: curve *a* shows a linear relationship between the two variables, while curves *b* (convex) and *c* (concave) are non-linear. Each of these three curves is based on a number of different parameters, and their influence are investigated in this section.

For all of the three possible curve shapes (a, b and c) for expressing waste percentage as a function of shelf life, the waste percentage is set between 0 and 1; 0 representing the case of no wastage and 1 and complete wastage respectively. In Figure 4.4, the orange (dotted) line shows a linear relationship. The grey (solid) line shows a decrease in wastage

with increasing shelf life at a reducing rate, and the blue (dashed) line indicates a decrease in wastage with increasing shelf life at an accelerated rate. Each of these three possible curves will be examined to determine the final production costs of the product when the production process omits freeze-drying.

#### 4.2.4 Effective unit cost

The linear relationship between shelf life and waste percentage, curve *a*, will be considered first. The relationship between the costs of hypothermal storage and shelf life was also included in the analysis, following Eq. (4.8).



**Figure 4.6** Relationship between costs of hypothermal storage and shelf life of product

As an example, Figure 4.6 shows the relationship between the cost (*c1*) of hypothermal storage and the shelf life of decellularised skin product.

As wastage is incurred when the shelf life of the product is not long enough its full consumption to meet demands before the expiry date, the concept of effective unit cost (EUC) is introduced, to represent the original unit production costs ( $c_0+c_1$ ) as a function of time in which the product remains viable. Therefore:

$$EUC = (c_0 + c_1)/(1 - waste\%) \text{ or} \quad (4.9)$$

$$EUC = OUC \times (1 - waste\%)$$

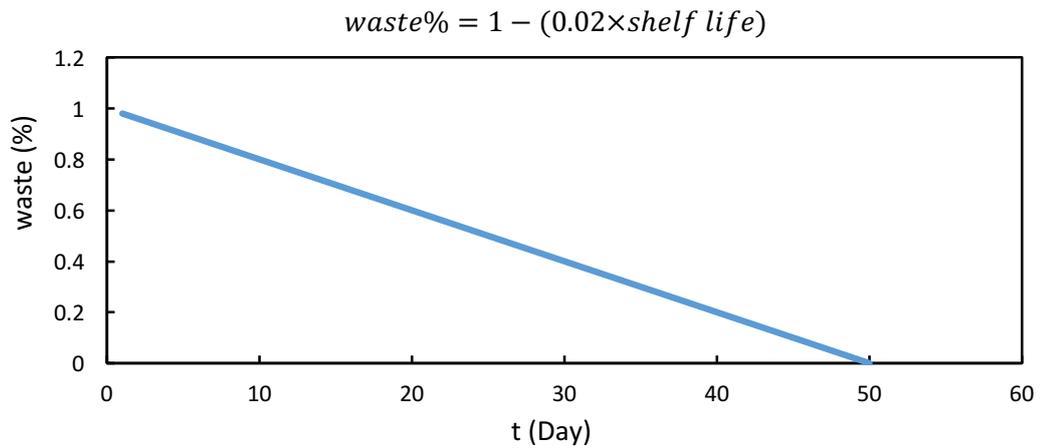
Where  $EUC$  is the effective unit cost;

$OUC$  is original unit cost, i.e. that for producing every product item from the plant;

$c_0$  is original unit production cost without freeze-drying or hypothermal storage;

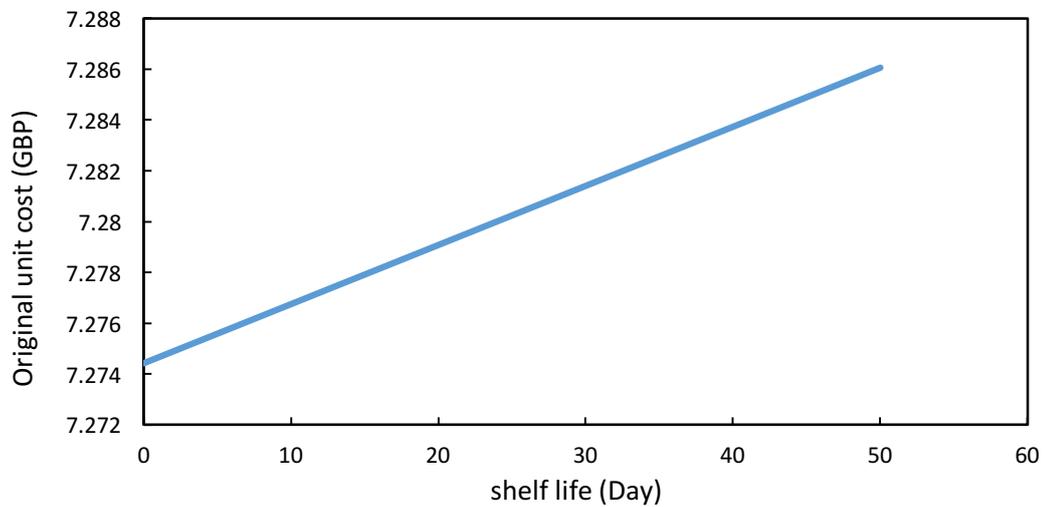
$c_1$  is original unit cost of hypothermal storage.

In this work, the EUC is compared in two cases a) when the production process incorporates freeze-drying; and b) when freeze-drying is replaced by hypothermal storage. The shelf life of freeze-dried products usually falls between one to two years. As a result, it can be assumed that the quantity of decellularised skin produced will be used within its shelf life and the production cost will therefore be equal to the effective cost.

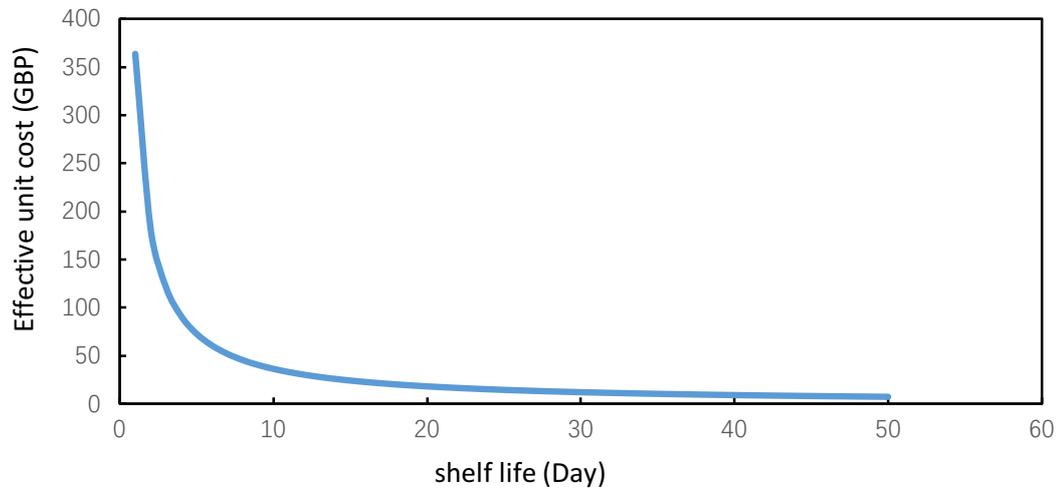


**Figure 4.7** Relationship between waste percentage and shelf life for  $\theta=0.02$

Figure 4.7 illustrates the effect of wastage percentage vs. shelf life for  $waste\%=1-(0.02 \times shelf\ life)$ , while Figures 4.8 and 4.9 show the corresponding OUC and EUC as a function of shelf life, respectively.



**Figure 4.8** Relationship between OUC and the shelf life of the product



**Figure 4.9** Relationship between effective cost and shelf life while  $waste\% = 1 - (0.02 \times \text{shelf life})$

For the case where  $waste\% = 1 - (0.02 \times \text{shelf life})$ , it is clear that the effective cost is much higher than the original cost for short shelf lives. This means that the waste percentage is too high for the alternative production method to be cost-effective. As the shelf life of the product increases, the waste percentage decreases, and the gap between the effective cost and the unit production cost is reduced. When the shelf life is sufficiently long, the wastage tends towards zero, and the effective cost is equal to the original unit production cost. The point at which the effective cost and original production cost become the same depends on the relationship between the waste percentage of the product and its shelf life – this will be further discussed later.

In the next section, the three types of relationship between waste percentage and shelf life are examined in detail. The curves of effective cost vs shelf life will be generated for each type of relationship, with different parametric values.

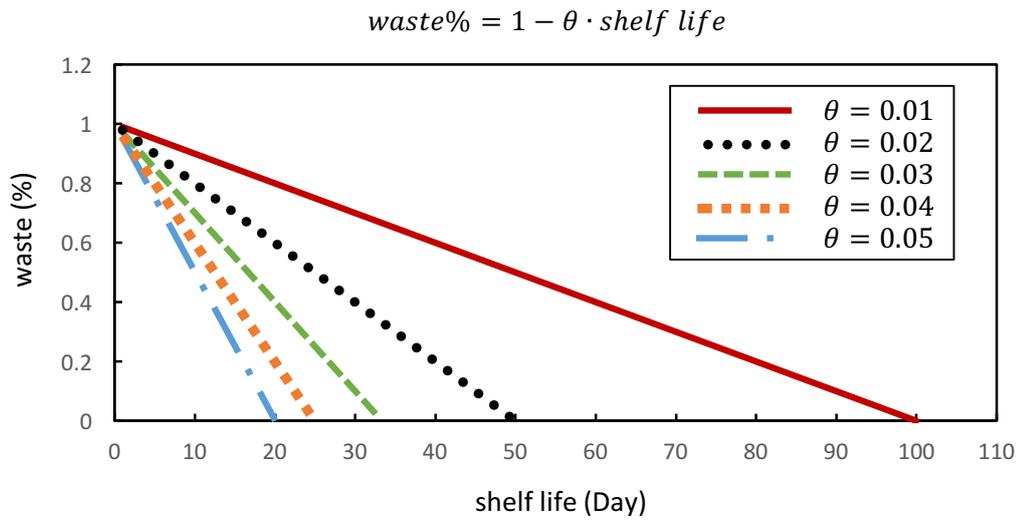
## 4.3 RESULTS AND DISCUSSION

### 4.3.1 Linear relationship between waste percentage and shelf life

In this section, it is assumed that the waste percentage decreases linearly as a function of shelf life. The role of hypothermal storage is to compensate for the temporary mismatch between consumption and production, by providing a duration where this mismatch can be reduced or ideally eliminated. A parameter describing the relationship between the waste percentage and shelf life will be introduced as an indicator of the extent of temporary mismatch between production and consumption:  $\theta$ . For example, because of a sporadic decline in demand, only 80% of the product was consumed. In this case, the  $\theta$  times the shelf life value is 0.8; therefore, the waste percentage is 20%. Thus, the waste can be deduced as:

$$\text{Waste percentage} = 1 - (\theta \cdot \text{shelf life}) \quad (4.10)$$

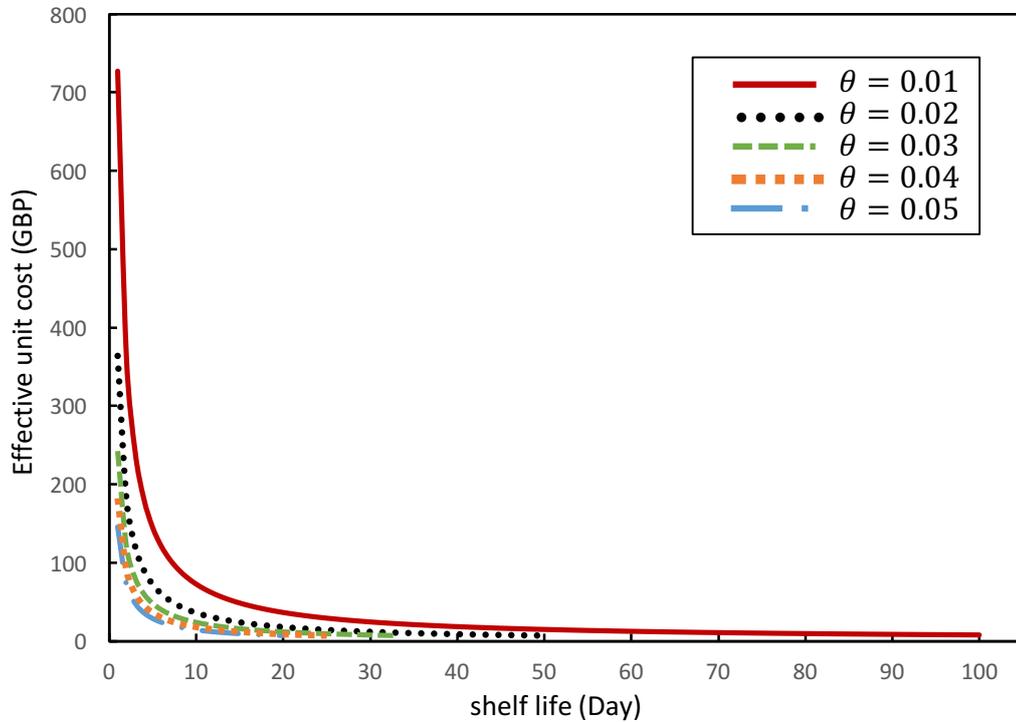
Based on this linear rule, the next stage is to determine how the effective cost changes as a function of the shelf life the product. This was done by examining five different gradients of linear waste percentage vs. shelf life curves to determine the effect of the gradient on the behaviour of the effective cost vs. shelf life curves.



**Figure 4.10** Linear relation between shelf life and waste percentage for different values of  $\theta$

Figure 4.10 shows the five linear waste percentage–shelf life curves with the five different consumption/production ratios, ranging from between 0.01 to 0.05. From the blue line to the red line, the value of  $\theta$  decreases (from 0.05 to 0.01), and the corresponding decrease in waste percentage with increasing shelf life becomes more gradual. In the case of the blue line ( $\theta = 0.05$ ) where  $waste\% = 1 - (0.05 \times shelf\ life)$ , the waste percentage decreases rapidly when the shelf life increases. In this case, when the shelf life reaches 20 days, the waste percentage reaches 0, which means that the effective cost has reached its nadir and matches the original production cost. In the case of the red line ( $\theta = 0.01$ ), where the  $waste\% = 1 - (0.01 \times shelf\ life)$ , the rate of decrease in waste percentage is at its lowest, and therefore, a shelf life of 100 days for complete consumption of the product is required to avoid wastage. The other curves also demonstrate that the greater the effect of the shelf life on wastage (i.e. the bigger the consumption–production ratio), the lower the shelf life required to avoid wastage. It should be noted that these analyses only

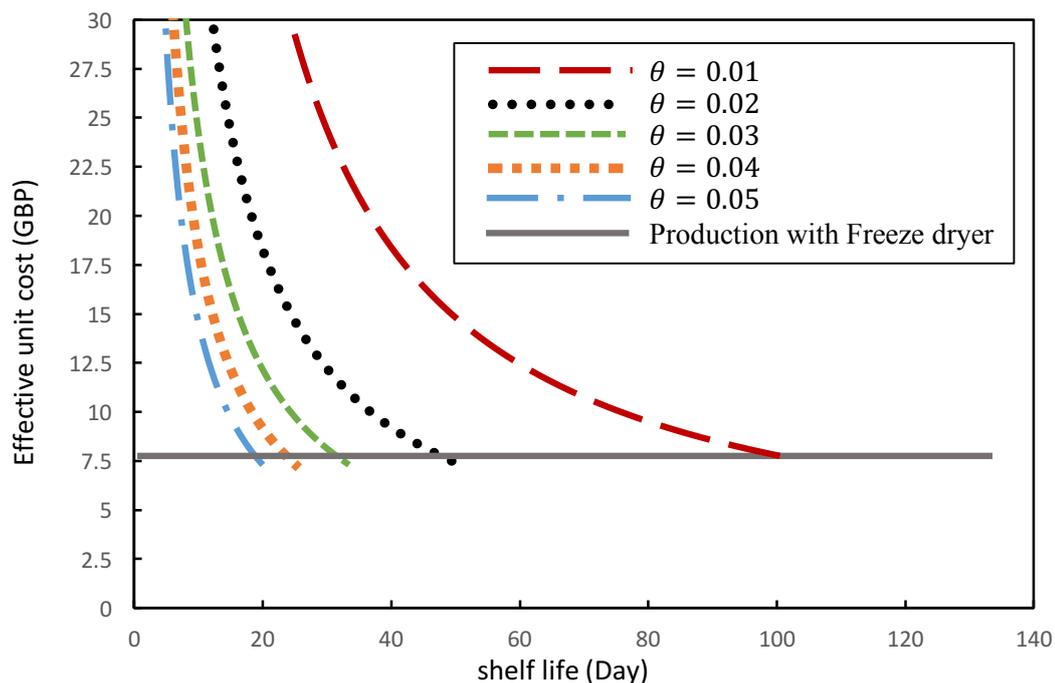
consider realistic cases, where the waste percentage is positive.



**Figure 4.11** EUC against shelf life for  $\text{waste\%} = 1 - \theta \cdot \text{shelf life}$  with different values of  $\theta$

The aim of this study is to examine the effect of the shelf life on the EUC, as shown in Figure 4.11. In this figure, the lines from blue to red represent the results for values of  $\theta$  equal to 0.05, 0.04, 0.03, 0.02 and 0.01 respectively, which corresponds to the waste percentage–shelf life lines that are shown in Figure 4.9.

The original unit production cost for all of the curves shown in Figure 4.6 is the same. However, it is clear that different relationships between the waste percentage and the shelf life lead to different effective cost curves.



**Figure 4.12** EUC against shelf life while  $waste\% = 1 - \theta \cdot shelf\ life$  of production without freeze dryer compared with the unit production cost with freeze-dryer

Figure 4.12 shows a zoomed-in segment of the lower EUC region of Figure 4.10, to allow the EUC for the five different shelf life–waste percentage relationships to be compared with the unit cost of production with freeze drying, which was earlier determined to amount to 7.75 GBP. This comparison is necessary to reveal scenarios where the shelf life the production process without freeze-drying becomes a cheaper alternative.

**Table 4.2** Relationship between shelf life and EUC while  $\theta = 0.05$

Shelf life (days)	EUC (GBP)	Waste percentage
18	8.09	10%
19	7.66	5%
20	EUC=OUC	0%

Table 4.2 analyses the case where  $\theta=0.05$ . In this case, a shelf life of 20 days is required

to achieve zero wastage, and for the EUC to match the original production unit cost. As the shelf life decreases, the waste percentage becomes greater, which leads to an increase in EUC. Therefore, in this case, the effective cost is cheaper than the production cost with freeze-drying (7.75 GBP) when the shelf life of the product is greater than or equal to 19 days.

**Table 4.3** Relationship between shelf life and EUC while  $\theta = 0.04$

<b>Shelf life (days)</b>	<b>EUC (GBP)</b>	<b>Waste percentage</b>
23	7.91	8%
24	7.58	4%
25	EUC=OUC	0%

Table 4.3 details the waste percentage and the shelf life that result from our the second hypotheses ( $\theta = 0.04$ ). In this case, the effective cost is cheaper than the production cost with freeze-drying (7.75 GBP) when the shelf life of the product is greater than or equal to 24 days.

Similarly, the cases of  $\theta = 0.03$ , 0.02 and 0.01 have a zero wastage shelf life of 33, 50 and 100 days and an economical shelf life (i.e. one leading to a cheaper solution than the process with freeze drying) of 32, 48 and 95 days, respectively.

**Table 4.4** Minimum shelf life required for EUC being lower than the unit cost with freeze-dryer under different  $\theta$  values

<b>Waste percentage and shelf life relation under different <math>\theta</math> values</b>	<b>Minimum shelf life (t) required for EUC being lower than the unit cost with freeze-dryer</b>	<b>Waste percentage</b>
Waste%=1-(0.01×shelf life)	$t \geq 95$	4%
Waste%=1-(0.02×shelf life)	$t \geq 48$	4%
Waste%=1-(0.03×shelf life)	$t \geq 32$	4%
Waste%=1-(0.04×shelf life)	$t \geq 24$	4%
Waste%=1-(0.05×shelf life)	$t \geq 19$	5%

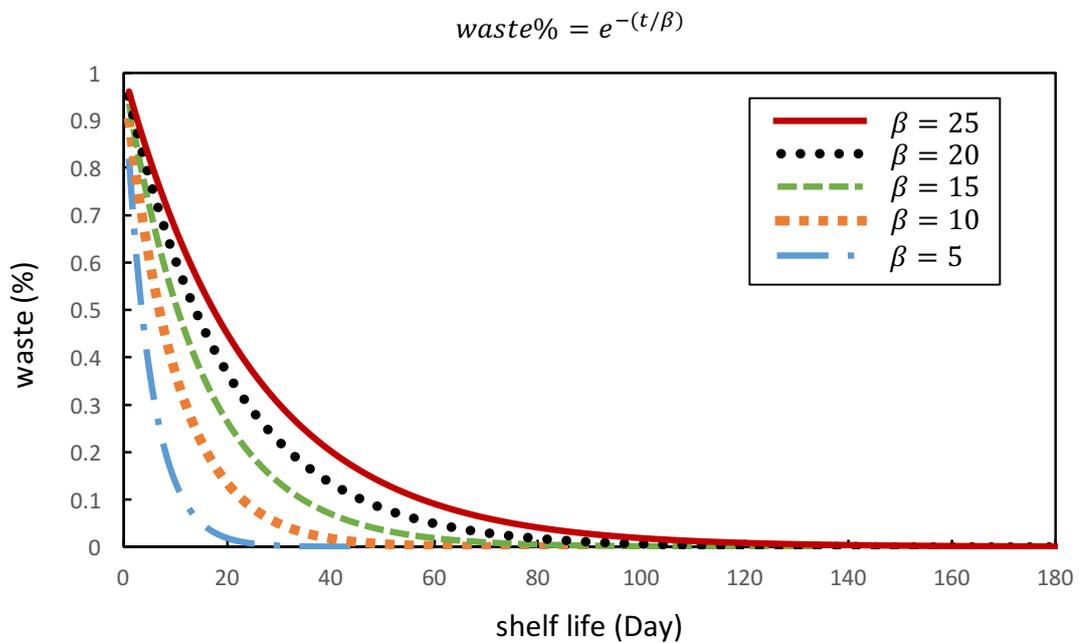
Tables 4.4 contains the empirical results derived from the first type of waste percentage–shelf life curve. The examples listed above indicate in the absence of freeze drying, a longer shelf life is required to overcome production costs when the waste percentage decreases slowly. When the waste percentage decreases as a function of shelf life at an extremely slow rate, the decrease in EUC due to a decrease in waste percentage does not overcome the corresponding increase in the combined production and storage costs. When searching for the value of  $\theta$  which equalises EUC; i.e. to the unit cost of the process with freeze drying (7.75 GBP), the critical value of  $\theta$ , which indicates a rate of wastage reduction where hypothermal storage becomes more economically viable than freeze drying, was determined to be 0.000488. When  $\theta$  is lower than 0.000488, i.e. when the waste percentage improves too slowly, the alternative production method will be always more expensive than the original method, regardless of the length of the shelf life. In addition, it can be observed from Table 4.4 that for a linear relationship between shelf life and waste percentage, the waste percentage generally needs to be less than 5% for

hypothermal storage to incur lower production costs than the approach that incorporates freeze-drying.

### 4.3.2 Curve relationship (b) (convex) between waste percentage and shelf life

This section investigates the scenario when a convex curve (b) is used to describe the relationship between waste percentage with increasing shelf life. In this example, the shelf life of the product does not vary linearly with waste accumulation but is instead represented by an exponential function. The basic formula of these type of curves is given by:

$$\text{Waste percentage} = e^{-\left(\frac{t}{\beta}\right)} \quad (4.11)$$

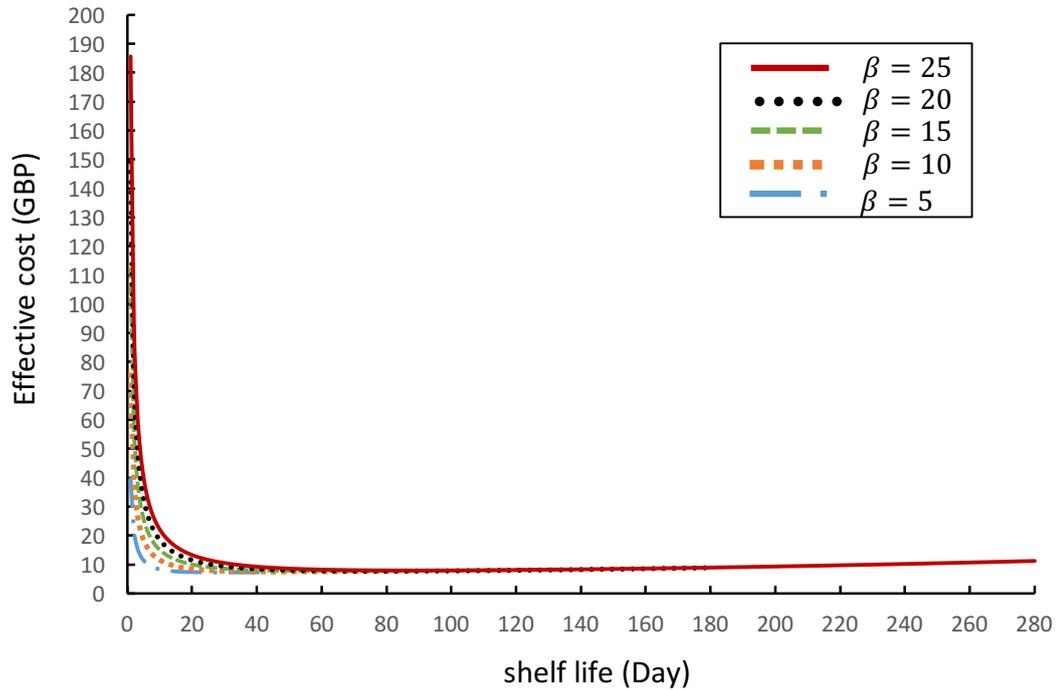


**Figure 4.13** Waste percentage and shelf life curve of  $waste\% = e^{-(t/\beta)}$  with different values of  $\beta$

For the five curves shown in Figure 4.13, the values of  $\beta$  are different. The  $\beta$  values for each of the curves are given in the figure legend and range from 5 to 25.

For the blue curve in Figure 4.13, with  $\beta = 5$ , the waste percentage decreases dramatically with changes to the shelf life, and approaches 0 if the product remains viable for 30 days. In this scenario, there is almost no wastage if the product has a shelf life of more than 30 days. As the value of  $\beta$  increases, the gradient of the curve is reduced. As a result, the rate at which the waste percentage is reduced in response to increments in shelf life is slower; i.e. any further waste reduction necessitates a greater relative increase in shelf life. Furthermore, as this type of curve is described by an exponential function, the waste percentage will never reach 0 but will instead approach 0 as the shelf life leads to infinity. In this situation, the EUC only approaches the OUC. The shelf lives shown in Figure 4.13 represent an EUC that is numerically equal to the OUC to up to two decimal places, corresponding to a waste percentage that is close to 0. Here, the most informative part of the graph – the segment that is closer to the origin – will be investigated and discussed.

$$\text{effective cost} = \text{original cost} / (1 - \text{waste}\%)$$

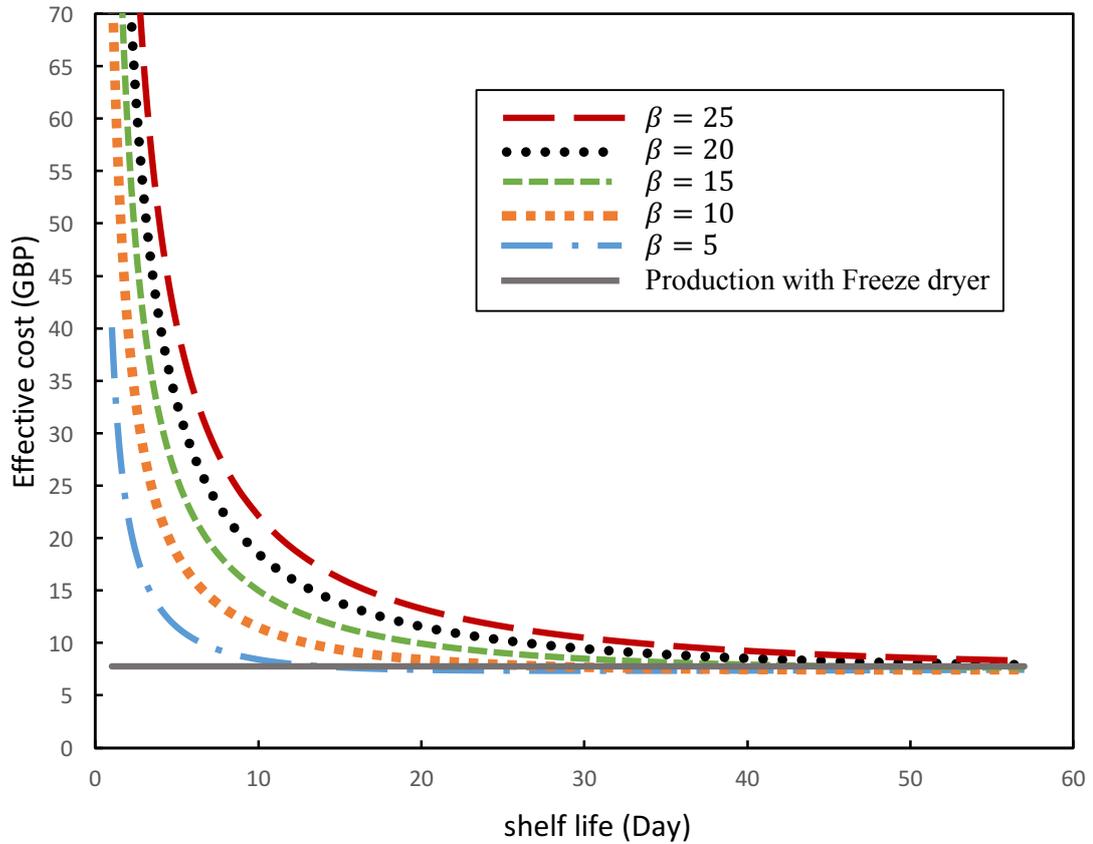


**Figure 4.14** EUC against shelf life for  $\text{waste}\% = e^{-(t/\beta)}$  for different values of  $\beta$

The curves with different gradients share the same OUC. However, the diversity in rates where the waste percentage is decreased by increasing shelf life results in differences in their corresponding effective cost curves. With the procedure described in the section 4.3.1, the corresponding curves of EUC against shelf life can be generated.

Figure 4.14 shows the EUC against shelf life for the five different shelf life–waste percentage relationships. As indicated in this figure, the EUC decreases rapidly with increasing shelf life until it approaches its minimum value. As shelf life increases beyond this point, the EUC reverses its decreasing trend and begins to increase, however at a very low rate.

$$EUC = OUC / (1 - \text{waste}\%)$$



**Figure 4.15** EUC against shelf life for  $\text{waste}\% = e^{-(t/\beta)}$  of production without freeze dryer compared with the unit production cost with freeze-dryer

Figure 4.15 shows a part of Figure 4.14 together with the unit production cost of production with a freeze-dryer, which is invariant to the shelf life of the product. The unit production cost with a freeze-dryer is GBP 7.75, and is represented by the horizontal grey line. The five EUC curves from blue to red are the EUC–shelf life curves generated from the waste percentage–shelf life curve with the  $\beta$  values of 5, 10, 15, 20 and 25, respectively.

**Table 4.5** Relationship between shelf life and EUC while  $\beta = 5$ 

<b>Shelf life (days)</b>	<b>EUC (GBP)</b>	<b>Waste percentage</b>
14	7.75	6%
15	7.66	5%
44	7.28 minimum	0%
46	7.29 (EUC=OUC in 2 d.p.)	0%

As shown in Table 4.5, for  $\beta = 5$ , the value of the EUC is equivalent to the OUC (up to two decimal places) with a shelf life of approximately 46 days. However, as a result of the initial rapid decline in waste percentage with increasing shelf life, the required duration for the effective cost of hypothermal storage to become lower than the cost of the conventional production method (that is, with the use of a freeze-dryer) is only 15 days.

**Table 4.6** Relationship between shelf life and EUC while  $\beta = 10$ 

<b>Shelf life (days)</b>	<b>EUC (GBP)</b>	<b>Waste percentage</b>
28	7.76	6%
29	7.70	5.5%
81	7.30 Minimum	0.03%
89	7.30 (EUC=OUC in 2d.p.)	0%

As shown in Table 4.6, for  $\text{waste}\% = e^{-\frac{t}{10}}$ , the waste percentage is 5.5% and the EUC becomes cheaper than the conventional method when the shelf life reaches 29 days. The EUC reaches a minimum at the shelf life of 81 days, after which it increases at a much slower pace, the EUC is equal to the OUC (up to two decimal places) when the shelf life

reaches 89 days.

Using the same procedure, for the case  $\beta = 15, 20$ , and  $25$ , a gradual increase in the EUC is achieved when the shelf life is greater than 115, 147 and 218 days respectively. In addition, they have an economical shelf life (i.e. one leading to a cheaper solution than the process with freeze drying) of 43, 57 and 71 days, respectively.

**Table 4.7** Shelf life required for EUC being lower than the unit cost with freeze-dryer under different  $\beta$  values

<b>Waste percentage and shelf life relation under different <math>\beta</math> values</b>	<b>Shelf life (t) required for EUC being lower than the unit cost with freeze-dryer</b>	<b>Waste percentage</b>
$\text{Waste}\% = e^{-t/5}$	$t \geq 15$	5%
$\text{Waste}\% = e^{-t/10}$	$t \geq 29$	5.5%
$\text{Waste}\% = e^{-t/15}$	$t \geq 43$	5.6%
$\text{Waste}\% = e^{-t/20}$	$t \geq 57$	5%
$\text{Waste}\% = e^{-t/25}$	$t \geq 71$	5.8%

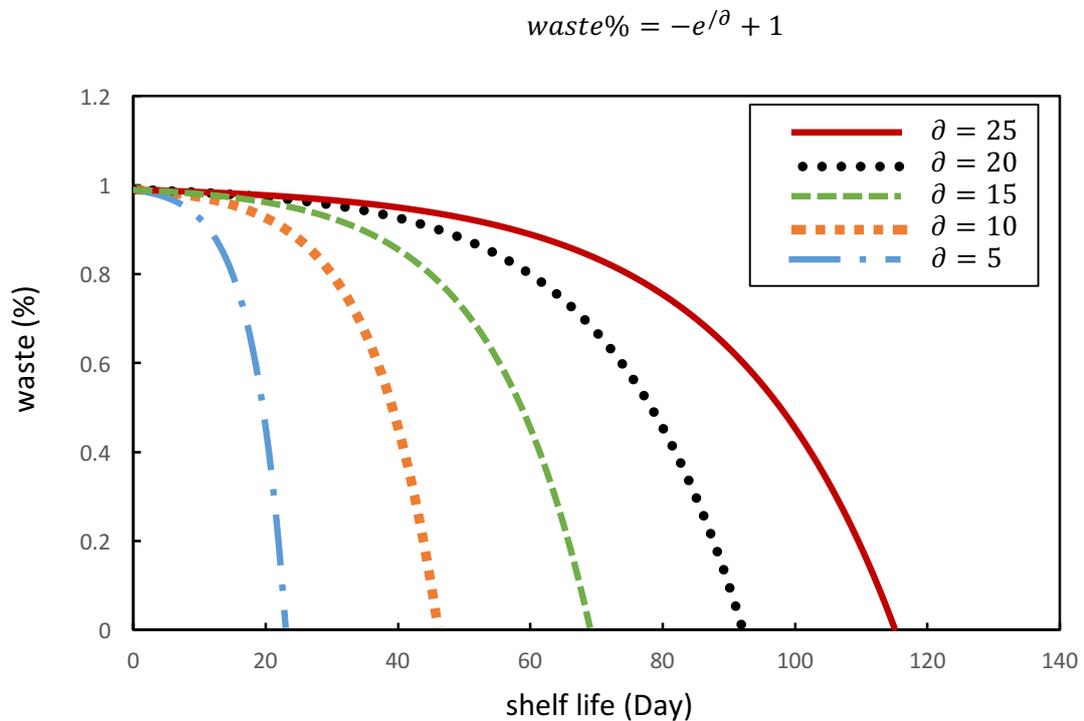
Table 4.7 contains the empirical results that have been derived from the graphs. They show the shelf lives that are required for the alternative production method to be more cost-effective than the use of a freeze-dryer.

In summary, for convex waste percentage–shelf life relationships, the reduction in EUC that is achieved by lowering waste percentage (through increasing shelf life) outweighs any additional storage costs that result from the additional shelf life if the shelf life of the product falls within the ranges that are listed in the table above, unless the rate of decrease in waste percentage becomes too low. These ranges are influenced by the parameter,  $\beta$ ,

and are valid only when  $\beta$  is lower than its critical value of 368. Beyond this level, hypothermal storage will not be more cost-effective than freeze drying. Also, when the waste percentage is lower than 5%, the EUC for the alternative production method is generally lower than the unit production cost of using a freeze-dryer.

### 4.3.3 Curve relationship (c) (concave) between waste percentage and shelf life

For concave curve shape, we consider only the segments of the curve where the waste percentage remains positive. In these examples, the waste percentage decreases slowly at first but increases rapidly beyond a certain shelf life.



**Figure 4.16** Waste percentage and shelf life curve of  $\text{waste}\% = -e^{t/\partial} + 1$  with different values of  $\partial$

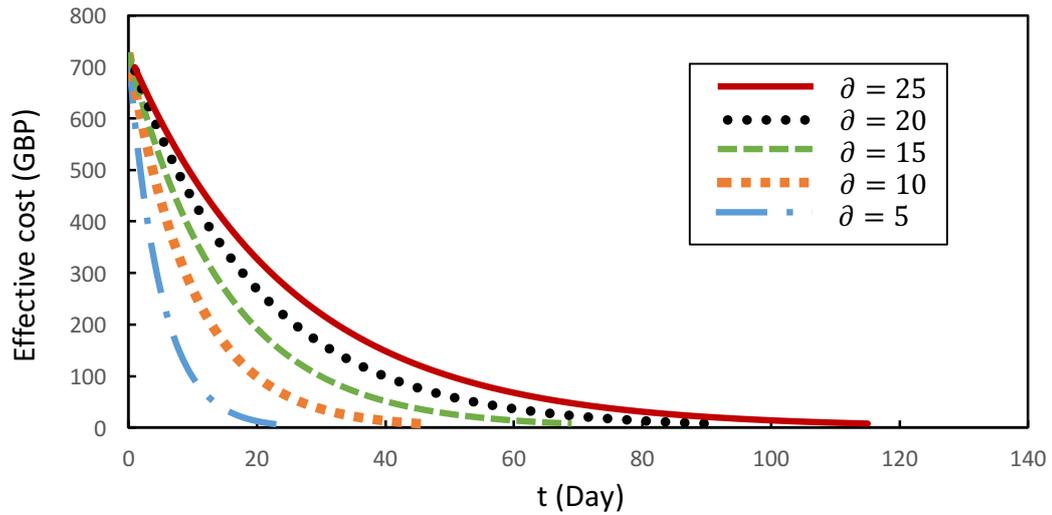
The basic formula for these curves is represented by:

$$\text{Waste percentage} = \frac{-e^{t/\partial}}{100} + 1 \quad (4.12)$$

Five different values of  $\partial$  are used in this formula to adjust the shape of the curve. For the curves shown in Figure 4.16, the values of  $\partial$  from left to right (that is, from blue to red) are 5, 10, 15, 20 and 25, respectively. Only the positive part of these curves is considered.

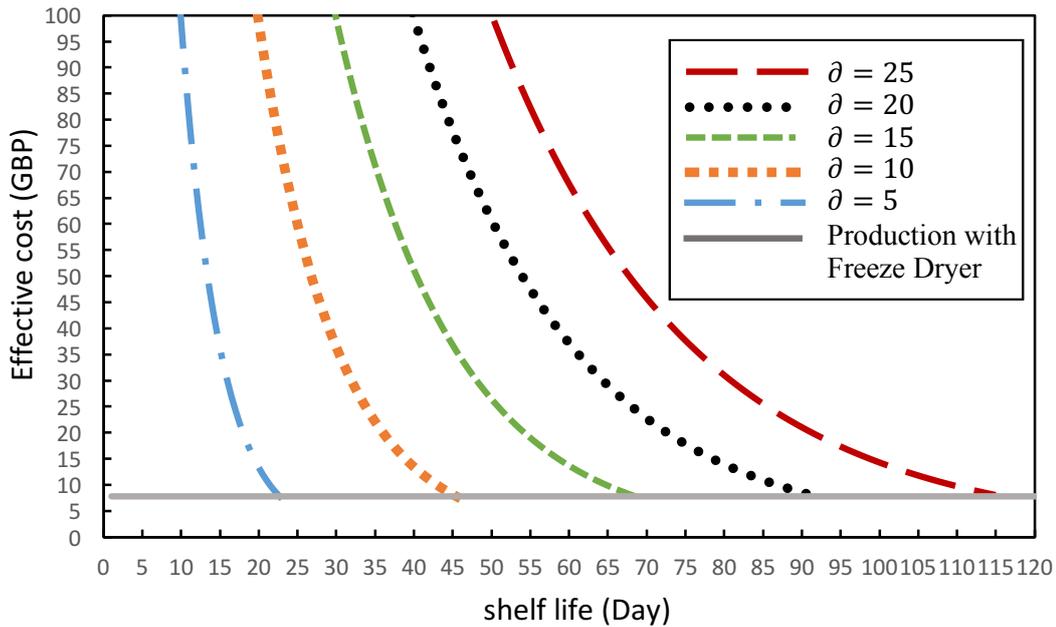
For the blue curve in Figure 4.16, where  $\partial = 5$ , the waste percentage decreased dramatically to almost 0 within 23 days, indicating that wastage can be avoided for shelf lives greater than 23 days. As the value of  $\partial$  rises, the rate at which an increasing shelf life leads to a reduction in waste percentage decreases, thereby necessitating longer shelf lives to avoid wastage. The minimum (positive) values of waste percentage for  $\partial$  values of 5, 10, 15, 20 and 25 are achieved when the shelf lives are 23, 46, 69, 91 and 114 days, respectively.

The OUC shown in Figure 4.7 is shared for all the curves. However, the rates of decrease in waste percentage vary with respect to the lengthening of shelf life, and contribute to different effective cost curves. Using the same methodology as sections 4.3.1 and 4.3.2, the corresponding EUC against shelf life curves can be generated.



**Figure 4.17** EUC against shelf life while  $\text{waste}\% = \frac{-e^{t/\partial}}{100} + 1$  for different values of  $\partial$

The third possible shape (c) of the curve shows a continual decrease in waste percentage with increasing shelf life; resulting in EUC–shelf life curves that resemble those in the previous section. When the decrease in effective cost due to the reduction in waste percentage exceeds the increase in cost that is incurred by an increase demand for storage capacity, hydrothermal storage becomes more cost effective than the original production method. The unit production cost of using a freeze-dryer (GBP 7.75) is illustrated and compared with the EUC curves shown in Figure 4.17.



**Figure 4.18** EUC against shelf life while  $\text{waste}\% = \frac{-e^{t/\theta}}{100} + 1$  of production without freeze dryer compared with the unit production cost with freeze-dryer

The changes in effective cost with shelf life for the third type of waste percentage–shelf life curve are illustrated in Figure 4.18. The grey line indicates the freeze-dryer unit production cost (7.75GBP), and remains constant with respect to the shelf life of the product.

**Table 4.8** Relations between shelf life and EUC while  $\theta = 5$

Shelf life (days)	EUC (GBP)	Waste percentage
22	8.93	18.5%
23	7.31	0.5%
$\geq 24$	–	<0

When  $\theta = 5$ , the rapid fall in the waste percentage would numerically make it negative at 24 days. The effective production cost for production with hypothermal storage decreases to 7.34 GBP at this time for a shelf life of 23 days, which is lower than the cost

of the original method.

**Table 4.9** Relations between shelf life and EUC while  $\partial = 10$

<b>Shelf life (days)</b>	<b>EUC (GBP)</b>	<b>Waste percentage</b>
45	8.09 GBP	10%
46	7.32 GBP	0.5%
$\geq 47$	–	$< 0$

For  $\partial=10$ , the waste percentage decreases more slowly. The waste percentage becomes negative when shelf life reaches 47 days, as indicated in Table 4.9. In this case, the implication is that the shelf life of the product must be at least 46 days for the effective cost of the alternative method to be lower than the cost of using a freeze-dryer.

With the same procedure, cases  $\partial = 15, 20$ , and  $25$ , experience a rapid fall in the waste percentage that will make the EUC numerically negative at 70, 93 and 116 days respectively. In addition, they have an economical shelf life (i.e. one leading to a cheaper solution than the process with freeze drying) of 69, 91 and 114 days, respectively.

**Table 4.10** Minimum shelf life required for EUC being lower than the unit cost with freeze-dryer under different  $\partial$  values

<b>Waste percentage and shelf life relation under different <math>\partial</math> values</b>	<b>Minimum shelf life required for EUC being lower than the unit cost with freeze-dryer</b>
$\text{Waste}\% = \frac{-e^{t/5}}{100} + 1,$	$t \geq 23$
$\text{Waste}\% = \frac{-e^{t/10}}{100} + 1,$	$t \geq 46$
$\text{Waste}\% = \frac{-e^{t/15}}{100} + 1,$	$t \geq 69$
$\text{Waste}\% = \frac{-e^{t/20}}{100} + 1,$	$t \geq 91$
$\text{Waste}\% = \frac{-e^{t/25}}{100} + 1,$	$t \geq 114$

Table 4.10 contains the empirical results derived from the third set of waste percentage–shelf life curves. They indicate minimum shelf lives that must be met for the alternative production method to be more cost-effective than production with a freeze-dryer.

For this set of waste percentage–shelf life curves, the waste percentage must generally fall below 0.5% for hydrothermal storage to be feasible. There exists a critical value of the parameter  $\partial$ , beyond which the EUC will always be costlier than the UC of the case with freeze drying with a finite storage length. For this case, the critical value of the parameter is 440.

#### **4.3.4 Discussion**

We have shown that because the waste percentage is dependent on the shelf life of the product, the EUC of the production method that excludes freeze drying is a function of

the relationship between the waste percentage and shelf life. For the alternative method to be adopted, a much quicker reduction in waste percentage is required so that the alternative method to be economically advantageous. In contrast, if the waste percentage is reduced too slowly, the EUC of the alternative production method will remain higher than the conventional method of producing decellularised skin. The indicated critical values are case-specific to this modelled study, and in these cases the existence of the critical values does not really pose an issue, as they rather represent extremely slow reduction of waste percentage by the extension of shelf life; in reality the reduction percentage is most likely to be higher. However, in general, one should not ignore the fact that due to the existence of critical values, replacing freeze drying with hypothermal storage might not be able to offer a superior solution.

#### **4.4 SUMMARY**

For each of the possible relationship between waste percentage and shelf life, the EUC of the alternative production method (that is, the method in which the freeze-dryer is replaced by hypothermal storage) is affected by two factors: waste percentage and the original storage cost. A decrease in waste percentage is achieved by increasing the shelf life, which will reduce the EUC of the alternative production method. However, the increase in shelf life will also lead to an increase in the original cost of storage.

When the relationship between the waste percentage and the shelf life is taken to be linear,

the increase in shelf life is associated with a linear drop in waste percentage from 100% to 0%. For the alternative approach of hypothermal storage to result in lower costs of production as compared to conventional approach which employs freeze-drying, the waste percentage must be lower than approximately 5% and  $\theta$  should have a value that is greater than 0.000488

In the second type of waste percentage–shelf life relationship, the EUC of using hypothermal storage is lower than the conventional production cost when the waste percentage is sufficiently low. However, the increase in storage costs will overcome the decrease in EUC as a result of the reduction in the waste percentage. In this scenario, when the value of  $\beta$  is lower than 368, there always exists a range of shelf life in which the EUC of the method using hypothermal storage lower than that of the conventional production method.

Finally, in the third possibility of waste percentage–shelf life relationship, the waste percentage must be lower than 0.5% for the EUC of the alternative production process to be lower than the unit cost of the conventional approach of producing decellularised skin. In order for this situation to occur, the value of the parameter  $\partial$  must be lower than the critical value of 440.

# **CHAPTER 5**

## **VALUE CHAIN ANALYSIS OF DECELLULARISED SKIN**

### **5.1 INTRODUCTION**

#### **5.1.1 Commercialisation in regenerative medicine industry**

Regenerative medicine is an emerging field with the potential to enhance patient well-being and deliver improvements in healthcare through therapies which can repair, restore or regenerate damaged tissue. Due to its rapid growth and medical importance, economic growth will be significantly stimulated by regenerative medicine if its products can be effectively commercialised. In 2007, there were approximately 170 regenerative firms worldwide, with commercial revenue amounting to upwards of 15 billion USD. According to Lysaght and colleagues[12], listed firms have a combined capital value of approximately 47 billion USD. Since radically new concepts have entered the market, regenerative medicine has become one of the key players in the pharmaceutical market and is attracting more and more attention from the different healthcare domains, such as the biotechnological industry. However, without significant advancement in its

production strategy, its high cost would provide an obstacle to its commercialisation to the masses.

While the quality of regenerative medicine in UK is ranked first in the world, recent research[84] has found an overwhelming consensus within the scientific community in acknowledging that its translation and commercialisation is less successful than in the USA and other developed countries. It was generally noted that healthcare organisations in the UK were not well equipped to take advantage of their scientific lead. Furthermore, those surveyed also suggested that poor commercialisation might affect the ability of the UK to maintain its worldwide scientific lead.

Currently, a few sectors in the UK have commercialised regenerative medicine successfully. For example, cartilage products and skin soft tissue have been commercialised by some biological companies. However, the manufacturing cost of these products are higher compared to currently available therapies, i.e. the substantial cost of development and testing via clinical trials can make it difficult for industries to attain a profit margin. Similarly, many biotechnology companies must partner with larger firms to complete production of the high research and development costs and low revenue in the early years of product commercialisation. Given these difficulties, some companies have decided to follow a mature business strategy, where some products are obtained via public healthcare, while others, such as bio-aesthetic products, are paid for by patients directly.

### **5.1.2 Regenerative medicine products**

The first tissue engineering product to be commercialised was a biological skin substitute, which is used to treat diabetic foot ulcers and, more recently, developed for the treatment of severe burns [85-88]. In 2001, Dermagraft was approved for treatment of diabetic foot ulcers by the US FDA; the developing company, Advanced Tissue Sciences (San Diego, CA., USA), was established in 1987, but went bankrupt in 2009. Dermagraft is a product consisting of a bio-absorbable mesh scaffold, onto which human fibroblasts are seeded and allowed to divide and grow. In addition, a variety of substances comprising dermal collagen are secreted during this process. Ultimately, a three-dimensional human dermal substitution, which contains metabolically active living cells is generated. Dermagraft has a shelf life of six months and has to be shipped in a frozen condition.

For regenerative medicine, the up-front cost of therapy is often much higher than the cost incurred during conventional treatment. For example, the price of treating a diabetic foot ulcer with regenerative medicine products often amount to tens of thousands of US dollars as compared to the minimal costs incurred during conventional treatment options[89]. Hüsing et al.[90] estimated that the cost of engineered skin lies between 9.92 - 20.85 euros per cm<sup>2</sup>, while the cost of conventional treatment is approximately 0.37 - 8.66 euros per cm<sup>2</sup>. However, treatment period for regenerative medicine is much shorter than conventional treatment strategies, and the corresponding expenditure towards other avenues of medical support such as hospitalisation, nursing, and medical follow-up are

less significant. Conventional treatment regimens for diabetic foot ulcer can amount to up to a year of treatment and from the initial in-patient stay, where the majority of the costs of the patient's treatment is owed to the community healthcare provider; the latter costs can be avoided when regenerative medicine is the choice of treatment.

### **5.1.3 Features of value chain of regenerative medicine product**

Birch and Racher[91] and Kelley[92] described regenerative medicine products, and their functions, to be extremely delicate and multifunctional. As compared to biopharmaceuticals, live products have a diminished shelf life and require strict cryogenic storage procedures for their preservation. It also has a lengthy product delivery period, extended lead times and difficulties sustaining a usable better record, despite the technological advantages of the current era. In order to effectively produce and sell a cell-based product, whether autologous or allogeneic, on the current market, these issues should be counteracted with intensified communication and synchronisation among producers, suppliers, transporters and customers. The industry must act to improve these connections through better administration and scheduling.

The value chain analysis, which outlines the main processes in the logistical movement of regenerative medicine products from its creation to customer consumption, allows the vigorous evaluations of factors concerning finance, logistical needs and any risks that are associated with the entire system[93], This evaluation of these factors allows all involved

– suppliers, manufacturers, transport and quality control personnel – to manage and coordinate their operations more efficiently, which can be difficult due to conflict of interests and poor communication between researchers, consumers and healthcare specialists. However, this can be problematic and challenging for traditional intellectual property and commercialisation routes. Additionally, products such as stem cell-based products, which are extremely sensitive to environmental influences, are impacted by robustness of logistics. In consequence, the value chain for decellularised skin, which represents the key activities for the delivery of this product to the market, should consider robust logistical needs, costs and risks[93].

#### **5.1.4 Objective of this chapter**

Previous chapters have considered the optimal design and scheduling for the production of decellularised skin. In this chapter, we perform further cost analysis and propose cost minimisation strategies that can be incorporated into the production process. By performing a value chain analysis, the production chain can be examined with greater resolution. All activities – from manufacturing to application – and the total cost incurred during the lifetime of the decellularised skin product are evaluated in this chapter. Thereafter, the value chain analysis – following the framework proposed by Porter[1] – will be performed. The latter enables us to evaluate the costs incurred during the stages and processes that evolve prior to the authorisation of the decellularised skin product for use by the patient. Since all associated costs would be uncovered during the analysis, we

could identify the major cost drivers and devise strategies to replace or reduce their contribution to the production cost. The importance of this work is to contribute to an understanding of why patients are expected to pay such high prices for regenerative medicine products and to uncover the challenges that prevent the wide dissemination of these products; finally, we hope that our suggestions for improvement to alleviate production costs can be implemented so that more may benefit from the promise of regenerative medicine.

## **5.2 METHODOLOGY**

### **5.2.1 The value chain approach**

Value chain analysis is one approach to strategic planning. All companies make long-term decisions that impact on long-term profitability and their competitiveness. Because some of these decisions can turn out to be mistakes, strategic planning formalises and scrutinises the decision-making process, which can reduce the possibility of making a poor and costly decision. In summary, strategic planning is an important step that allows a company to attain or maintain its competitive advantage.

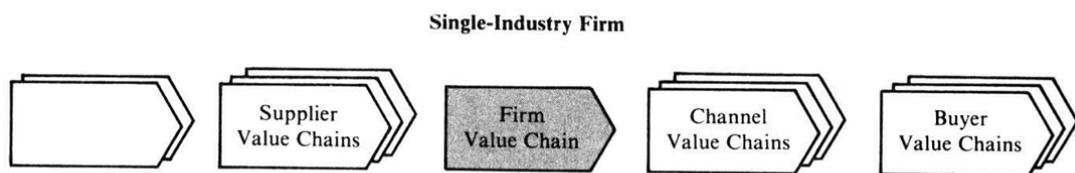
Since cost management requires a broad focus, a strategic planning framework contributes by combining internal data about a firm's capabilities with external information (that can include ideas about its competitive environment) and presents the information in a format that guides resource allocation. A value chain analysis presents

the view of an organisation (company, firm, factory etc.), portraying a manufactured product (or service) as a system of subsystems that consists of inputs, transformation processes and outputs. Each input, transformation process, and output involves the acquisition and consumption of resources – money, labour, materials, equipment, buildings, land, administration and management. How value chain activities are carried out can influence production costs and affect profits[94]. Value chain analysis, in providing a framework for strategic planning, has the following characteristics [95]: (1) it focuses on identifying the source of sustainable competitive advantage; and (2) values the importance of complex linkages and interrelationships in the activities within the production chain as well as by activities within the buyer's and supplier's value chain.

The first difference between value chain planning and other approaches is that it highlights identifying the source of competitive advantage. Competitive advantage helps a firm sustain itself against competition and insures against the evolution of the industry. Competitive advantages are earned by creating value - for a buyer - that surpasses the cost of its generation[95]. Competitive advantage can be created in three ways: by working on (1) overall cost leadership; (2) differentiation; and (3) focus. Firstly, a low-cost strategy focuses on providing an equivalent quality of services or goods at a lower cost than competitors in the industry, or matching the cost with a product of superior quality. The second strategy focuses on differentiating oneself from competitors; this strategy is primarily focused on creating a unique position in the market, by providing

services or goods that are unique to the market. The final strategy is focused on meeting a specific niche that satisfies a specific group of buyers, segment of the product line or geographic market. This strategy is usually fulfilled by joining market niches where competition is the weakest, or by possessing a technological advantage. The last strategy usually succeeds by avoiding direct competition. However, it may also have a low-cost advantage, or an advantage in differentiation, or both. For the production of decellularised skin, cost leadership appears to be the most applicable strategy.

There are two components that make up value chain analysis: the industry value chain and the firm's internal value chain. The industry value chain is composed of all the value-creating activities within the industry, beginning with the first step of purchasing raw inputs materials, and ending with the complete delivery of the product to the customers/patients[96].



**Figure 5.1** Scheme of industry value chain[1]

The supplier value chain in an industry is responsible for delivering the inputs that will be used within the firm value chain. In the biotech industry, the suppliers' bargaining power is weak, since the valuation of biotech companies is driven by intellectual property. Unlike other industries, the proprietary nature of biotech industries does not force these

companies to have a heavy reliance on suppliers. The inputs that are required by the biotech firm, such as scientific tools and testing equipment, are highly specialised; therefore, most suppliers market must serve a range of industries other than the biotech industry. Therefore, for our study, it is not critical to understand importance of the supplier's value chain. However, there is a need to introduce these elements if the full value chain is to be examined.

The channel value chain indicate a channel that the product passes through before arriving at the customer and that may affect the buyer's behaviour[1]. For example, Argos can be seen as a channel value chain within the furniture industry in the UK. A similar channel is currently not observed within the biotech industry.

The buyer value chain defines the role of the company whose products are determined by a buyer's needs[1]. The bargaining power of buyers in the biotech industry is moderate to high [1], depending on how a product can be differentiated from those created by competitors. The major buyers include all healthcare firms, ranging from small private practices to large, state-run hospitals and health networks. A majority of successful biotechnology drugs, especially orphan drugs, are extremely differentiated, leaving the buyer's bargaining power at a minimum. However, if the submarket is based on sufficient competition, the bargaining power of these large corporate buyers will increase significantly. Thus, a good strategy for reducing the product's overall cost is to examine the buyer's value chain for potential contact points.

We therefore examine the ‘firm value chain’ in the production of decellularised skin and identify areas where activities within the ‘buyer value chain’ intersect with the ‘firm value chain’. The outbound logistic in the firm value chain might be the input of the buyer value chain; therefore, the cost of activities within the ‘firm value chain’ and ‘buyer value chain’ are interdependent. For example, the elimination of a freeze-dryer during skin production might decrease the operation cost of the firm value chain, but increases the storage cost that is sustained by the healthcare provider, i.e. the buyer value chain. Therefore, the main purpose of examining the ‘buyer value chain’ is to find activities that are vertically linked to the processes of the ‘firm value chain’, and to propose cost reduction strategies within this network.

Based on empirical results and information from market research or the literature, the value chain analysis for the industries that manufacture decellularised products will be assessed, and, more importantly, potential improvements will be suggested to enhance their competitive advantage.

### 5.2.1.1 Identifying value activities

The value chain incorporates multifaceted interdependencies between buyers, suppliers and producers. The value chain exposes financial factors within the market and allows scrutiny of the sources of differentiation [97]. These aspects show that the value chain is not an assemblage of independent actions, but represent an interconnected series of activities. These activities can be manually executed or performed using technology. In addition, financial assets can represent machinery or exist as part of an inventory. The activities, which require financing for its execution, can be divided into two major categories: primary activities and supporting activities.

There are nine significant activities, according to Porter[1], which companies perform, that can be further categorised as either primary or supporting activities. Each cost category is divided into well-defined activities, with the primary group incorporating five areas.



Figure 5.2 Firm value chain framework[1]

### ***Primary activities***

Primary activities are concerned with the production, preservation, support and the eventual sale of the merchandise. The different areas are:

#### *Inbound logistics*

This relates to material handling, warehousing, inventory regulation, arrangements and preparations for transport, and the product's arrival to suppliers. These are all the activities related to reception, storage and distribution.

#### *Operations*

This area refers to practices that fine-tunes inputs into the final product, including equipment preservation, assembly, packaging, product testing, and facility procedures.

#### *Outbound logistics*

These are procedures that follow the product's journey after it has been created, including its retrieval, housing and delivery to its destination. This relates to activities such as warehousing, material handling, delivery and order processing.

#### *Marketing and sales*

Activities associated with creating routes for buyers to purchase the product and that induce them to perform the latter – such as advertising, promotion, sales force, quoting, channel selection, channel relations and pricing – belong to this category.

### Service

Service refers to procedures that enable or increase product satisfaction and to activities that sustain the product's value. This could include fittings, repair, training, access to parts and product modifications.

### ***Support activities***

The second group of activities include four areas that support the performance of primary activities by introducing technology, human resources and purchasable aids.

### Procurement

Purchased inputs are usually related to primary activities, although they are present in support activities as this group includes value activity, where purchased inputs always exist. A company's value chain may integrate purchasable additions to assist the product's development, including machinery, office equipment and furniture, buildings, warehouses, and laboratory appliances. These are all assets, but supplies and raw materials are also required.

### Technology development

This description includes miscellaneous activities, which help to advance and manage the products.

### Human resource management

This category encompasses all activities relating to personnel, including their recruitment, training, development and compensation. The employee's skill and motivation levels are

evaluated to improve competitive advantage. Also, the expenses involved in training and recruitment are examined. Moreover, human resource management facilitates the completion of the value chain.

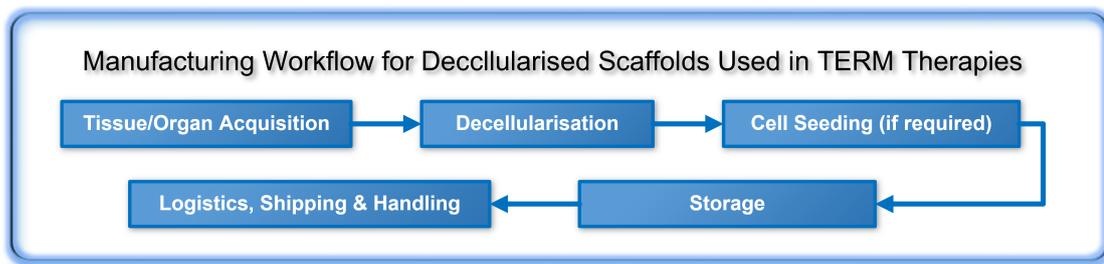
### *Firm infrastructure*

Numerous activities are associated with firm infrastructure, including general management, planning, financing, accounting, legal areas, governmental business and effective management. The whole value chain is reinforced by infrastructure, unlike the case with other support activities.

## **5.2.2 Application of the value chain framework**

### ***5.2.2.1 Manufacturing road map for tissue engineering and regenerative medicine technologies***

There are four main manufacturing approaches to providing tissue engineering and regenerative medicine (TERM)-based therapy: (a) manufacturing allogeneic (universal donor) TERM therapies; (b) manufacturing autologous (patient-specific) TERM products; (c) manufacturing decellularised scaffolds for TERM therapies; and (d) bioprinting for TERM therapies[98]. Figure 5.3 (below) shows the workflow for the decellularised scaffold.



**Figure 5.3** Manufacturing workflow for decellularised scaffolds[98]

The workflow shown in Figure 5.3 contains the general processes that are required in the manufacture of decellularised skin scaffolds. In this case, the raw material (tissue) is porcine skin, which is purchased from an approved and regulated hogger, as discussed in Chapter 3. The decellularisation process is followed by a sterilisation and washing process. In our case, the cell seeding process is not required. The approval of the completed product is required before it is allowed to undergo clinical testing, which is required for the product to be sold to the public. Since allogeneic and autologous treatments are not performed, shipping and handling make up the final processes.

The manufacturing process is less complex for decellularised scaffolds than for cell-based products; scaffolds are often developed as an off-the shelf product, and modifications are carried out only at the clinical site of use[98].

The individual value activities can be classified into the five primary activities and four support activities discussed in Section 5.2.2, and the costs of manufacturing can be assigned to the relevant value activities.

### 5.2.2.2 Cost activities of decellularised skin production

Table 5.1 below gives an overview of the activities that convert the raw materials into the final products. In order to analyse the activities in the firm value chain and compare them with those in the buyer value chain, the costs of the associated activities are calculated for each patient. The quantity of decellularised skin product that is required for the treatment of burns is estimated to be an average of ten sheets of skin per patient. The details of the production costs for ten sheets of skin are given in Table 5.1.

**Table 5.1** Cost in firm value chain per ten sheets of skin

<b>Cost category</b>	<b>Cost item</b>	<b>GBP/patient</b>
Electricity cost	Tank bioreactor	0.1
	Freeze-dryer	2.4
	Packaging machine	0.03
	Hypothermal storage	0.0001
Chemical cost	Sterilisation	27.6
	Fat removal	20.45
	Decellularisation	24.3
Capital cost	Tank bioreactor	0.34
	Freeze-dryer	8.78
	Packaging machine	1.18
	Hypothermal storage	0.04

The cost items in Table 5.1 are aggregated into cost categories based on the cost of activities within the value chain system, as shown in Table 5.2.

**Table 5.2** Cost categories for decellularised skin production

<b>Cost category</b>	<b>Price/GBP for ten sheets of skin</b>
Cost of transport	0.4
Cost of storage before production	0.04
Production (electricity)	2.53
Purchase of materials	0.6
Purchase of chemicals	72.38
Purchase of equipment	10.34
Transport	0.4
Hire of labour	0.17
Cost of GMP	4.34
Approval	4.34
Marketing	4.34

Although the total cost for the approval of the product is approximately 565,000 GBP, it represents a one-time payment, i.e. before the product enters the market for the first time. Therefore, based on interviews, we approximated approval and regulation costs to amount to 10% of the production cost. Since these costs usually include an assessment of GMP (good manufacturing practice) and product approval, we assigned the costs for approval and GMP to make up approximately 5% of the production cost each. Since the marketing cost is incurred only once, when the product is brought to the market, it is also estimated to make up 5% of the total production cost. The costs of transport was determined based

on the average cost of the cold chain; while the labour cost is estimated based on the average labour wage in the UK.

The above costs were then allocated to the relevant activities, according to the differentiated roles identified in the value chain system, as shown in Table 5.3.

**Table 5.3** Percentage of the cost category in the value chain framework

	<b>Activity category</b>	<b>Cost category (GBP)</b>	<b>Percentage in total</b>
<b>Primary activity</b>	Inbound logistic	Cost of transportation: 0.4	0.4%
		Cost of storage before production: 0.04 pounds	0.04%
	Operation	Production (electricity): 2.53	2.53%
		Cost of chemical: 72.38	72.38%
	Outbound logistic	Transport: 0.4	0.4%
	Market and sale	Approval and marketing: 8.68	8.68%
Service	–	–	
<b>Support activity</b>	Firm infrastructure	Cost of GMP: 4.34	4.34%
	Human resource management	Hire labour: 0.17	0.17%
	Technology development	–	–
	Procurement	Purchase of equipment/storage: 10.34	10.4%
		Purchase of raw material: 0.6	0.6%

The allocation of costs by percentage to each part of the value chain, as shown in the table above, is represented graphically in Figure 5.5. These costs are analysed further in the discussion of results. The end use of this product is its surgical application; this forms part of the buyer's value chain and is discussed in a later section.

### 5.2.2.3 Buyer (healthcare provider) value chain



**Figure 5.4** Value chain framework adapted to healthcare provider[99]

In the current study, health care providers represent the buyers of the product. In the same way as enterprises achieve success by creating value for customers, health care organisations achieve success by creating value for patients, physicians and other stakeholders that rely on their services[99]. This value is generated from the quality of the healthcare services – including the professionalism of the staff, the effectiveness of treatments and the availability and provision of information pertaining to medication. The organisational value chain is an effective means of describing how and where value can

be created[99]. However, certain modifications are required so that the existing system can be adapted for the interpretation of this value chain, since a health care organisation provides a service rather than a product in this case. In our scenario, value is created by the service delivery subsystem (involving the primary activities of the health care organisation) and by the effective use of the support subsystem (support activities of healthcare organisation). The value chain discussed below is adapted from the value chain used in business organisations in order to more closely reflect the value-adding components that are relevant to health care.

The three elements of service delivery – pre-service, point-of-service and after-service – are the primary value activities of the service (product) of health care and primarily include operational processes and marketing activities. They are supported by the activities that facilitate them and improve service (product) delivery. The support activities for healthcare organisation include organisational culture, organisational structure and strategic resources. They are the subsystems that support service delivery by ensuring and inviting a supportive atmosphere[99]. Although not always apparent, such support systems and the value they add are critical for an effective and efficient organisation.

The buyer's value chain should include the direct and indirect usage of the product after the product has been sent to the buyer as "raw material". Decellularised skin is a product that is used to promote and aid the healing of ulcers or burns; this study, therefore, utilises

burn treatment as an example where a similar tissue-engineering product is used in treatment. The overall cost breakdown for burn patients that are treated with tissue engineering dermal substitution have been described[100]. The data were obtained from burn centres and other hospitals in the Netherlands, and therefore, the expenses have been converted from euros to sterling using the current exchange rate. The cost of treatment was estimated by taking the average expenditure of 23 patients who paid for the treatment of burns that range in size from 10–300 cm<sup>2</sup>. The dermal substitution material used is Matriderm, a structurally intact matrix of bovine type I collagen with elastin, which is used to promote dermal regeneration[101]. The original cost breakdown is further described in the Appendix of this thesis. In the current study, these costs are aggregated and allocated according to the value chain framework by classifying each cost activity into one of nine cost categories. The original cost breakdown is shown in Table 5.4.

**Table 5.4** Cost category in healthcare provider of burn treatment

<b>Cost category</b>	<b>Cost/GBP</b>	<b>Percentage</b>
Transport	192	0.7%
Hospital burn care	19,077	70%
Diagnostic	1,173	4.3%
Treatment	4,123	15%
Outpatient	502	1.8%
Other healthcare	2,117	7.7%
Clinical consultant	254	0.9%
<b>Total</b>	<b>27,438</b>	<b>100%</b>

The cost categories in Table 5.4 are allocated according to the healthcare value chain framework illustrated in Figure 5.4.

***Primary activities/service delivery process***

Pre-service: Marketing research, target market, services offering/branding, pricing, distribution, logistics, promotion.

Allocated activities: Transport and clinical consultant.

Point-of-Service: Clinical operations, marketing.

Allocated activities: hospital burn care, treatment.

The hospital burn care category includes all the direct application cost activities of the product, which are listed in Table 5.5 and wound care, intramural medication etc.

After-Service: Follow-up, billing, follow-on.

Allocated activities: other health care.

This cost category includes: rehabilitation centre, home (nursing) care (if needed), and extramural physiotherapy.

***Supporting activities***

Organisational culture: Shared assumptions, shared values and behavioural norms.

Although there are no activities that have been allocated in this category that relate to burn treatment with dermal substitution, there might be activities pertaining to other treatment strategies that fit this description.

Organisational structure: Function, division, matrix.

Allocated activities: Outpatient burn care.

The outpatient burn care category includes occupational burn care, occupational therapy, and other service supporting the main service (burn wound treatment), such as skin therapist, after-care nurse etc.

Strategic resources: Financial, human, information, technology.

Allocated activities: Diagnostic.

In the diagnostic category, swabs, lab tests, and main treatment support technologies such as X-ray and computed tomography scans are included.

In the clinical consultation category, physiotherapist, occupational therapist, psychologist and skin therapist cost are included.

**Table 5.5** Direct application cost of decellularised skin

<b>Cost category</b>	<b>GBP</b>	<b>Percentage</b>
Personnel	612	46%
Equipment	124	9.3%
Materials	100	7.5%
Housing/overhead (35.5%)	494	37.1%
<b>Total direct burn costs</b>	<b>1,330</b>	<b>100%</b>

Table 5.5 presents the direct application costs of the product, which include the per person cost of personnel, equipment, material and housing for the burn treatment. As before, these values are calculated using the average costs for 23 patients who suffer burn wounds

that are between 10 and 300 cm<sup>2</sup> wide. In this example, the cost of activities, excluding material costs, are adapted from those given in reference[100], and are also based on the direct wound treatment cost per patient. The material cost activity is replaced by the price of the decellularised skin (total cost of firm value chain). The material cost is only 7.5% of the total application cost of the product.

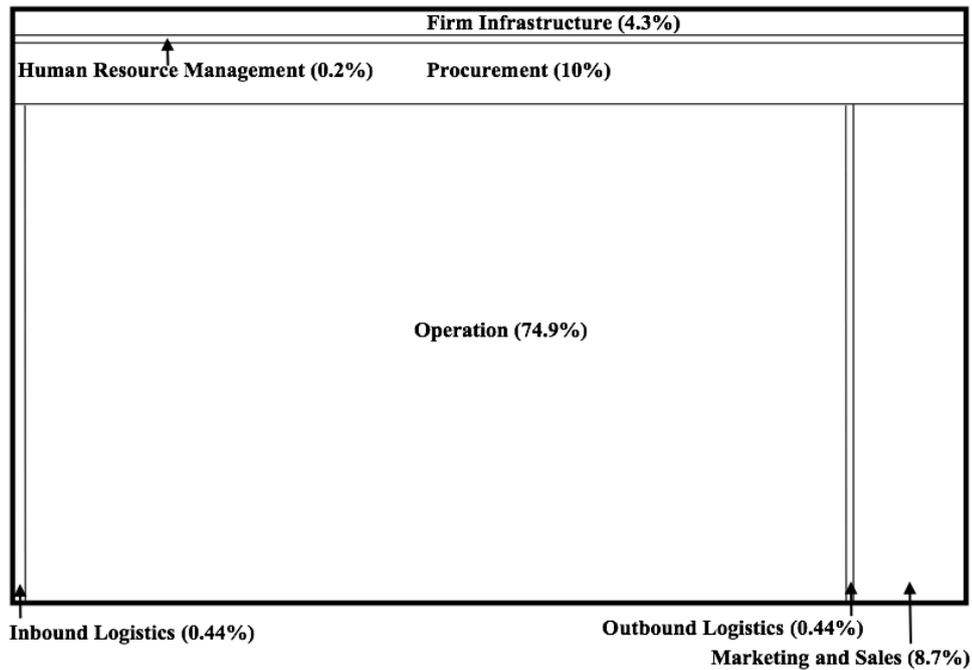
In the value chain of the buyer, that is, the healthcare provider/hospital, all cost activities consist of burn treatment as the point-of-service value activity, and all cost activities that support the main treatment are included. Table 5.4 lists the most important cost categories incurred for a hospitalised burns patient, including wound treatment and supporting health care costs. The cost breakdown per patient in the reference study is allocated according to the health care value chain system[100]. The total direct burns cost listed in Table 5.5 is included in the treatment category in Table 5.4. The remainder of the costs, excluding direct application costs, are categorised according to the activities that were identified in the value chain of the health care organisation; and these are presented in Table 5.4.

### **5.3 RESULTS AND DISCUSSION**

Using Porter's firm value chain structure[1], the manufacturing costs for decellularisation (firm value) were determined. The percentage that each individual cost contributes to the total manufacturing cost can be established, as demonstrated in the activity cost category

and the corresponding percentages are shown in Figures 5.5 and 5.6. The total cost activities of the product can be discussed using three different scopes. With the first scope, we focus on the costs in the firm value chain; they are mostly incurred in the period between the delivery of raw materials and the completion of the final product, i.e. prior to the transport of the completed product to the respective buyers (healthcare providers). The second scope considers the direct application fees of the product that is incurred during wound treatment. Here, the costs accumulated in the first scope of investigation are represented by the material costs when considering the direct application cost of the product. In the third scope, the costs making up the first two points of investigation, as well as all other unaccounted health care costs relating to the burn treatment, will be discussed and analysed. Here, the costs that add up in the first two levels of investigation make up part of the costs of the treatment category.

The proportions of the value chain can be drawn to reflect the distribution of costs and assets among activities, as shown in the figure below.



**Figure 5.5** Distribution of operation costs and assets in firm value chain

### 5.3.1 Firm value chain

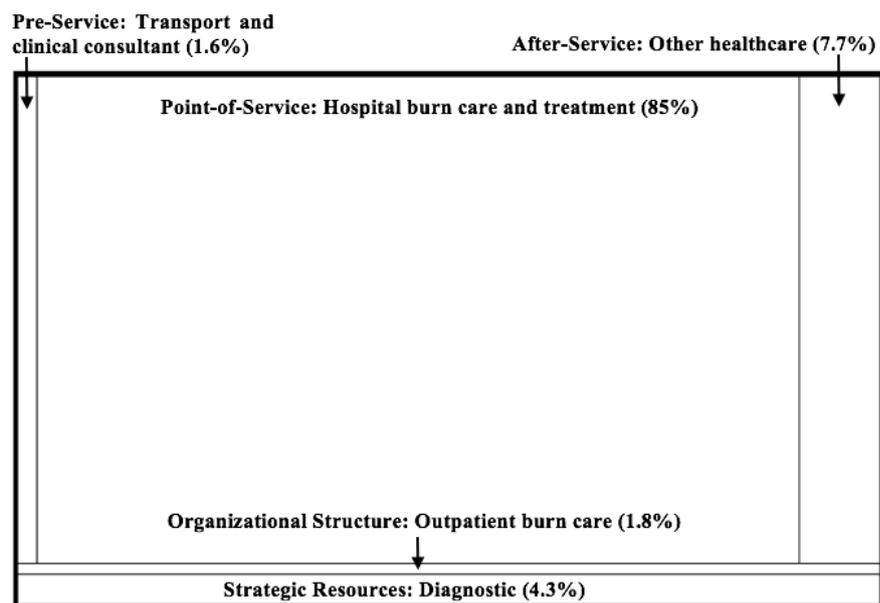
From Figure 5.5, the critical cost category in firm value chain is *operation*, and this consists of electrical and chemical costs that amount to 74.9% of the total cost of cost activities within the firm value chain. Therefore, according to the value chain analysis for the production of decellularised skin, the ‘hot spots’ that need to be addressed lie within these sectors, and production cost may be reduced by using equipment that require less electricity (or by reducing the running time) or by finding cheaper chemical alternatives.

### 5.3.2 Buyer value chain

The buyer in this scenario is the health care provider. As the buyer’s product is a service, the existing system needs to be modified to enable its value chain to be appropriately

interpreted. The value chain illustrated below has been adapted from the value chain used in business organisations to more closely reflect the value-adding components for health care organisations.

Table 5.4 assesses the full-cost category of treatment for burn patients and the percentage of each cost category. The data is obtained from the first work to fully assess the cost inventory on burn patient dermal substitution within a clinical trial[100]. In the third scope, the overall costs for burn treatment, which includes all health care costs except the product application costs, are analysed based on the healthcare value chain system. The cost categories and corresponding percentages are illustrated in Figure 5.6.



**Figure 5.6** Distribution of operation costs in healthcare provider value chain

Figure 5.6 shows that 85% of the total burn treatment costs arise from hospital treatment and care. Within this category, the third highest cost is the interventional treatment cost of the study wound, which are the total costs considered during our second level of

investigation. Although it is the third highest cost activity and occupies 46% of the total treatment costs, it amounts only to approximately 7% of the overall cost. As indicated in Table 5.4, the transport, outpatient and clinical consultant costs amount to 0.7%, 1.8% and 0.9% of the overall cost respectively, i.e. they account for a small proportion of the overall cost of burn treatment. In addition, these are costs that will be incurred regardless of the type of treatment.

There are some limitations in the accuracy of cost data, which arises from the huge variations in cost between patients in the sample group, and the limited sample size[100]. Secondly, with the limited literature available, some inventory costs were estimated, and included only information on the costs of foam, tube and wound dressing for a typical burn injury. Finally, the listed costs are mostly researched from burn treatment facilities across the Netherlands; while the cost of burn treatment is likely to vary in different parts of the world, arising from a varying approach to treatment and how care is accessed. Although the buyer value chain framework can be found in the literature, the data refers to a separate but similar product, which nevertheless is different from the product that is studied within this thesis; as data directly related to our product of interest is not currently available.

## **5.4 SUMMARY**

In this chapter, a value chain analysis has been conducted for a decellularised skin product

using three different scopes of investigation. In the first scope, the cost activities of converting raw materials to the final product are considered and analysed based on the firm value chain framework. At approximately 86 % of the total cost, the production cost (which includes the purchase of electricity and chemicals) is the most expensive component. For the second scope, the direct product application cost is considered; the costs of the product (total cost considered in scope one) occupy only 7.5 % of the total application cost. The third scope considers all the healthcare costs for a burns patient who uses a similar product as the main treatment material. The total direct application cost (costs considered in scope two) is only 4.8 % of the total healthcare cost. Therefore, to make the cost of decellularised skin products more accessible, it is important to optimise each activity in the whole value chain instead of focusing solely on optimising the costs that are incurred during the production stage.

## **Chapter 6**

# **CONCLUSIONS AND FUTURE WORK**

### **6.1 SUMMARY OF WORK COMPLETED**

This project has studied decellularised skin as a simple regenerative medicine product at both the production level and the value chain level. In Chapter 3, an optimisation model designed to minimise the production costs proposed by Floudas and Lin is adapted and validated as a base model for the optimisation of decellularised skin production. The final optimisation model for the production of decellularised skin was developed with three cases (DS48, DS55, DS168) that were of increasing complexity. In particular, the DS168 model was solved to determine the most optimal choices of equipment and production scheduling for a period of one week. In Chapter 4, a possible alternative production method for decellularising skin is investigated, which replaces the costly freeze-drying step with hypothermal storage. The production process is re-optimised and the new production cost of this alternative production method is determined. The shelf life needed for the more cost-effective production of decellularised skin using the alternative method is also quantified, using three possible graphical representation of the relationships between the shelf life and the product wastage. In Chapter 5, the value chain analysis for

decellularised skin production was examined. All the costs incurred in the conversion of the raw material into the final product and the costs of product application are estimated and evaluated.

## **6.2 KEY FINDINGS**

### **6.2.1 Key findings in optimisation of the production process**

The final version (DS168) of the optimisation model for co-optimisation of production scheduling and equipment selection takes the most general issues into account and shows the applicability of this type of process system engineering approach to tissue engineering products. In particular, the model was able to reasonably identify parallelisation in certain production tasks to improve production efficiency. For the particular production system studied in this work, the optimisation results show that the majority of the expenditure is due to chemical and electricity costs; equipment costs were relatively marginal and did not affect the production economics significantly.

### **6.2.2 Key findings in the analysis of freeze-dryer replacement**

Regarding all the possible relationships between waste percentage and shelf life, the effective unit cost (EUC) of the alternative production method is influenced by two factors: waste percentage and the cost of using hypothermal storage. The decrease in waste percentage due to the increase in shelf life tends to reduce the EUC of the alternative production method, but an increase in shelf life would lead to an increase in

the cost of storage. The net economic impact is therefore determined by the trade-off between these two functions.

For the first type of shelf life–waste percentage relationship, the link between the waste percentage and the shelf life was assumed to be linear. We found that the alternative method that employs hypothermal storage only becomes cheaper than freeze drying, in terms of EUC, when the waste percentage is lower than approximately 5% (following the shelf life becoming sufficiently long) and has a  $\theta$  value (the linear parameter) that is greater than 0.000488.

For the second (convex) type of waste percentage–shelf life relationship, there exists a period of shelf life – bound by an upper and lower limit – where production becomes more cost-effective with hypothermal storage than with the method that incorporates freeze-drying. The higher cost-effectiveness of the alternative method manifests particularly when the value of the convex parameter ( $\beta$ ) is lower than 368 and when the waste percentage is less than 0.5%.

Finally, for the third (concave) type of waste percentage–shelf life relationship, the waste percentage must be lower than 0.5% for the EUC of the alternative production process to be lower than the unit cost of the conventional decellularised skin production method; and this occurs when the shelf life is sufficiently long. Also, in order for this situation to occur, the value of the parameter,  $\partial$ , must be lower than the critical value of 440.

Overall, this part of the study shows that the conditions required for the hypothermal storage to be more advantageous than freeze-drying are dependent on the exact relationship between shelf life and waste percentage.

### **6.2.3 Key findings in value chain analysis**

The value chain for the production of decellularised skin was investigated at three different levels. Firstly, we found that the critical cost is incurred within the “operation” category, which consists of electricity and chemical costs that amount to 74.9% of the total cost. Secondly, we found that within the direct application cost of the product, the production cost (i.e. that of the first scope) occupies only 7.5% of the total cost and that personnel-related costs occupied the majority of costs incurred during its application. Finally, we observed that for the total health care cost for a patient whose burns are treated with a decellularised skin product, the treatment cost (total application cost) amounts to only 15% of his expenditure, while the cost of hospitalisation accounts for the majority of the total cost incurred. This part of the work indicates that instead of focusing only on manufacturing, the entire value chain must be examined to uncover the extent of cost saving potential in the production of decellularised skin to achieve optimal cost reduction.

### **6.3 LIMITATIONS AND FUTURE WORK**

The limitations of the optimisation model employed in this study relate to whether the model parameters are sufficiently accurate. Since the complete production process and price of equipment was not adequately described in published journals, information concerning these two avenues might contribute to errors in our study. In addition, the decellularised skin production process was not validated against a real case. Furthermore, not all possible constraints were identified as information relating to the complete production of decellularised skin was not fully available. Therefore, in order to build on this research, the researcher may interview the relevant experts and personnel involved to obtain missing key information and parameters. In addition, the current model was applied in this work only to this specific decellulised skin production process; future work may explore its application to other tissue engineering or decellularised products.

Next, in relation to elimination of freeze dryer, the proposed relationships between shelf life and waste percentage were based on possibility rather than actual experimentation. Therefore, the models can be improved by obtaining empirical data on the relationship between the shelf life of decellularised skin products and their waste percentage, by examining their dynamics in real operations.

The limitations of the value chain analysis of decellularisation skin production are similar to the shortcomings of production process optimisation, as the information of many

respects was based on a similar product studied in the literature, hence should not be regarded as an exact analysis precisely for the decellulised skin, although the approach implemented is considered to be applicable to this and other types of tissue engineering products. Future work may be conducted to collect information directly pertaining to this product, possibly with tuning of the list of activities accordingly.

## References

- [1] M. E. Porter, *Competitive Advantage: Creating and Sustaining Superior Performance*: Free Press, 1985.
- [2] I. V. Yannas, *Tissue and organ regeneration in adults : extension of the paradigm to several organs*, Second edition. ed. New York: Springer, 2015.
- [3] C. E. Pullar, *The physiology of bioelectricity in development, tissue regeneration, and cancer*. Boca Raton, Fla. ; London: CRC Press, 2016.
- [4] F. Obregon, C. Vaquette, S. Ivanovski, D. W. Hutmacher, and L. E. Bertassoni, "Three-Dimensional Bioprinting for Regenerative Dentistry and Craniofacial Tissue Engineering," *J Dent Res*, vol. 94, pp. 143S-52S, Sep 2015.
- [5] W. Cui, Y. Zhou, and J. Chang, "Electrospun nanofibrous materials for tissue engineering and drug delivery," *Science and Technology of Advanced Materials*, vol. 11, p. 014108, 2010.
- [6] R. P. Pirraco and R. L. Reis, "Tissue engineering: new tools for old problems," *Stem Cell Rev*, vol. 11, pp. 373-5, Jun 2015.
- [7] M. D. Li, H. Atkins, and T. Bubela, "The global landscape of stem cell clinical trials," *Regen Med*, vol. 9, pp. 27-39, Jan 2014.
- [8] M. Rao, L. Ahrlund-Richter, and D. S. Kaufman, "Concise review: Cord blood banking, transplantation and induced pluripotent stem cell: success and opportunities," *Stem Cells*, vol. 30, pp. 55-60, Jan 2012.
- [9] D. Cyranoski, "Stem cells cruise to clinic," *Nature*, vol. 494, p. 413, Feb 28 2013.
- [10] D. S. Couto, L. Perez-Breva, and C. L. Cooney, "Regenerative medicine: learning from past examples," *Tissue Eng Part A*, vol. 18, pp. 2386-93, Nov 2012.
- [11] T. P. Zwaka, "Stem cells: Troublesome memories," *Nature*, vol. 467, pp. 280-1, Sep 16 2010.
- [12] M. J. Lysaght, A. Jaklenec, and E. Deweerd, "Great expectations: private sector activity in tissue engineering, regenerative medicine, and stem cell therapeutics," *Tissue Eng Part A*, vol. 14, pp. 305-15, Feb 2008.
- [13] D. A. Tsitsikas, D. Warcel-Sibony, H. E. Oakervee, S. G. Agrawal, M. Smith, D. C. Taussig, *et al.*, "A Phase II Trial of Sequential Treatment with Cytoreductive Therapy and Reduced Intensity Conditioning Allogeneic Stem Cell Transplantation for Relapsed/Refractory Acute Myeloid Leukaemia, High-Risk MDS and Other High Risk Myeoid Malignancies: An Interim Report," *Blood*, vol. 116, p. 3480, 2015.
- [14] J. L. Fox, "Rare-disease drugs boosted by new Prescription Drug User Fee Act," *Nat Biotechnol*, vol. 30, pp. 733-4, Aug 2012.
- [15] C. Mason, M. J. McCall, E. J. Culme-Seymour, S. Suthasan, S. Edwards-Parton, G. A. Bonfiglio, *et al.*, "The global cell therapy industry continues to rise during

- the second and third quarters of 2012," *Cell Stem Cell*, vol. 11, pp. 735-9, Dec 7 2012.
- [16] W. Yang, "Biotech weathers 2Q12 slump," *Nature Biotechnology*, vol. 30, pp. 738-738, Aug 2012.
- [17] A. Husain, A. Hassan, D. M. K. Al-Gobaisi, A. Al-Radif, A. Woldai, and C. Sommariva, "Modelling, simulation, optimization and control of multistage flashing (MSF) desalination plants Part I: Modelling and simulation," *Desalination*, vol. 92, pp. 21-41, 1993.
- [18] M. Turkoglu and A. Sakr, "Mathematical modelling and optimization of a rotary fluidized-bed coating process," *International Journal of Pharmaceutics*, vol. 88, pp. 75-87, 1992.
- [19] N. J. Samsatli and N. Shah, "An Optimization Based Design Procedure for Biochemical Processes," *Food and Bioproducts Processing*, vol. 74, pp. 232-242.
- [20] M. P. Avraam, N. Shah, and C. C. Pantelides, "Modelling and optimisation of general hybrid systems in the continuous time domain," *Computers & Chemical Engineering*, vol. 22, pp. S221-S228, 1998.
- [21] C. A. Méndez, J. Cerdá, I. E. Grossmann, I. Harjunkoski, and M. Fahl, "State-of-the-art review of optimization methods for short-term scheduling of batch processes," *Computers & Chemical Engineering*, vol. 30, pp. 913-946, 5/15/ 2006.
- [22] C. A. Floudas and X. Lin, "Continuous-time versus discrete-time approaches for scheduling of chemical processes: a review," *Computers & Chemical Engineering*, vol. 28, pp. 2109-2129, 10/15/ 2004.
- [23] E. Kondili, C. C. Pantelides, and R. W. H. Sargent, "A General Algorithm for Short-Term Scheduling of Batch-Operations .1. Milp Formulation," *Computers & Chemical Engineering*, vol. 17, pp. 211-227, Feb 1993.
- [24] A. P. F. D. BarbosaPova and C. C. Pantelides, "Design of multipurpose plants using the resource-task network unified framework," *Computers & Chemical Engineering*, vol. 21, pp. S703-S708, 1997.
- [25] P. Castro, A. P. F. D. Barbosa-Pova, and H. Matos, "An improved RTN continuous-time formulation for the short-term scheduling of multipurpose batch plants," *Industrial & Engineering Chemistry Research*, vol. 40, pp. 2059-2068, May 2 2001.
- [26] M. A. Shaik and R. Vooradi, "Unification of STN and RTN based models for short-term scheduling of batch plants with shared resources," *Chemical Engineering Science*, vol. 98, pp. 104-124, Jul 19 2013.
- [27] E. H. Bowman, "The Schedule-Sequencing Problem," *Operations Research*, vol. 7, pp. 621-624, 1959.
- [28] P. Kall, "System Modeling and Optimization - International Federation for Information-Processing," *Lecture Notes in Control and Information Sciences*, vol. 180, pp. R5-R5, 1992.

- [29] G. Blau, B. Mehta, S. Bose, J. Pekny, G. Sinclair, K. Keunker, *et al.*, "Risk management in the development of new products in highly regulated industries," *Computers & Chemical Engineering*, vol. 24, pp. 659-664, Jul 15 2000.
- [30] D. Subramanian, J. F. Pekny, and G. V. Reklaitis, "A simulation-optimization framework for Research and Development Pipeline management," *Aiche Journal*, vol. 47, pp. 2226-2242, Oct 2001.
- [31] J. M. Pinto and I. E. Grossmann, "Optimal Cyclic Scheduling of Multistage Continuous Multiproduct Plants," *Computers & Chemical Engineering*, vol. 18, pp. 797-816, Sep 1994.
- [32] N. Lamba and I. A. Karimi, "Scheduling parallel production lines with resource constraints. 1. Model formulation," *Industrial & Engineering Chemistry Research*, vol. 41, pp. 779-789, Feb 20 2002.
- [33] S. M. Wang, H. G. Moon, and S. H. Ki, "Topology optimization of automobile reinforcement," *Optimization of Structural and Mechanical Systems, Proceedings*, pp. 94-100, 1999.
- [34] M. T. M. Rodrigues, L. G. Latre, and L. C. A. Rodrigues, "Short-term planning and scheduling in multipurpose batch chemical plants: a multi-level approach," *Computers & Chemical Engineering*, vol. 24, pp. 2247-2258, Oct 1 2000.
- [35] I. E. Grossmann and R. W. H. Sargent, "Optimum Design of Multipurpose Chemical-Plants," *Industrial & Engineering Chemistry Process Design and Development*, vol. 18, pp. 343-348, 1979.
- [36] R. Egli, C. Petit, and N. F. Stewart, "Moving coordinate frames for representation and visualization in four dimensions," *Computers & Graphics*, vol. 20, pp. 905-919, Nov-Dec 1996.
- [37] C. A. Crooks, K. Kuriyan, and S. Macchietto, "Integration of Batch Plant-Design, Automation, and Operation Software Tools," *Computers & Chemical Engineering*, vol. 16, pp. S289-S296, May 1992.
- [38] A. P. Barbosapova and S. Macchietto, "Detailed Design of Multipurpose Batch Plants," *Computers & Chemical Engineering*, vol. 18, pp. 1013-1042, Nov-Dec 1994.
- [39] X. Zhang and R. W. H. Sargent, "The optimal operation of mixed production facilities - A general formulation and some approaches for the solution," *Computers & Chemical Engineering*, vol. 20, pp. 897-904, Jun-Jul 1996.
- [40] X. X. Lin, C. A. Floudas, S. Modi, and N. M. Juhasz, "Continuous-time optimization approach for medium-range production scheduling of a multiproduct batch plant," *Industrial & Engineering Chemistry Research*, vol. 41, pp. 3884-3906, Aug 7 2002.
- [41] S. L. Janak, X. X. Lin, and C. A. Floudas, "Enhanced continuous-time unit-specific event-based formulation for short-term scheduling of multipurpose batch processes: Resource constraints and mixed storage policies," *Industrial & Engineering Chemistry Research*, vol. 43, pp. 2516-2533, May 12 2004.

- [42] S. L. Janak, X. X. Lin, and C. A. Floudas, "Enhanced continuous-time unit-specific event-based formulation for short-term scheduling of multipurpose batch processes: Resource constraints and mixed storage policies (vol 43, pg 2529, 2002)," *Industrial & Engineering Chemistry Research*, vol. 44, pp. 426-426, Jan 19 2005.
- [43] L. S. Jennings, K. L. Teo, F. Y. Wang, and Q. Yu, "Optimal Protein Separation," *Computers & Chemical Engineering*, vol. 19, pp. 567-573, May 1995.
- [44] K. F. Wang, T. Lohl, M. Stobbe, and S. Engell, "A genetic algorithm for online-scheduling of a multiproduct polymer batch plant," *Computers & Chemical Engineering*, vol. 24, pp. 393-400, Jul 15 2000.
- [45] S. Hollensen, *Marketing Management: A Relationship Approach*: Pearson Education, Limited, 2014.
- [46] K. Manova, "Firms and credit constraints along the global value chain: Processing trade in China," in *CESifo Forum*, 2014, p. 8.
- [47] T. W. Gilbert, T. L. Sellaro, and S. F. Badylak, "Decellularization of tissues and organs," *Biomaterials*, vol. 27, pp. 3675-3683, Jul 2006.
- [48] J. D. Mellor, *Fundamentals of freeze-drying*: Academic Press, 1978.
- [49] A. G. Bruzzone, F. Longo, M. Massei, L. Nicoletti, and M. Agresta, "Safety and Security in Fresh Good Supply Chain," *International Journal of Food Engineering*, vol. 10, pp. 545-556, Dec 2014.
- [50] W. S. Sheridan, G. P. Duffy, and B. P. Murphy, "Optimum Parameters for Freeze-Drying Decellularized Arterial Scaffolds," *Tissue Engineering Part C-Methods*, vol. 19, pp. 981-990, Dec 1 2013.
- [51] D. F. Ross, *Competing Through Supply Chain Management: Creating Market-Winning Strategies Through Supply Chain Partnerships*: Springer US, 2013.
- [52] J. D. Wisner, K. C. Tan, and G. K. Leong, *Principles of Supply Chain Management: A Balanced Approach*: Cengage Learning, 2014.
- [53] A. Pandey, R. Höfer, M. Taherzadeh, M. Nampoothiri, and C. Larroche, *Industrial Biorefineries and White Biotechnology*: Elsevier Science, 2015.
- [54] J. J. Coyle, C. J. Langley, R. A. Novack, and B. Gibson, *Supply Chain Management: A Logistics Perspective*: Cengage Learning, 2012.
- [55] M. Christopher, *Logistics and Supply Chain Management: Creating Value-adding Networks*: FT Prentice Hall, 2005.
- [56] J. Davies and N. Joglekar, "Supply Chain Integration, Product Modularity, and Market Valuation: Evidence from the Solar Energy Industry," *Production and Operations Management*, vol. 22, pp. 1494-1508, Nov 2013.
- [57] E. L. Olson, "Green Innovation Value Chain analysis of PV solar power," *Journal of Cleaner Production*, vol. 64, pp. 73-80, Feb 1 2014.
- [58] R. M. Monczka, R. B. Handfield, L. C. Giunipero, and J. L. Patterson, *Purchasing and Supply Chain Management*: Cengage Learning, 2015.

- [59] N. Ahmed, Jagmohan, S., Chauhan, H., Anjum, P.G. and Kour, H., "Different drying methods: Their applications and recent advances," *International Journal of Food Nutrition and Safety*, vol. 4, pp. 34-42, 2013.
- [60] D. Vandeweyer, S. Lenaerts, A. Callens, and L. Van Campenhout, "Effect of blanching followed by refrigerated storage or industrial microwave drying on the microbial load of yellow mealworm larvae (*Tenebrio molitor*)," *Food Control*, vol. 71, pp. 311-314, 1// 2017.
- [61] R. Fitriana and N. Stacey, "A Value Chain Analysis of Fish Products: Case study from Pantar Island, Eastern Indonesia," 2014.
- [62] L. Manning, "Corporate and consumer social responsibility in the food supply chain," *British Food Journal*, vol. 115, pp. 9-29, 2013.
- [63] P. A. Santi and S. B. Johnson, "Decellularized Ear Tissues as Scaffolds for Stem Cell Differentiation," *Jaro-Journal of the Association for Research in Otolaryngology*, vol. 14, pp. 3-15, Feb 2013.
- [64] K. K. Sinha and E. J. Kohnke, "Health Care Supply Chain Design: Toward Linking the Development and Delivery of Care Globally," *Decision Sciences*, vol. 40, pp. 197-212, May 2009.
- [65] X. Lin and C. A. Floudas, "Design, synthesis and scheduling of multipurpose batch plants via an effective continuous-time formulation," *Computers & Chemical Engineering*, vol. 25, pp. 665-674, May 1 2001.
- [66] C. A. Floudas and X. X. Lin, "Mixed integer linear programming in process scheduling: Modeling, algorithms, and applications," *Annals of Operations Research*, vol. 139, pp. 131-162, Oct 2005.
- [67] G. A. Sears and R. H. Clough, *Construction Project Management*: John Wiley & Sons, Inc., 1991.
- [68] Method for preparing allograft acellular dermal matrixes, 2012. [Online]. Available: <https://encrypted.google.com/patents/CN102580153A?cl=en> [Accessed: 14/01, 2017].
- [69] Minimum wage up to £6.50 an hour, 2014. [Online]. Available: <http://www.bbc.co.uk/news/business-26543267>. [Accessed: 14/01, 2017].
- [70] Water storage tank price from Tanks Direct. [Online]. Available: [http://www.tanks-direct.co.uk/1000\\_litre\\_water\\_tanks](http://www.tanks-direct.co.uk/1000_litre_water_tanks). [Accessed: 14/01, 2017].
- [71] Freeze Dryer price from Cuddon. [Online]. Available: <http://www.cuddonfrozefreeze.com/products/>. [Accessed: 14/01, 2017].
- [72] Freeze Dryer price from Alibaba. [Online]. Available: [http://www.alibaba.com/product-detail/High-efficiency-with-tray-vacuum-freeze\\_60074105861.html](http://www.alibaba.com/product-detail/High-efficiency-with-tray-vacuum-freeze_60074105861.html). [Accessed: 14/01, 2017].
- [73] Bioreactor price from Alibaba. [Online]. Available: [http://www.alibaba.com/product-detail/100L-Single-Layer-Bioreactor-Industrial-100L\\_60058981457.html](http://www.alibaba.com/product-detail/100L-Single-Layer-Bioreactor-Industrial-100L_60058981457.html). [Accessed: 14/01, 2017].

- [74] Pharmacy refridgerators' price list from Medisave. [Online]. Available: <http://www.medisave.co.uk/diagnostics-equipment/medical-refrigeration/pharmacy-fridges/shopby/manufacturer-labcold.html>. [Accessed: 14/01, 2017].
- [75] Pharmacy refridgerators' price list from Labcold. [Online]. Available: <http://www.labcold.com/pharmacy-refrigeration/intellicold-pharmacy>. [Accessed: 14/01, 2017].
- [76] Peracetic acid price from Sigma-Aldrich. [Online]. Available: <http://www.sigmaaldrich.com/catalog/search?term=peracetic+acid&interface=All&N=0&mode=match%20partialmax&lang=en&region=GB&focus=product>. [Accessed: 14/01, 2017].
- [77] Sodium chloride price from Sigma-Aldrich. [Online]. Available: [Accessed: 14/01, 2017].
- [78] Sodium hydroxide price from Sigma-Aldrich. [Online]. Available: [Accessed: 14/01, 2017].
- [79] Brij 58 price from Sigma-Aldrich. [Online]. Available: [Accessed: 14/01, 2017].
- [80] Sodium carbonate anhydrous price from Sigma-Aldrich. [Online]. Available: [Accessed: 14/01, 2017].
- [81] Trypsin-EDTA (0.05%), phenol red price from ThermoFisher. [Online]. Available: [Accessed: 14/01, 2017].
- [82] Ammonium sulfate price from Molbase. [Online]. Available: [Accessed: 14/01, 2017].
- [83] R. G. Van Buskirk, J. M. Baust, K. K. Snyder, A. J. Mathew, and J. G. Baust, "Hypothermic storage and cryopreservation," *BioProcess Int*, vol. 2, 2004.
- [84] D. Wanless, *Securing Good Health for the Whole Population: Final Report*. H.M. Stationery Office, 2004.
- [85] G. D. Gentzkow, S. D. Iwasaki, K. S. Hershon, M. Mengel, J. J. Prendergast, J. J. Ricotta, *et al.*, "Use of dermagraft, a cultured human dermis, to treat diabetic root ulcers," *Diabetes Care*, vol. 19, pp. 350-354, Apr 1996.
- [86] W. H. Eaglstein and V. Falanga, "Tissue engineering and the development of Apligraf(R), a human skin equivalent," *Clinical Therapeutics*, vol. 19, pp. 894-905, Sep-Oct 1997.
- [87] G. F. Purdue, J. L. Hunt, J. M. Still Jr, E. J. Law, D. N. Herndon, I. W. Goldfarb, *et al.*, "A multicenter clinical trial of a biosynthetic skin replacement, Dermagraft-TC, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds," *Journal of Burn Care & Research*, vol. 18, pp. 52-57, 1997.
- [88] D. M. Smith, "Practicalities to Translation from the Clinic to the Market," *Chemical Biology in Regenerative Medicine: Bridging Stem Cells and Future Therapies*, pp. 203-215, 2014.
- [89] D. J. Williams and P. C. Hourd, "Business models and leadership styles in small medical device and bio-science businesses - examples in a region and their

- implications," *Proceedings of the 26th Annual International Conference of the Ieee Engineering in Medicine and Biology Society, Vols 1-7*, vol. 26, pp. 5131-5134, 2004.
- [90] B. Husing, B. Buhrlen, and S. Gaisser, "Human Tissue Engineered Products–Today's Markets and Future Prospects, Annex of the Final Report for Work Package 1: Analysis of the actual market situation–Mapping of industry and products," *Fraunhofer Institute for Systems and Innovation Research, Karlsruhe, Germany*, vol. 54, 2003.
- [91] J. R. Birch and A. J. Racher, "Antibody production," *Advanced Drug Delivery Reviews*, vol. 58, pp. 671-685, Aug 7 2006.
- [92] B. Kelley, "Very large scale monoclonal antibody purification: The case for conventional unit operations," *Biotechnology Progress*, vol. 23, pp. 995-1008, Sep-Oct 2007.
- [93] S. Liyanage, R. Wink, and M. Nordberg, *Managing path-breaking innovations: CERN-ATLAS, Airbus, and stem cell research*: Greenwood Publishing Group, 2007.
- [94] Porter's Value Chain. [Online]. Available: <http://www.ifm.eng.cam.ac.uk/research/dstools/value-chain/>. [Accessed: 14/01, 2017].
- [95] M. Hergert and D. Morris, "Accounting Data for Value Chain Analysis," *Strategic Management Journal*, vol. 10, pp. 175-188, Mar-Apr 1989.
- [96] F. Elloumi, "Value chain analysis: A strategic approach to online learning," *Theory and practice of online learning*, p. 61, 2004.
- [97] J. K. Shank and V. Govindarajan, *Strategic Cost Management: The New Tool for Competitive Advantage*: Free Press, 1993.
- [98] J. Hunsberger, O. Harrysson, R. Shirwaiker, B. Starly, R. Wysk, P. Cohen, *et al.*, "Manufacturing Road Map for Tissue Engineering and Regenerative Medicine Technologies," *Stem Cells Translational Medicine*, vol. 4, pp. 130-135, Feb 2015.
- [99] P. M. Ginter, *The Strategic Management of Health Care Organizations*: Wiley, 2013.
- [100] M. J. Hop, M. C. T. Bloemen, M. E. van Baar, M. K. Nieuwenhuis, P. P. M. van Zuijlen, S. Polinder, *et al.*, "Cost study of dermal substitutes and topical negative pressure in the surgical treatment of burns," *Burns*, vol. 40, pp. 388-396, May 2014.
- [101] Minimum wage up to £6.50 an hour. [Online]. Available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3038402/>. [Accessed: 14/01, 2017].

## Appendix: Overall cost of burns treatment (e)

Cost category	Euro	GBP
<b>Transport hospital</b>	226	192
<b>Hospital intramural burn care</b>		
Hospital days	14,672	12,471
ICU days	5,985	5,087
Re-admittance days	1,712	1,455
Day care	74	63
Total intramural [95% CI]	22,443	19,077
<b>Diagnostic procedures</b>		
Swabs	575	489
Lab tests	491	417
Others	314	267
Total diagnostic procedures [95% CI]	1,380	1,173
<b>Treatment</b>		
Interventional treatment study wound	2,218	1,885
Surgical treatment other wounds	615	523
Wound care	897	762
Medication, intramural	279	237
Other treatment (blood products, pressure garments, reconstructive other wounds)	841	715
Total treatment [95% CI]	4,850	4,123
<b>Outpatient burn care</b>		
Occupational burn care	413	351
Occupational therapy	105	89
Plastic surgery	55	47

Physiotherapist	6	5
Others (skin therapist, after-care nurse, nurse practitioner)	12	10
Total outpatient burns care [95% CI]	591	502
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<b>Other healthcare costs</b>		
Rehabilitation centre	1,774	1,508
Home (nursing) care	585	497
Extramural physiotherapy	131	111
Total other healthcare costs [95% CI]	2,490	2,117
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<b>Clinical consultations</b>		
Physiotherapist	135	115
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