A Model-Based Approach to Address the Commercialisation Challenges of Autologous Cell Therapies

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List of Publications

1. Lam C, Meinert E, Alturkistani A *et al.* Decision Support Tools for Regenerative Medicine: Systematic Review. *J. Med. Internet Res.* 20(12), e12448 (2018).
2. Lam C, Meinert E, Halioua-Haubold C-L*,* Carter A, Yang A, Brindley D, Cui Z*.* Systematic review protocol: an assessment of the post-approval challenges of autologous CAR-T therapy delivery. *BMJ Open* 9(7), e026172 (2019).
3. Lam C, Meinert E, Yang A, Brindley DA, Cui Z. Decisions in the Development Lifecycle of Cell and Gene Therapies. In: *Second Generation Cell and Gene-based Therapies*. Elsevier, 597–632 (2020).
4. Lam C, Meinert E, Yang A, Cui Z. Tackling the unique challenges of capacity planning for autologous cell therapies. *Cytotherapy* 22(5), S148–S149 (2020).
5. Lam C, Meinert E, Yang A, Cui Z. Comparison between centralized and decentralized supply chains of autologous chimeric antigen receptor T-cell therapies: a UK case study based on discrete event simulation. *Cytotherapy* 000, 1–19 (2021).
6. Lam C, van Velthoven MH, Meinert E. Developing a blockchain-based supply chain system for advanced therapies: Protocol for a feasibility study. *JMIR Res. Protoc.* 9(12), 1–6 (2020).
7. Lam C, Van Velthoven MH, Meinert E. Application of internet of things in cell-based therapy delivery: Protocol for a systematic review. *JMIR Res. Protoc.* 9(3), 1–6 (2020).
8. Lam C, Meinert E, Yang A, Cui Z. Impact of fast-track regulatory designations on strategic commercialisation decisions for autologous cell therapies. *Regenerative medicine* (submitted paper)

Abstract

Whilst many cell therapy products have been approved over the last 20 years, very few have achieved commercial success. With the increasing number of clinical trials and approved autologous cell therapy products, and high-value investment activities in the sector, making informed decisions for the commercialisation of these therapies is more and more critical.

This thesis makes an original contribution to knowledge by systematically breaking down the commercialisation challenges of autologous cell therapies into operational, tactical, and strategic level problems and employ a model-based approach in (1) modelling and assessing the needle-to-needle supply chain of autologous cell therapies, (2) capacity planning, and (3) further understanding the uncertainties in the commercialisation of autologous cell therapies.

Three models were designed and implemented to address this multi-level problem. Firstly, a discrete event simulation is used to identify the patient-to-patient supply chain bottlenecks to inform decisions to improve efficiency. Secondly, a mixed-integer linear programming problem was formulated to simultaneously optimise capacity planning and product portfolio selection. Finally, a risk-adjusted net present value valuation model, supported by an adaptive neuro-fuzzy inference system, was proposed to aggregate the learnings from past commercialised products and the operational and tactical models to aid investment and global entry decisions for the commercialisation of autologous cell therapies.

The developed supply chain and capacity planning models were used to simulate hypothetical United Kingdom case studies based on data collected from industry. The final valuation model was applied to a global case study to evaluate project valuation under

uncertainties. The results of the modelling studies were found to be consistent with real-world observations and the models obtained can be useful for the cell therapy industry to make better decisions in commercialising life-saving therapies.

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List of Abbreviations

ANFIS	Adaptive Neuro-Fuzzy Inference System
API	Active Pharmaceutical Ingredient
ATMP	Advanced Therapeutic Medicinal Products
CAPEX	Capital expenditures
CAR-T	Chimeric antigen receptor (CAR) T-cell therapy
C>	Cell and gene therapy
CNC	Controlled not classified
COG	Cost of Goods
DES	Discrete Event Simulation
EMA	European Medicines Agency
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
GAMS	General Algebraic Modelling System
GMP	Good Manufacturing Practice
hPSC	Human pluripotent stem cells
iPSC	Induced pluripotent stem cells
IQ	Installation Qualification
JV	Joint Venture
KPI	Key performance indicator
M&A	Merger and acquisitions
mAb	Monoclonal Antibody
MILP	Mixed-integer linear programming
MSC	Mesenchymal Stem Cells

NHS	National Health Service
NMDA	Chinese National Medical Products Administration
NPV	Net Present Value
OQ	Operational Qualification
PCR	Polymerase Chain Reaction
PDMA	Pharmaceuticals and Medical Devices Agency
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RDBMS	Relational Database Management Software
rNPV	Risk-adjusted Net Present Value
TALENS	Transcription Activator-Like Effector (TALE)-Nucleases
UK	United Kingdom
US	United States
VBA	Visual Basic for Applications
ZFNs	Zinc Finger Nucleases

Chapter 1 Introduction

This chapter will introduce the general background of cell therapies, their commercialisation history (Section 1.1) and subsequently discuss the motivations and research questions of this DPhil project (Section 1.2). Finally, Section 1.3 will provide an overview of the thesis structure.

1.1 Cell therapy overview

Cell therapy is defined as the infusion or transplantation of cells to replace or repair damaged tissue and/or cells, and autologous cell therapies refer to transplantation of cells removed from a person, processed and returned to the same person. Since the first recorded blood transfusion in 1818 for the treatment of postpartum haemorrhage, the modality has evolved to become the 4th pillar of modern medicine [1]. In the last decade, there was an exponential growth in research and the number of clinical trials in the field [2]. According to industry reports, there are over 360 novel cell and gene therapies ranging from early to late stages of clinical development for the treatment of over 100 diseases in 2020 [3]. According to the Research and Markets Cell and Gene Therapy Global Market Opportunities and Strategies report, the global cell and gene therapy market reached nearly $4,390.3 million in 2020 with a compound annual growth rate of 25.5% since 2015 and is expected to reach over $30 billion in 2030 [4].

Cell therapy indications range from wound care [5], cartilage repair [6], cancers [7], neurological and neurodegenerative diseases such as Parkinson's disease [8], Alzheimer's and Huntington's disease [9] to infectious diseases such as COVID-19 [10]. As the field matures, more and more products are getting approved and commercialised. The first commercial allogeneic cell therapy, HEMACORD, was a hematopoietic progenitor cells-cord cell therapy

which was approved by the US Food and Drug Administration in 2011 for use in unrelated donor haematopoietic progenitor cell transplantation procedures [11]; and the European Medicines Agency approved the first autologous cultured chondrocytes on porcine collagen membrane therapy, MACI, to treat cartilage defects of the knee [12]. It is estimated that about 350,000 patients will have been treated with 30-60 cell and gene therapy products by 2030 [13]. However, as it is still a relatively new modality, the number of currently approved products in the field is limited with even fewer achieving commercialisation success.

Since the approval of Transcyte in 1997, the field of regenerative medicine has seen a wave of products achieve regulatory approval with most of the products approved within the past 10 years (Figure 1.1). The diversity of products has shifted from mainly tissue-engineered products (mostly for wound care) to a mix of tissue-engineered and cell and gene-based therapies. The indications and planned scale of demand made a shift towards more orphan and niche applications.

The cost of treatment ranges from \$308 for 56cm^2 of wound care treatment in South Korea (information provided for by Tego Science, South Korea) to €1.1 million for UniQure's Glybera, a niche gene therapy indicated for lipoprotein lipase deficiency [14]. As these therapies are very expensive, loss of a batch can result in great loss for the company, hence ensuring a robust process for the manufacture and delivery of the therapy is critical.

Cell-based therapies are broadly divided into two classes. Autologous therapies are derived from the patients' own cells and allogeneic therapies which are derived from a donor's cells for many patients. As shown in Figure 1.1, nearly half of the commercialised products on the market are autologous in nature. From Li et al.'s review for clinical trial

landscape, the number of autologous therapy trials is consistently greater than the number of allogeneic ones [15].

However, commercial success does not come as a guarantee with regulatory approval. As shown in Table 1.1, four out of ten approved products were withdrawn, three of which were autologous. They were withdrawn for a variety of reasons from reimbursement issues (Glybera) [16] to complex supply chains [17]. 3 out of 10 regenerative medicine products approved in the EU were withdrawn due to commercial reasons and 1 was suspended by the EMA due to the closure of the authorized manufacturing facility, which drove the company into deciding not to renew its market authorization [18].

Additionally, several companies, from large and midsize pharmaceutical companies (Shire plc (Dublin, Ireland) [19] and GlaxoSmithKline plc (London, United Kingdom) [20]) to small enterprises (Dendreon (Seattle, United States), Advanced Tissue Sciences (San Diego, United States) [21]) have experienced bankruptcy or experienced difficulties in product development. For Dendreon, a lack of a sound reimbursement strategy is just one of the many reasons for its inability to achieve commercial success. Clinicians were deterred from administering the drug, not only due to the logistical complexity but also due to cost-effectiveness and reimbursement considerations [17].

This highlights the importance for advanced therapeutic medicinal product (ATMP) developers to make, given the risks and uncertainties, better and more informed investment and manufacturing decisions. Section 2.2 details the challenges in the commercialisation of cell therapies.

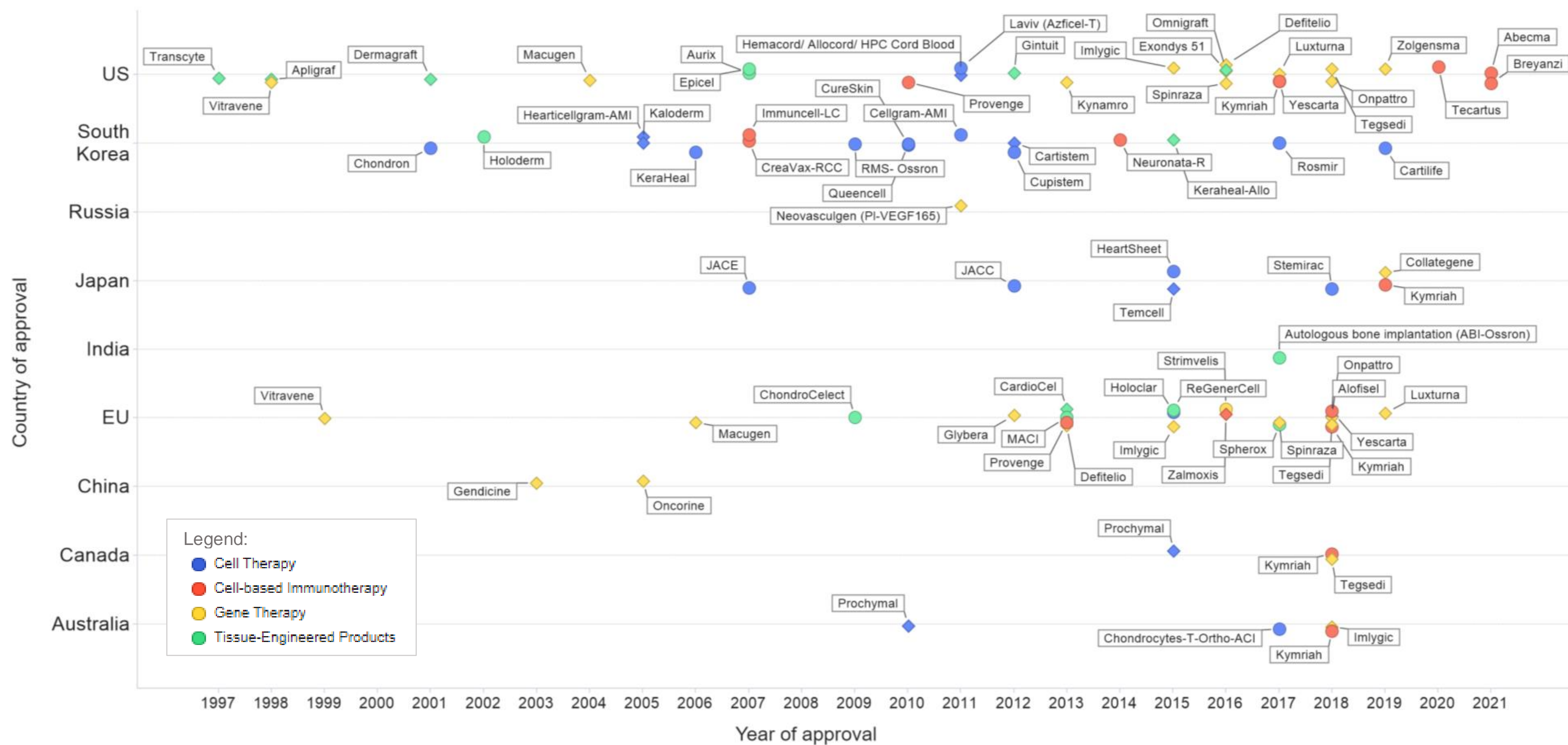


Figure 1.1 ATMP products approved in different countries from 1997 to 2021. Autologous products are shown in circles, allogeneic cell therapies and gene therapy products are shown in diamond markers.

Table 1.1 Table showing approved Advanced Therapeutic Medicinal Products in the European Union (until May 2018)[22]

#	Product	Marketing authorization (MA) holder	Date of approval	Withdrawn
1	MACI	Vericel Denmark ApS (Copenhagen, Denmark)	Jul 2013	MA suspended and not renewed by MA holder in 2014
2	ChondroCelect	TiGenix N.V. (Leuven, Belgium)	Nov 2009	MA withdrawn at request of MA holder on 30th November 2016
3	Strimvelis	Orchard Therapeutics (Netherlands) BV (Amsterdam, Netherlands)	May 2016	-
4	Spherox	Co.Don AG (Teltow, Germany)	Jul 2017	-
5	Alofisel	Takeda Pharma A/S (Taastrup, Denmark)	Mar 2018	-
6	Zalmoxis	MolMed (Milan, Italy)	Aug 2016	-
7	Glybera	uniQure (Amsterdam, Netherlands)	Oct 2012	MA expired and not renewed by MA holder in October 2017
8	Holoclar	Chiesi Farmaceutici (Parma, Italy)	Feb 2015	-
9	Provenge	Dendreon UK Ltd (London, United Kingdom)	Sept 2013	MA withdrawn at request of MA holder in May 2015
10	Imlygic	Amgen Europe B.V. (Breda, Netherlands)	Dec 2015	-

1.2 Motivation and research question

Post-approval challenges such as reimbursement, delivery and supply chain issues have proven to be a difficult hurdle for autologous therapies and were cited as part of the reasons for the commercial failure of Provenge (Dendreon, United States), an autologous cell therapy product for prostate cancer approved in 2010 [23].

With the expanding catalogue of autologous cell therapy products, e.g. Kymriah in August 2017 (Novartis, Switzerland) [24] and Luxturna (Novartis, Switzerland) in November 2018 [25], and high-value investment activities in the sector [26], making informed decisions for supply chain and capacity planning is more and more critical.

Since autologous cell therapies process patients' own cells and infuse the cells back into the patient, they are often time and temperature-sensitive and complicated by the logistics of tissue procurement and transport costs and time. Therefore, the industry is looking into moving away from traditional centralised facilities into smaller regional facilities. This forms an interesting supply chain and capacity planning question which is deeply relevant to the industry today and the key research question of this DPhil thesis – ***how can we commercialise and deliver autologous cell therapies at scale in a more robust and cost-effective way?***

The overall aim of contributing to the answer to the above question is pursued in this work along three objectives:

1. To develop a model-based approach in assessing and optimizing the *patient-to-patient supply chain* of autologous cell therapies
2. To develop a model-based approach in *regional capacity planning* for autologous cell therapies under specific relevant regulatory tracks
3. To develop a systematic approach to incorporating the *risks and uncertainties* in the commercialisation decisions of autologous cell therapies

The findings of this project can be applied by the industry to make better decisions in commercialising autologous cell therapies for unmet medical needs.

1.3 Thesis structure

This thesis was compiled in an integrated format, including conventional chapters and journal paper-based chapters. Chapter 1 introduces the problem, motivation and aims of this DPhil project and provides an overview of the structure of the thesis (Figure 1.2).

Chapter 2 reviews the current state of literature in the challenges of cell therapy commericalisation and the decisional tool approaches employed. The literature landscape informs the gaps in the literature and provides the basis for the scope of the project.

Chapters 3-5 are research chapters looking at commercialisation issues of autologous cell therapies at successive levels. Chapter 3 looks into the operational supply chain problem and compares the two models of manufacturing: decentralised vs centralised manufacturing. Extending the findings in Chapter 3, Chapter 4 looks into the tactical level problem of product portfolio and capacity investment decision optimisation using a mixed-integer linear programming approach. Further, Chapter 5 focuses on the strategic project valuation, evaluating the impact of cell therapy specific commercialisation barriers and proposing a systematic approach of aggregating learnings from current approved products to enhance the rNPV project valuation approach widely used by biotech companies and financial analysts to aid investment decisions.

Finally, Chapter 6 concludes the thesis with the research contribution, strength and limitations of the work and perspectives for future work.

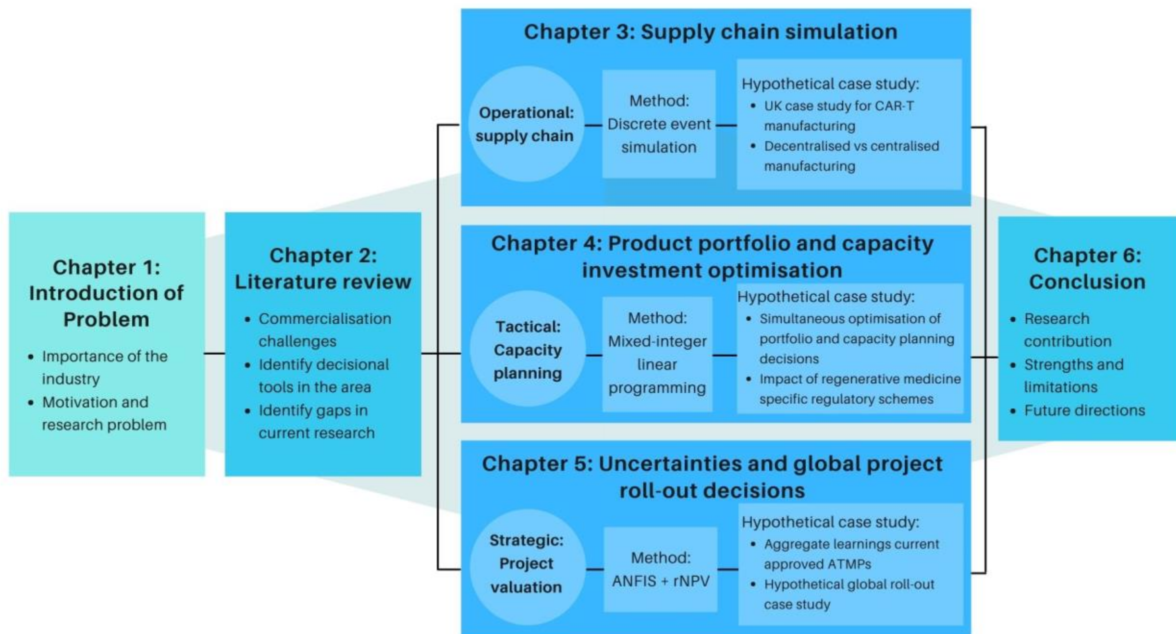


Figure 1.2 Thesis structure

Chapter 2 Literature review

This chapter presents an update to the following published articles/ book chapter:

Lam C, Meinert E, Alturkistani A, Carter A, Karp J, Yang A, Brindley D, Cui Z. Decision Support Tools for Regenerative Medicine: Systematic Review. *J. Med. Internet Res.* 20(12), e12448 (2018).

Lam C, Meinert E, Halioua-Haubold CL, Carter A, Yang A, Brindley D, Cui Z. Systematic review protocol: An assessment of the post-approval challenges of autologous CAR-T therapy delivery, (2019).

Lam C, Meinert E, Yang A, Brindley DA, Cui Z. Decisions in the Development Lifecycle of Cell and Gene Therapies. In: *Second Generation Cell and Gene-based Therapies*. Elsevier, 597–632 (2020)

2.1 Introduction

Decisional tools have been shown to be important in aiding complex decision-making and problem-solving since their advent in 1970s [27]. They have been widely used in various industries including healthcare [28], agriculture [29], environment [30], pharmaceutical, and biopharmaceutical industry for the understanding of cost structures, risks, technology evaluation, supply chains and capacity planning problems [31]–[34]. Although there is a wealth of decisional tools available, as presented in Chapter 1, cell and gene therapy is a relatively new drug modality with unique challenges and hence unique problems for decision-makers.

The first section of this chapter reviews the challenges in cell therapy commercialisation (Section 2.2). This provides an overview of the challenges for autologous and allogeneic cell therapies and highlights the importance for more robust decision-making processes for autologous cell therapies.

Section 2.3 discusses the current decisional tool and mathematical model landscape for regenerative medicine. This section discusses, in detail, the decision objectives, system boundary, problem formulation and modelling techniques used in literature.

Finally, Section 2.4 establishes the current gaps in research and discusses the computational methods to be used for this thesis.

2.2 Challenges in cell therapy commercialisation

Receiving market approval is just the beginning to another array of challenges. Since Mason and Hoare's 2007 conceptual framework [35] of regenerative medicine bioprocessing, many methodologies for coping with process development and manufacturing challenges of regenerative medicine have been proposed.

A summary of those challenges is presented in Table 2.1, whereby off-the-shelf components and service components of the new therapies need to be well identified and optimally provided to the market by the most suitable parties.

Autologous cell therapies depend more on a service model requiring creative and innovative business and manufacturing solutions for commercial success.

Table 2.1 Commercialisation challenges for allogeneic and autologous therapies (Table published in [22])

Challenge	Allogeneic	Autologous
Scientific		
Donor source	**Ethical issues** Cell and tissues (such as umbilical cord) must be 'ethically-sourced' [36] **Establishing cell banks** A two-tiered cell banking system is required, and cryo-storage space is required. Immunophenotyping, differentiation potential and karyotyping are required [37]. **Risk of transferring pathogens from donor to recipients** [38]	**Regulated sites of collection** Tissue/ cell procurement can only be done in regulated sites, hence limits the widespread use of autologous therapies [39] **Variability between patients** Intrinsic variability in the cells/tissues collected impact the cell expansion phase and final product quality[40], [41]. Novartis recently reported that the cell variability impacted the final viable cell percentage causing it to fail meeting the stringent commercial specifications [42]
Product understanding	**Complex therapies require more product understanding for definition of critical process parameters and quality attributes** Use of a target product profile approach for aligning the process with the desired product to overcome process development related issues such as high cost of goods, poor product characterisation, process inconsistencies and product limitation [43], [44]	
Safety and efficacy	**Risk of immunological rejection** Whilst allogeneic MSC are shown to modulate immune responses[45], other cell types may require more elaborate (and complex) genetic modification techniques to lower chance of rejection [46]	**Efficacy related to the quality of source material** [42] **Better clinical trial designs** [47]

Challenge	Allogeneic	Autologous
Technological		
Cell expansion	**Lot-size challenges** Traditional planar cultures are labour intensive and the process is not robust, hence the requirement of better cell culture technologies and methods [48]	**Expanding to adequate cell numbers and viability** Dependent on patient cell quality as mentioned above
Scale up/out	**Centralized facility** Traditional pharma scale up model [49]	**Decentralized model** Complex supply logistics, small lot sizes, short shelf lives of products, limited time available for transport of cells from patients and therapy to patient are drivers for decentralized small facilities. However establishing product comparability between sites requires expensive validation and clinical qualification tests [41], [50], [51]
Raw and ancillary material	**Media supply (serum or serum-free)** Changes in serum type impacts cell expansion and final product quality [52] **Genome-editing materials** The main ways of genome-editing include transcription activator-like effector (TALE)-nucleases (TALENS), zinc finger nucleases (ZFNs), CRISPR/Cas system and viral vectors [53]. Viral vector shortages anticipated by industrial experts due to the increase of cell and gene therapies [54]	

Technology options	**Large scale cell culture** Control of oxygen, nutrients, fluid flow, mass transfer and shear becomes more difficult as scale increases and these, in turn, impact the cell quality [55] **Limited downstream technology options for larger scale** [55]	**Small scale cell culture** Require more automation and process integration to reduce manual labour and errors to achieve better process robustness [56], [57]
Facility design	**Similar to biopharma large scale facilities**	**Cross-contamination risks for parallel production** Facility designs should prevent cross-contamination shall multiple patients' cells are handled at the same time. Other risk mitigation strategies, e.g. time segregation can also be employed [58]
Quality control and characterization	**Product characterization** Development of appropriate potency assays [59]	**Batch-to-batch variability** Development of appropriate potency assays [59] **Quality control tests for each batch** Time and cost of QC tests for each batch (for each patient) [60]
Cost of goods	**Relatively lower** [38]	**Higher cost of goods for personalized treatment** Does not benefit from economies of scale and QC tests have to be conducted for each batch [38]
Product storage and distribution	**High cost of inventory** Due to cryogenic storage requirement. For products that are not cryopreserved, the shelf life is short (discussed in next section) [55] **Challenging cold and ultra-cold chain distribution** [61]	**Challenging cold and ultra-cold chain distribution both for cell collection and delivery** [61]

Challenge	Allogeneic	Autologous
Commercialisation		
Partnering opportunities	**Less incentive to outsource/partner**	**Outsourcing to contract manufacturing organizations** Complex logistics and cost considerations drive outsource decisions **Partner/outsource to regional companies** The service model and potential risks of the therapies drive partnering decisions with companies in foreign markets as more training is required at the point-of-delivery [62], [63]
Business model	**Off-the-shelf business model** [55]	**Service-based business model** [55]

2.3 Decisional tools for regenerative medicines

Decisional tools or decision-support tools are tools that can be used to support complex decision-making and problem solving. As mentioned previously, decisional tools have been widely used to support evidence-based decision making in various industries from agriculture to healthcare. It is worth noting that the refinement of decision-making processes through repeatable models allows continuous feedback and subsequent continuous improvement. These tools are widely used by strategists, for example at consulting firms, as a methodical and quantitative approach to address common biases in human judgement and decision making [64].

As a relatively new therapeutic modality, whilst cell and gene therapies face different obstacles, similar decision-support techniques can be applied to support complex decision making in investment, product development and subsequent manufacturing. Models tailored to industry requirements have to be designed with reasonable and industry-relevant assumptions, especially considering regulatory needs, to realise the power of decision models. Through providing a better understanding of processes, risks and cost drivers, decisional tools are used to help build valid commercial and use cases to influence decision makers in making important business and bioprocess decisions, from technology choice and process change, to supply chain and project portfolio management [65]–[69]. One such example is the shift from stainless steel to single-use production strategies for biologics over the last 15 years across the biopharmaceutical industry, which allowed faster campaign turnover, lower initial capital costs, and manufacturing cost savings [70]–[72]. In addition, decisional tools have been used extensively for monoclonal antibody and vaccine manufacturing decisions and have proven to be useful for understanding cost structures and risks in order to inform decisions in various areas, including technology evaluation, facility fit, and capacity planning [33], [65], [70], [73]–

[75]. A systematic review detailing the decisional tool landscape for regenerative medicine was conducted [76] and this section will summarise key findings from the review and the updated landscape since the publication of the review using the same search terms detailed in the systematic review.

2.3.1 Decision objectives

The first step towards constructing a methodology to decision-making is to establish the decision objective(s) or goal(s) of the decision-maker. There are usually three types of decisions: operational, tactical and strategic [77]. Operational decisions are generally made by lower-level management looking into short-term or day-to-day decisions. These include decisions such as the choice of technology to lower the COGs, scheduling decisions to meet demand, choice of suppliers etc. Tactical decisions are made by managers to plan and execute mid-term tactics to implement long-term decisions. These can be planning decisions such as capacity planning (in-house manufacturing vs. outsourcing), partnerships and collaborations, or when and how to implement process changes to meet anticipated demands. Strategic decisions are typically made by senior management to plan and support the long-term strategy of the company. For cell and gene therapy, these could be investment decisions, such as the entry to a foreign market or merger and acquisition (M&A) decisions.

With the recent approvals of therapies and an increase in M&A activities, these decisions are more vital than ever to set up the architecture for the manufacture, delivery and successful adoption of these life-saving therapies.

Table 2.2 Decision objectives in the cell and gene therapy industry studied in existing literature

Decision type	Examples of decisions	Reference
Operational	Optimisation of operational yield of cell expansion process for MSCs	[78]
	Managing biological variability	[79]
	Small scale manufacturing cost of goods	[80]
	Cost of goods optimisation of upstream process	[81]
	Cost of goods optimisation of downstream process	[82]
	Cost of goods for neutrophils	[83]
	Optimisation of red blood cell manufacturing	[84]
	Overall manufacturing process cost of goods optimisation	[85], [41], [86]
	CAR-T supply chains	[87], [88], [89]
Tactical	Timing of upstream process change for scale-up production Risk-adjusted net present value	[82]
	Capital investment and facility footprint	[90]
Strategic	Minimisation of developmental and investment risks of cell therapy project portfolio	[91]

Table 2.2 represents examples of decision objectives in the cell and gene therapy industry studied previously. As shown, most existing models focus on operational decisions for optimization of the costs for manufacturing or product development. Manufacturing COGs were further broken down to show sub-categories such as raw material, labour, consumables, and capital equipment. Product development costs relate to the investments that are required to bring the product from bench to bedside, including particularly clinical trial costs. Optimizing these costs is critical in the sustainable development of companies and to enable operational efficiency. Project net present value (NPV) is a commonly used method in project evaluation [92]. For example, through evaluating the NPV as an impact of process change in the development timeline, Hassan et al. were able to reflect the riskiness and benefits of making a process change from one technology to another.

2.3.2 Systems

Depending on the decision objectives, different system levels and boundaries are chosen for review:

2.3.2.1 System boundary

As defined by Driscoll et al [93], a system boundary is a physical or conceptual boundary that contains all the essential elements, subsystems and interactions necessary to address a systems decision problem. Different decision objectives motivate different definitions of systems boundaries.

The systems in the eligible publications can be generalized into two types: 1) Product development systems; and 2) Manufacturing and supply chain systems.

2.3.2.1.1 Product development systems

For higher-level decisions such as investment and process changes, corresponding system boundaries are more abstract. For example, McCall [91] defined their systems

boundary as being between preclinical trials and Phase III clinical trials in order to look into the costs of developing a cell therapy whilst Hassan et al. [82] defined its systems boundaries as being between Phase 1 clinical trials and regulatory approval in order to study the impact of process changes along the development phases on NPV of the project.

2.3.2.1.2 Manufacturing and supply chain systems

Whilst Ungrin et al. and Lambrechts et al. addressed optimisation of the cell expansion process upstream through experiments, bioprocess modelling and visualization [78], [94], Hassan et al. focused on process change impacts along the product development pathway using the change of upstream processing technology [82]. Particularly, the impact of process change and the timing for CAPEX investment in automated and scaled-up technologies for allogeneic MSCs were studied. A more general facility capital investment and footprint study was conducted to provide project-specific ratios for equipment purchase costs to facility footprint and capital investment to total equipment purchase cost for an improved estimation ratio to the Lang factor [90]. However, autologous cell therapies would require innovative manufacturing models allowing scale-out of manufacturing whilst ensuring reproducibility. Hence the impact of process changes and the timing for automation will have to be studied in future models, as the previous experienced gained with the practice of allogeneic MSCs cannot be translated for these more service oriented pharmaceutical modalities.

To bridge this gap, Simaria et al., Hassan et al., Weil et al., Harrison et al. and Jenkins et al. among others evaluated different technology options for the studied steps within their defined system boundaries to better understand the advantages, disadvantages and bottlenecks in adopting different technology options and their implications on manufacturing cost of goods [41], [81], [95]–[97].

More recently, the needle-to-needle supply chain of autologous cell therapies has been simulated to optimise the distribution time [89] and NPV of distribution network [88].

2.3.3.2 Product type

As shown in Table 2.3, most of the earlier studies focus on allogeneic therapies and mesenchymal stem cells. However, recently there are increasing interest in CAR-T therapies, especially after the approval of the first CAR-T product in 2017.

Table 2.3 Cell types discussed in literature

Cell type/ Transplant type	**Allogeneic**	**Autologous**	**Not specified**	**Not applicable**
MSC	[41], [82], [94], [97]			
CAR-T		[87], [88], [89]		
hPSC/iPSC		[85]	[78]	
Neutrophils	[83]			
Red blood cells	[84]			
Not specified	[81]			
Not applicable				[90], [91]

2.3.3.3 Handling of risks and uncertainties

Common themes incorporated into these manufacturing and development cost models are the risks and uncertainties lurking the industry. The major methods of capturing risks and uncertainties in the studied models are stochastic modelling, Latin Hypercube Sampling, Monte Carlo analyses and sensitivity analyses.

2.3.3.3.1 Deterministic vs. stochastic modelling

Deterministic models use discrete values. This means that for a certain input, the output will always be the same; whereas stochastic models have at least one quantity with random values, thereby leading to an ensemble of different outputs [93].

To account for the uncertain and variable nature of stochastic systems, probability distributions can be applied to parameters. With regard to cell and gene therapies, the product development duration [82], [91], the variable preference of quality attributes [96], the variability of source materials and manufacturing process are all uncertainties that should be accounted for. Also, Wang et al compared deterministic vs stochastic supply chains with adjustments for operational issues such as uncertainties in end-point treatment needs, inventory and quality of samples using a scenario-based uncertainty analysis [88].

2.3.3.3.2 Latin Hypercube Sampling and Monte Carlo simulation

McCall et al [91] categorized the risks into product risk factors and enterprise risk factors. Product risks were defined as risks that can harm the patient, namely the choice of cell type, manufacturing processes and delivery mechanism. Enterprise risks were defined as risks that affect the commercialisation of the product and the business developing the product, namely technical risks and market risks. The Latin Hypercube Sampling method was utilized to take into account the probability of failure and duration for each task along the product development pathway and the interdependencies. It is worthwhile to note that in this model, iterations caused by failures and impact of failures during each phase were taken into account using three matrices – design structure, rework probability and rework impact.

Hassan et al. simulated the risks and uncertainties of process change along the product development pathway through Monte Carlo analyses. To adjust the project NPV according to risk, a discount rate based on the riskiness and expected development time is employed [82].

2.3.3.3.3 Sensitivity analysis

"Sensitivity analysis is the study of how the uncertainty in the output of a model (numerical or otherwise) can be apportioned to different sources of uncertainty in the model input" [98]. In other words, it is a methodology that can be used to understand the relative impact and importance of input parameters on the final outcome. This is a very common strategy to account for uncertainties and identify key cost drivers [81], [85], [99]. As an example, for the upstream steps of production processes for mesenchymal stem cells, the main cost drivers were found to be microcarrier area, harvest density, media price and downstream yield [81]. While for processes requiring differentiation or gene-modification, the key cost drivers were consistently cited to be the efficiency of differentiation and gene-modification for both autologous and allogeneic processes of different cell types [85], [86]. These findings can subsequently allow R&D efforts to be focused on optimizing the manufacturing processes.

2.3.3.3.4 Hypothetical case studies

Hypothetical case studies are useful in filling the gaps where real data are not available. Different demand and dose size scenarios and the potential impact of these scenarios can be studied through these case studies for evaluating process bottlenecks while scaling up production and technology-switch sweet spot analysis. If higher demand for the product is anticipated, there is a greater tendency to switch to a more scalable system earlier on [81], [85], [86], [97]. "What-if" scenario analysis was employed by Wang et al to simulate the risk of reagent stock level and supplier disruption [89].

2.3.3.3.5 Fuzzy logic

Fuzzy logic is another common technique used systems modelling for uncertainty quantification and parameter estimation. Fuzzy logic was first introduced by Zadeh to aid

decision-making based on ambiguous data [100]. The method has been applied to a range of problems including energy [101], agriculture [102] and finance [103].

In pharmaceuticals, fuzzy logic has been used for the analysis of manufacturing facility conditions [104], [105] and for demand forecast for the supply of pharmaceutical products in distributed pharmacy network [106]. However, to date, there have been no application of fuzzy logic approach to ATMP commercialisation challenges.

2.3.3.4 Implementation

System implementation is the process of defining how the system should be built, ensuring that the system is operational and that the quality of the system is sufficient to deliver its purpose [107]. Whereas it is challenging to validate some of these models in a real-world scenario, there are other strategies that can be adopted to ensure credibility and validity of assumptions.

For simpler models, using Microsoft Excel with visual basic (VBA) has appeared to be sufficient. For single objective cost optimisation problems, an Excel model with mass balance, design, sizing, resource utilization and COGs equations, database of bioprocess technology and cost data combined with scenario analysis implemented using VBA may be sufficient for its purpose. Dedicated add-ons, such as Palisade Risk 6, allow Monte Carlo simulations and sensitivity analysis to be performed somewhat more easily.

However, VBA code is susceptible to Excel program upgrades. What is more, changing formats (e.g., adding a column or a row) may cause changes in the functions. C# or MATLAB allows more versatile coding experience and for models requiring many runs, e.g., uncertainty or stochasticity analysis; as a result these platforms may be more suitable.

For models with larger databases, it is worth examining relational database management software (RDBMS). RDBMS provides better scalability if the amount of data is

very large; moreover, links can be built in a more robust ways compared to spreadsheets. Visualization software tools such as Google Charts allow information to be easily updated and visualized, and hence these are very useful for presenting a lot of data in a meaningful way [94].

2.3.3.5 Model Validation

2.3.3.5.1 Data mining

Previous successes and failures statistics are very useful not only for benchmarking purposes but also for model validation. McCall et al. collected data from development programs surrounding orphan and non-orphan cell therapies [91] while Hassan et al collected information on clinical trial development times and failure rates of all 592 commercial cell therapy projects that entered development from 1981 to end of 2011. Such data from real commercial case studies are useful for informing assumptions and subsequently increase the validity of assumptions such as the development duration [82].

2.3.3.5.2 Laboratory experiments

Using experimental results to support key assumptions is a powerful tool in validation. For example, performance data of unit operations may not be as good as the vendor of the equipment in question may claim, or the use case may be different, hence leading to varying results. Also, conducting experiments with different cell types can give valuable insights to more precisely characterise the inherent variability of manufacturing processes, thus lending the model more credibility.

2.3.3.5.3 Expert validation

Expert validation of assumptions has also shown to be an important way of improving the credibility of models [89]. Cost and process data from industry experts are often used for cost modelling studies to improve the validity of the model. For instance, using data from

discussions with industry experts (including plant managers, business development managers, product managers from companies that work in the cell therapy space) Chilema et al conducted multi-attribute decision-making and stochastic cost analysis for allogeneic cell therapy manufacturing [108].

2.4 Key gaps in literature

Current literature has not looked into the operational performance of decentralised and centralised manufacturing with respect to the cost per treatment, resource utilisation, the time required from collection to delivery, system performance under demand pressure and system resilience to risks such as mix-ups and equipment failure. A better understanding of operational performance can lend itself into higher-level capacity and investment planning problems. In particular, the manufacturing of autologous CAR-T therapies in a given region with integrated and automated processing equipment, such as Miltenyi CliniMACS Prodigy (Miltenyi Biotec, Germany) deserves special attention. Using closed and automated equipment reduces the need for highly skilled labour and manufacturing process variability [109]; the importance of using such equipment in decentralised manufacturing has previously been highlighted [41], [56]. However, the granularity of day-to-day supply chain operations has not been sufficiently modelled to understand the process robustness of supply chains. Further to the operational problems, the opportunities of fast-track designations such as Breakthrough designation and orphan drug designation have not been extensively discussed in relation to capacity planning and NPV decisions.

To address this gap, this DPhil project aims to employ a model-based approach in assessing and optimizing (1) the needle-to-needle supply chain of autologous cell therapies, (2) subsequently capacity planning and (3) further understanding of the commercialisation barriers for the global roll-out for commercialisation of autologous cell therapies.

Chapter 3 Centralised vs decentralised supply chain of autologous chimeric antigen receptor T-cell therapies

This chapter presents the following published article:

Lam C, Meinert E, Yang A, Cui Z. Comparison between centralized and decentralized supply chains of autologous chimeric antigen receptor T-cell therapies: a UK case study based on discrete event simulation. *Cytotherapy* 23(5), 433–451 (2021).

Among all authors who contributed to the published article, CL conceived, designed and implemented the model and wrote the manuscript. EM, AY and ZC supervised the study and revised the manuscript.

Summary

As discussed in Section 2.2, supply chain challenge is one of the most important commercialisation challenges for cell therapies. Due to the geographical and logistical constraints of autologous cell therapies, decentralised manufacturing that takes place close to the point of care has been a manufacturing paradigm of heightened interest for autologous cell therapies. To compare the compare the operational feasibility and cost implications of manufacturing autologous chimeric antigen receptor T (CAR T)-cell products between centralized and decentralized schemes, a discrete event simulation model was built, and a UK case study was analysed.

The simulation results show that although centralized manufacturing offers better economies of scale, individual facilities in a decentralized system can spread facility costs across a greater number of treatments and better utilize resources at high demand levels, allowing for an overall more comparable cost per treatment. In general, raw material and consumable costs have been shown to be one of the greatest cost drivers, and genetic modification-associated costs have been shown to account for over one third of raw material

and consumable costs. Turnaround time per treatment for the decentralized scheme is shown to be consistently lower than its centralized counterpart, as there is no need for product freeze-thaw, packaging and transportation, although the time savings is shown to be insignificant in the UK case study because of its rather compact geographical setting with well-established transportation networks. In both schemes, sterility testing lies on the critical path for treatment delivery and is shown to be critical for treatment turnaround time reduction. Considering both cost and treatment turnaround time, point-of-care manufacturing within the UK does not show great advantages over centralized manufacturing. However, further simulations using this model can be used to understand the feasibility of decentralized manufacturing in a larger geographical setting.

Overall, Chapter 3 shows the operational merits and demerits of decentralised manufacturing and lays the foundation for further strategic capital investment optimisation decision in Chapter 4.

3.1 Introduction

With the expanding catalogue of cell and gene therapy products such as the first autologous chimeric antigen receptor T (CAR-T) cell therapy (Kymriah) in August 2017 [24] and Luxturna in November 2018 [25], the cell and gene therapy industry is moving from bench to bedside. In this transition, post-approval challenges such as reimbursement, delivery and supply chain issues have proven to be a difficult hurdle for autologous therapies and were cited as one of the reasons for Dendreon's commercial failure[23].

Traditionally, the biopharma industry has benefitted from the "Ford-ist" centralised manufacturing paradigm where the manufacturing is centralised, large-scale, highly efficient and standardised [110]. Through manufacture scale-up by moving from inefficient manual processes to automated large-scale bioreactors, manufacturers of biologics were able to bulk

produce consistently complex biological products such as monoclonal antibodies and drive down cost of goods, deliver effective treatments to patients [111], growing into an industry predicted to reach nearly $125 billion global annual sales in 2020 [112], [113]. This manufacturing and distribution model has been shown to offer benefits such as more efficient resource planning, easier monitoring and reducing cost per treatment through spreading regulatory, equipment and capital costs over a large volume of products[114]. The manufacturing of autologous cell products such as those for CAR-T therapy, however, does not benefit from the same extent of economies of scale. Firstly, due to the autologous personalised nature, manufacturing has to be scaled out and not scaled up, i.e. by using multiple sets of equipment running in parallel instead of using single larger equipment to deliver more products [50], [51], [115]. Secondly, autologous cell products are living cells that are very sensitive to environmental changes, have short shelf lives and are specific for patients. To enhance the flexibility of scheduling and manufacturing of these products, cryopreservation is usually performed [116] and hence the products must be delivered in a highly regulated, temperature-controlled and time-efficient manner[61]. Thirdly, variability in donor-specific raw material, manufacturing process, lot release testing and point-of-care handling and delivery techniques can all contribute to the product quality differences [117].

To tackle these challenges, the decentralised manufacturing model has been proposed as a potentially more attractive alternative to the centralised system [118], [119]. Decentralised or distributed manufacturing refers to a manufacturing paradigm with which manufacturing is smaller scale and distributed into a number of locations closer to end users of the products[120]. This allows less transportation time and raw material/ product freeze-thaw cycles, hence reducing transportation related costs and risks and preserving product quality. In other industries such as food[121], [122] and energy production[123],

decentralised manufacturing models have been evaluated with respect to economic costs, resource consumption and environmental impact [12], as well as supply chain reliability[123]. For the manufacturing of autologous cell therapies, Harrison et al. discussed the regulatory challenges and implications on the cost of goods [124], [125]. Using the United Kingdom (UK) as an example, Harrison et al. conducted a high-level study on the hub-and-node model, where a 'hub' facility is responsible for support functions (administrative work, research and development, process development, etc.) and 'node' facilities are responsible for the manufacturing [124]. Their study looked into the cost disparity amongst different regions in the UK and compared different degrees of decentralisation of quality control (QC), with a hybrid QC model where part of the QC burden is centralised[124]. Referring to the European Union (EU) guidelines on Good Manufacturing Practices (GMP) of Advanced Therapy Medicinal Products (ATMP) issued in 2017, the "hub" site would need to hold the marketing authorisation and is responsible for the oversight of the "node" sites for batch certification, release and quality assurance audits. The Qualified Person (QP) can use data/information/batch record established in the "node" site to release the product, and all deviations and non-conformity in the process must be well-documented and reported back to the "hub" site [126].

While decentralised manufacturing has been studied for cell therapies, a comprehensive comparison with the centralised model with respect to not only costs but also other performance aspects is still lacking. For example, therapies such as CAR-T which are intended for patients in critical conditions, e.g. in late stages of cancer, the time for the overall needle-to-needle delivery (and the associated risks of manufacturing and logistic failure) is critical for the patient's wellbeing. This was demonstrated in the ZUMA-1 trial, where out of 111 patients, 8% did not make the wait for treatment due to reasons including adverse events

(3.6%), death from disease progression (0.9%) and non-measurable disease before conditioning chemotherapy (1.8%) [127]. Therefore, evaluation of distributed manufacturing in aspects associated with time criticality is important [128].

This study aims to understand the operational performance of decentralised and centralised manufacturing with respect to the cost per treatment, resource utilisation, time required from collection to delivery, system performance under demand pressure and system resilience to risks such as mix-ups and equipment failure. In particular, the manufacturing of autologous CAR-T therapies in the UK is considered, with integrated and automated processing equipment, such as Miltenyi CliniMACS Prodigy (Miltenyi Biotec, Germany). Using closed and automated equipment reduces the need for highly skilled labour and manufacturing process variability [109]; the importance of using such equipment in decentralised manufacturing has previously been highlighted [41], [56]. The quantitative assessment has been enabled by using a discrete-event simulation (DES) model built in this work.

Discrete event simulation (DES) is a method of simulating the behaviour and performance of a real-life process, facility or system. Modelling systems as a series of events over a time period, DES can be used to quantify risk of disruption on the supply chain and hence test strategies that can mitigate these risks and identify strategies for making the system more efficient in resource-use or cost[129]. It has been applied for complex systems in a diverse fields including healthcare[130]–[132], biofuels supply chain[133] and agriculture[29], [134], [135]. DES has also been used in biopharmaceutical companies such as Genentech for quantifying risks within their supply chain network and inform inventory decisions[129]. Autologous CAR-T manufacturing and delivery is a process of a defined structure, but with uncertainty in process parameters and variable risks, for which we show

in this work that DES can offer a realistic tool for the analysis of various decision alternatives, particularly for the comparison between centralised and decentralised paradigms. The learning from this work has the potential to inform the future decisions of relevant companies on the manufacturing paradigms for autologous cell therapies.

3.2 Methods

This section describes the process flow and performance indicators of a typical autologous CAR-T therapy from cell collection to final product delivery based on published literature. The data collection process, assumptions and parameters used for the UK case study and the method of cost calculations are also presented. The process flow and the associated parameters form the basis of a discrete event simulation model of the CAR-T therapy manufacturing and delivery, which has been used to support the evaluation of costs and other performance aspects of the centralised and decentralised systems.

3.2.1 Process description

A representative process flow of a CAR-T therapy delivery, as modelled in this work, is shown in Figure 3.1 [136], [137]. A typical treatment process involves the patient first being treated at, or referred to, a designated approved treatment centre. Such centres have to be trained on processes for cell collection, cryopreservation, transport, chain of identity, safety management and logistics handling, and need to be FACT accredited [138]. If the CAR-T treatment is deemed suitable for the patient, the treatment centre will coordinate with a manufacturing centre to discuss whether there are available slots for processing. T cells will then be collected from the patient by leukapheresis at the treatment centre. These T cells will then be cryopreserved or frozen and packed for shipping via a qualified cold chain logistics provider which has to work closely with the treatment centre [139]. The shipping process for such temperature-sensitive patient live cells is monitored closely [140]. If at any point the

process fails, on a case-by-case basis, the manufacturer decides whether to collect new samples from the patient or for the out-of-specification product to be administered through an expanded access protocol free of charge [141].

All starting materials, cells, consumable and reagents arriving at the manufacturing facility have to first be checked by the quality assurance team before entering the manufacturing process. Quality assurance (QA) plays an important role in autologous therapies to ensure all the processes conducted in parallel are produced in a consistent manner [128]. In the context of CAR-T manufacturing, it is to manage the batch record of each batch of product, visual inspection of materials and general production oversight. Quality Control (QC) tests to check for mycoplasma in the sample from donors are conducted upon receipt of sample. NAT-based mycoplasma testing is assumed to reduce the time required for testing [142].

The sample received is thawed and processed using an enclosed automated equipment where it is enriched and activated with CD3/CD28 conjugated beads before transduction with a lentiviral vector, which is then expanded, washed and formulated. The product is finally cryopreserved in vapor-phase liquid nitrogen for despatch. The expansion media used is prepared in an isolator in a Grade D environment or a biosafety cabinet in a Grade B cleanroom environment. Throughout the manufacturing process, in-process control tests to check for viability, cell count and phenotype of the cells are conducted. The formulated product is subjected to QC release tests (Table 3.1) before getting released by the Quality Personnel (QP) [118], [136]. For the decentralised paradigm, the Qualified Person (QP) is shared across facilities in different geographical locations. In accordance with the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

issued in 2017 by the commission of European Communities [126], the QP can rely on data and information supplied by decentralised sites for batch release.

Table 3.1 QC testing for a typical autologous CAR-T product [138]

Test	Purpose
Virology screening	Ensure starting material is disease free
Cell count and viability testing	In-process: to ensure cell expansion process is as intended Product release: to check if cell count and viability meet specification
Flow cytometry	Determination of cell composition, viability and phenotypes (transduction, differentiation, proliferation capacity, exhaustion) [143]
Enzyme-linked immunosorbent assay (ELISA)	Functional assay for gene expression levels
Mycoplasma testing (PCR)	Ensure raw material and product released are free of mycoplasma contamination
Sterility testing	Culture test to ensure product sterility
Endotoxin testing	Ensure product is free of endotoxins

Throughout the manufacturing process, the treatment centre has to be updated with the progress in order to schedule pre-conditioning chemotherapy over 4 days for the patient 2 to 14 days before the infusion. Once the treatment centre is ready, the cryopreserved product is packaged into a liquid nitrogen dewar for despatch and sent to the treatment centre via a qualified cold chain logistics provider. The shipment is then received by the hospital, verified and prepared. The thawing of the product should be coordinated with the transfusion. The patient receives acetaminophen and an antihistamine 30-60 minutes before the CAR-T cells get administered through standard IV infusion which lasts less than 30 minutes. This procedure can be either in-patient or out-patient, but due to the risk of adverse reactions,

emergency equipment and intensive care units should be available at the treatment centre [140], [144], [145].

The key performance indicators (KPIs) considered and the rationale for their consideration are shown in Table 3.2. Through simulation studies on systems with different configurations, this work predicts these KPIs and identifies the process bottlenecks for further optimisation.

Table 3.2 Key performance indicators and rationale for choice of KPI

Key performance indicator	Rationale
System throughput	Maximise the total number of therapies delivered within the time horizon specified
Cost of each therapy delivered	Minimise the cost of each therapy
Turnover of each therapy	Minimise the time required for each therapy from needle-to-needle: including cell collection, manufacturing, quality control and packaging and treatment delivery time
Resource utilization:	
Personnel	The higher the utilisation, the less wastage in the system
Equipment	The higher the utilisation, the less wastage in the system

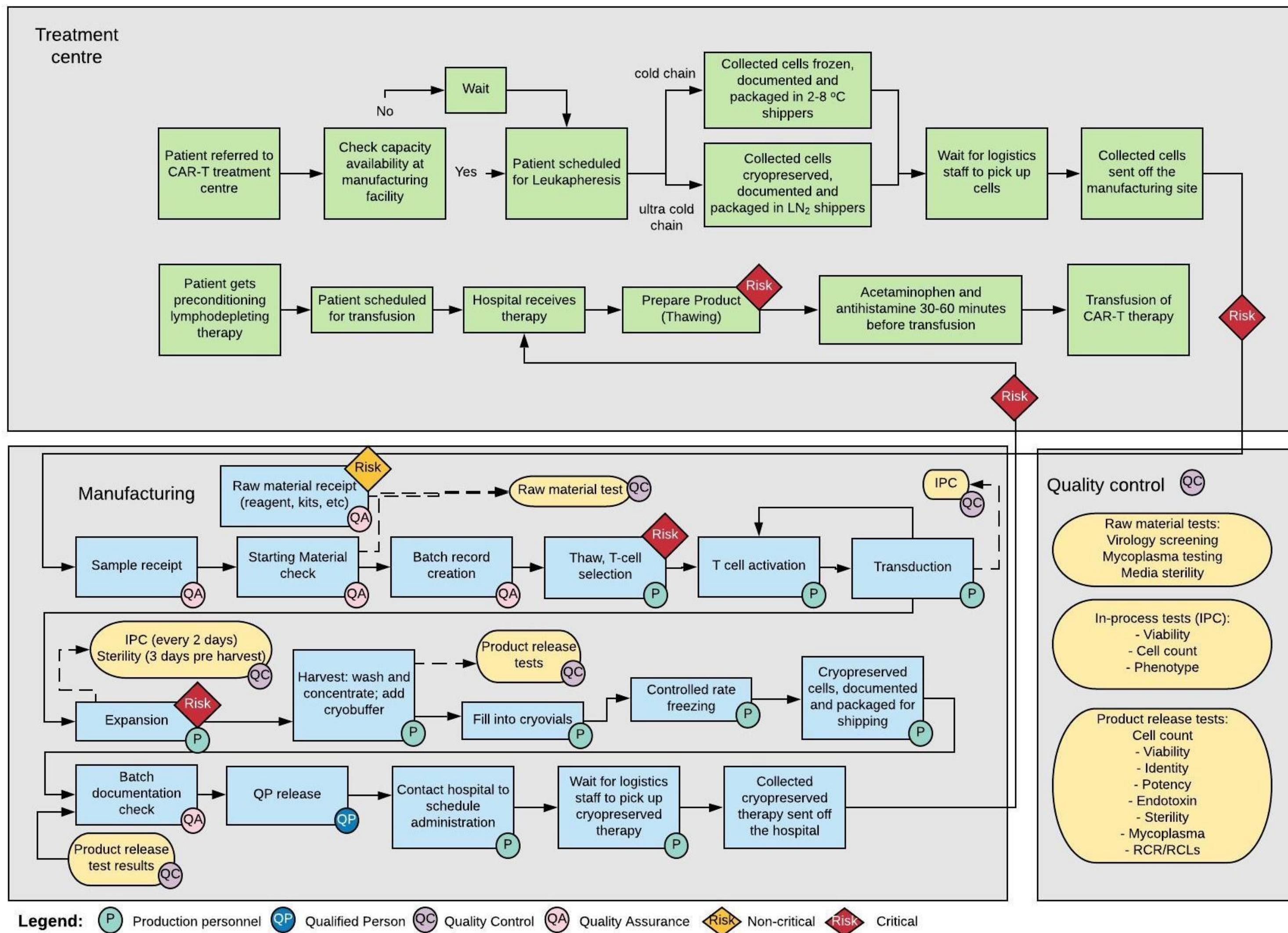


Figure 3.1 Typical process flow of a CAR-T therapy delivery (Green: events in hospital/treatment centre; blue: production activities; yellow: QC activities

3.2.2 Data collection process

The process flow, duration and material requirements were collected through review of literature (as cited in the process description section).

One-on-one interview sessions were carried out with experts from four companies to supplement process data collected from literature. Process requirements and cost data for the manufacturing process and quality control panels were kindly provided by Dr Michael Schenk, Clinical Application Specialist at Miltenyi Biotec (Cologne, Germany). The process requirements and cost data were cross validated with literature [118], [137].

Logistics and supply chain related data were collected through discussion with Mr Najib Rehman, Digital Automation Lead at ATMPS (London, United Kingdom) which is a blockchain-based supply chain platform for cell and gene therapies. Equipment cost data was provided by China Regenerative Medicine International (Hong Kong), a contract manufacturing facility based in Hong Kong. Environmental monitoring system design and cost assumptions were based on discussions with Miss Janice Wallace, Applications Engineer at Pharmagraph (Wokingham, United Kingdom).

3.2.3 Cost calculation

Costs per treatment are calculated through addition of all fixed and variable costs over a year divided by the total number of treatments delivered in the year. Cost assumptions are available in Appendix 3.2.

3.2.3.1 Annual facility costs (F)

The facility costs for hospitals (F_H) are calculated by multiplying the number of hours required for usage of an operating theatre (H_{OT}) by cost per hour (h_{OT}) (Eq 3.1). It is assumed that the preconditioning lymphodepleting therapy and the final transplant will be conducted in an operating theatre.

Facility capital costs are proportional to the anticipated demand and manufacturing capacity. Facility costs for manufacturing (F_M) and QC facilities (F_{QC}) are calculated by summation of capital costs and operating costs (Eq 3.2a-3.2c). Capital costs are based on floor space required by equipment multiplied by the number of each equipment (n) depreciation factor (d). One meter is allowed around width (W) and depth (D) of each equipment for exhaust. Extra working space for operation and cleaning and a GMP working space multiplier (g) is applied to account for indirect working space such as gowning activities (Eq 3.2a).

Operational costs for manufacturing facilities are calculated based on the cleanroom classification and area (f) multiplied by the number of air changes required per hour for the cleanroom class, A_D for Grade D and A_{CNC} for CNC areas respectively, and the HVAC utility cost per square meter per hour (c_{HVAC}). The Lang factor (Lf), a cost factor used for capital cost estimation, is applied to account for the installation and supporting costs of the equipment. (Eq 3.2d-e)

The summation of all facility costs incurred in the hospital, manufacturing and QC gives the total facility cost (Eq 3.2f).

$$F_H = H_{OT} * h_{OT} \qquad \textit{Eq 3.1}$$

$$f_{m,D} = \left(\sum_{m,D} (W_{m,D} + 1) * (D_{m,D} + 1) * n_{m,D} \right) * g \qquad \textit{Eq 3.2a}$$

$$f_{m,CNC} = \sum_{m,CNC} (W_{m,CNC} + 1) * (D_{m,CNC} + 1) * n_{m,CNC} \qquad \textit{Eq 3.2b}$$

$$f_{qc,CNC} = \sum_{qc,CNC} (W_{qc,CNC} + 1) * (D_{qc,CNC} + 1) * n_{m,CNC} \qquad \textit{Eq 3.2c}$$

$$F_M = f_{m,D} * Lf * C_D * d + f_{m,CNC} * Lf * C_{CNC} * d + v * 365 + f_{m,D} * h_m * A_D * c_{HVAC} * 24 * 365 + f_{m,CNC} * h_m * A_{CNC} * c_{HVAC} * 24 * 365 \qquad Eq\ 3.2d$$

$$F_{QC} = f_{qc,CNC} * Lf * C_{CNC} * d + f_{qc,CNC} * h_m * A_{CNC} * c_{HVAC} * 24 * 365 \qquad Eq\ 3.2e$$

$$F = F_H + F_M + F_{QC} \qquad Eq\ 3.2f$$

3.2.3.2 Annualised capital/equipment costs (E)

All equipment is assumed to be depreciated over ten years, i.e. depreciation factor (d) assumed to be 10%. The total annualised equipment cost (E) is the summation of equipment used in the hospital (E_h), manufacturing equipment in Grade D cleanrooms ($E_{m,D}$), manufacturing equipment in CNC cleanrooms ($E_{m,CNC}$), QC equipment in CNC cleanrooms ($E_{qc,CNC}$) and equipment for transportation (E_t) multiplied by the depreciation factor (d) (Eq 3.3). The list of equipment and their costs can be found in Appendix 3.2a. The number of integrated automated platforms (Prodigy, Miltenyi Biotec) available is pre-specified based on the anticipated demand level (Table 3.4).

$$E = (E_h + E_{m,D} + E_{m,CNC} + E_{qc,CNC} + E_t) * d \qquad Eq\ 3.3$$

3.2.3.3 Annual maintenance and service contract costs (M)

Maintenance and service contract costs per year (M) are assumed to be 20% (ms) on the depreciated capital cost for both manufacturing equipment (M_m) (Eq 3.4a) and QC equipment (M_{qc}) (Eq 3.4b) [146]. The annual maintenance and service contract costs are given by the summation of both (Eq 3.4c).

$$M_m = \left(E_{m,D} + E_{m,CNC}\right) * ms \qquad Eq\ 3.4a$$

$$M_{qc} = E_{qc,CNC} * ms \qquad Eq\ 3.4b$$

$$M = M_m + M_{qc} \qquad Eq\ 3.4c$$

3.2.3.4 Annual raw material/consumable costs (R)

Raw material and consumables used throughout the supply chain including the hospital (R_h), manufacturing ($R_{m,D}$, $R_{m,CNC}$), QC ($R_{qc,CNC}$), transportation (R_t) and personnel gowning (R_{gown}), are summed. The personnel gowning costs are given by the cost of each aseptic gown (c_{gown}) multiplied by the shifts of production staff (s_p) per day and the number of days in a year. The costs are accumulated within the discrete event simulation over the course of a year, and is computed using Eq 3.5b. The list of raw materials and associated costs is provided in the Appendix 3.2a.

$$R_{gown} = c_{gown} * s_p * 365 \qquad \textit{Eq 3.5a}$$

$$R = R_h + R_{m,D} + R_{m,CNC} + R_{qc,CNC} + R_t + R_{gown} \qquad \textit{Eq 3.5b}$$

To account for bulk material and equipment discounts, discounts are applied based on annual demand (Table 3.3).

Annual demand	Discount applied
100	0%
200	10%
500	20%

Table 3.3 Bulk discounts on raw material and equipment

3.2.3.5 Annual labour costs

Hospital based staff costs (L_h) are calculated by the work hours (h_{nurse}, $h_{pharmacists}$, h_{doctor}, $h_{support}$) and the hourly costs of hospital staff including nurses ($L_{h,nurse}$), pharmacists ($L_{h,pharmacist}$), doctors ($L_{h,doctor}$) and support staff ($L_{h,support}$) (Eq 3.6). Transportation-related labour costs (L_t) are calculated by logistics staff hourly rate (L_{lt}) multiplied by product transportation hours (h_t) as shown in Eq 3.7.

Manufacturing staff costs (L_M) is given by the summation of the annual salaries of staff (production personnel (L_P), quality control personnel (L_{QC}), quality assurance personnel (L_{QA}) and qualified person (L_{QP})) multiplied by the number of shifts of the personnel per day (number of shifts of QC personnel per day (s_P), number of shifts of QC personnel per day (s_{QC}), number of shifts of QA personnel per day (s_{QA}), number of shifts of QP per day (s_{QP})) as specified in Table 3.4. (Eq 3.8)

$$L_h = L_{h,nurse} * h_{nurse} + L_{h,pharmacist} * h_{pharmacist} + L_{h,doctor} * h_{doctor} + L_{h,support} * h_{support} \quad \text{Eq 3.6}$$

$$L_t = L_{lt} * h_t \quad \text{Eq 3.7}$$

$$L_m = L_P * s_P + L_{QC} * s_{QC} + L_{QP} * s_{QP} + L_{QA} * s_{QA} \quad \text{Eq 3.8}$$

3.2.3.6 Annual transportation costs

Transportation costs (TR) are accounted for by the number of hours required (h_t) and the cost per hour (TR_t) as the amount of fuel, cold chain maintenance is time dependent (Eq 3.9). While LN_2 shipping dewars are limited, limitations of lorry capacity are not considered.

$$TR = TR_t * h_t \quad \text{Eq 3.9}$$

3.2.3.7 Total annual cost

The total cost (TC) is the summation of all aforementioned annual costs (Eq 3.10). The cost per treatment is the total cost per year divided by the total number of treatments delivered in the year ($T_{treatment}$) (Eq 3.11).

$$TC = F_H + F_M + F_{QC} + E + M + R + L_h + L_m + TR \quad \text{Eq 3.10}$$

$$C_{treatment} = \frac{TC}{T_{treatment}} \quad \text{Eq 3.11}$$

3.2.4 Model implementation

The discrete event simulation model was built with ExtendSim 9 (ImagineThat! Inc, San Jose, USA), which is a software platform purposefully built to model continuous, discrete event, discrete rate and agent-based systems[147]. The simulation was set up to run for 50 repeats. To look into a short-term operational decision, the time horizon of one year was selected for each of the studied scenarios such that operations scheduling decisions within the year can be studied. The adoption of the same random input variables between the centralised and decentralised schemes, for fair comparison, was ensured by using the same random seeds for a pair of demand scenarios. A first-in-first-out approach is adopted for queues. On top of this, the stochasticity in patient interarrival times, unit operation process duration and risk of mix-ups were considered through applying triangular distributions to the variables to understand the risk and process robustness of these decision alternatives using Monte Carlo simulations. The assumptions and cost data used in this study can be found in Appendix 3.2.

Results from the simulations were exported to Microsoft Excel 2016 (Microsoft Corporation, WA) for computing the cost of goods per treatment, treatment turnaround time and resource utilisation.

3.2.5 Hypothetical case study

The aim of the simulation case study is to develop a discrete event simulation to examine the needle-to-needle process of autologous CAR-T. A hypothetical case study with the United Kingdom as an exemplar is used and the results are compared with other published cost models.

3.2.5.1 Case study set-up

Figure 3.2 Distribution of advanced treatment centres in the UK

The UK has been chosen as a case study to demonstrate the application of the simulation model at several annual demand scenarios. In the UK, there are currently 10

advanced treatment centres. Figure 3.2 shows the distribution of these centres around the UK and the coordinates of these locations can be found in Appendix 1. The distance between the facility and treatment centre locations impacts the transportation time and hence related costs. For the centralised scheme, it is assumed that one facility will satisfy the demand from all the 10 advanced treatment centres while for the decentralised scheme, each treatment centre is assumed to have its own small-scale facility to meet its local demand (10 manufacturing facilities in total across the country) with a centralised QP for product release.

The annual demand and the number of treatment centres are based on the draft interim specification for the delivery of CAR-T therapy for treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, published by the NHS in 2017 [148]. The annual demand has been estimated to be around 200 cases per year. For this study, we have looked into three demand levels in terms of the number of patients per year: low demand (100), anticipated demand (200) and high demand (500).

The assumed numbers of equipment and personnel shifts per day (8 hours per shift) for a total of 6 scenarios are summarised in Table 3.4, defined by combining the centralised ("C") and the decentralised "D" schemes with the three demand levels (100, 200, 500). To avoid mix-ups and potential of cross contamination, it is assumed that each production personnel can handle a maximum of two sets of integrated processing equipment at the same time during the core working hours from 08:00 to 24:00 (personal communication, Miltenyi Biotec). A production personnel is tasked with handling emergency and alerts outside core working hours. To account for training hours, vacation and sick days, the maximum utilisation of personnel is set to be 80%. These values correspond to the minimal amount of resources

needed to allow no system bottleneck and a reasonable level of equipment utilisation rates (80±2%) at the designated demand.

3.2.5.2 Demand stress

To investigate the impact of demand stress in case of poor estimation of demand at planning stage, we simulated each scenario at its designated demand level, referred to as the base case (100, 200, or 500 patients per year), and also at patient demand increased in 5%, 10%, 15%, 20%, 30% and 50%. As trained labour and equipment take time to become operationally ready, the availability of resources in each scenario is assumed unchanged with unexpected demand increase.

Table 3.4 Resource input for centralised vs decentralised scenarios for different demand levels

	C100	D100	C200	D200	C500	D500
Production personnel (shifts per day)	5	30	5	50	21	50
QC personnel (shifts per day)	5	30	5	30	5	30
QA personnel (shifts per day)	1	10	1	10	1	10
Qualified Person (QP)	1	1	1	1	1	1
Integrated Processing equipment (#)	4	10	8	10	19	20

3.2.5.3 Risk assumptions

Quality risk points discussed by Trainor et al [128] are considered and risk probabilities are benchmarked and assigned based on published data. In this study, we simulated the risk of patient material mix up at two potential occurrences, hospital to facility and facility to hospital. The lower bound (0.02%) and higher bound (0.08%) of the risks were benchmarked against blood bag mix-ups documented by Bolton-Maggs et al [149]. Where mix-ups or failures occur, the batch will be reneged and discarded, as out-of-specification drugs cannot be sold [141].

3.3 Results

This section will discuss the results of simulation and the observed trends in cost and resource utilisation, timeliness of delivery and response of the centralised and decentralised schemes under demand stress.

3.3.1 Base case (under nominal demand levels): Cost and resource utilisation

The costs per treatment for three demand levels, accounting for both hospital, manufacturing and transportation costs, are shown in Table 3.5. The per treatment costs range from around $70,336 in the high demand centralised manufacturing scenario to $168,185 in the low demand decentralised manufacturing scenario. The results are reasonably comparable with the previously estimated cost of around $95,780 per dose for autologous CAR-T [52] and a COG breakdown analysis comparing manual and fully automated process for 5,000 patients showed COG per batch ranging from $84,827 to $116,685 [150]. These costs are significantly higher than the costs estimated previously for allogeneic CAR-T cell therapy, e.g. around $7,000 to 8,000 ([51], not including hospital or transportation costs) and $4,460 [52] per dose. Exact comparison of results from different studies can be difficult given their difference in the inclusion of various cost items. However, in general it is expected that autologous CAR-T is costlier than its allogeneic counterpart, as the latter allows better scale up and production of off-the-shelf products.

In both centralised and decentralised schemes, the per-treatment cost is reduced as demand increases (Table 3.5). The required resources assumed for the decentralised scheme are greater than that for the centralised scheme to achieve the same production level (Table 3.4), hence the resource utilisation rates are lower except for production personnel at the high demand scenario (Figure 3.3A).

As the demand increases, resources such as labour, equipment and facility can be better utilised and shared amongst more treatments (Figure 3.3A). This is particularly apparent for the decentralised cases, where smaller local facilities in hospitals can benefit from better utilisation of all resources, especially with the use of integrated process equipment (Prodigy).

For decentralised manufacturing, there is a minimal number of equipment and personnel required at each facility and hence the utilisation rates of resources are low for demand levels of 100 and 200 patients per year. The difference in utilisation rate of production personnel and equipment between decentralised and centralised schemes reduces as annual demand reduces, while the utilisation rate of QC and QA personnel for centralised manufacturing increases at a much faster rate than in the decentralised scheme (Figure 3.3B). It is noted at high demand level, production personnel and equipment are better utilised in the decentralised scheme. This is due to the constraint of maximum of 2 equipment handled per personnel to prevent cross contamination and mix-ups. If the constraint is relaxed, it would be easier to utilise resources to a better extent.

As the qualified person (QP) can sign off batches based on data sent from decentralised facilities, the utilisation rate of QP is based on the number of treatments delivered, hence there is no change in the utilisation rate of QP between centralised and decentralised facilities (Figure 3.3B).

Table 3.5 Cost breakdown per treatment for all scenarios

Scenario	Centralised			Decentralised		
Annual demand	100	200	500	100	200	500
Raw material/ Consumables	63,070.37	65,248.89	58,564.47	57,816.23	50,520.09	50,821.99
Labour	6,024.64	26,818.55	3,807.78	16,138.81	3,486.03	7,918.13
Capital/ equipment	3,456.43	14,296.25	1,977.06	6,629.62	1,092.43	2,746.37
Facility	39,691.88	59,166.73	29,962.10	36,164.93	15,036.39	22,686.62
Transportation	30.34	N/A	64.13	N/A	30.47	N/A
Others (Service and maintenance)	405.81	2,654.43	263.48	1,230.94	170.78	514.85
Per treatment cost ($)	112,679.47	168,184.86	94,639.00	117,980.53	70,336.19	84,687.96

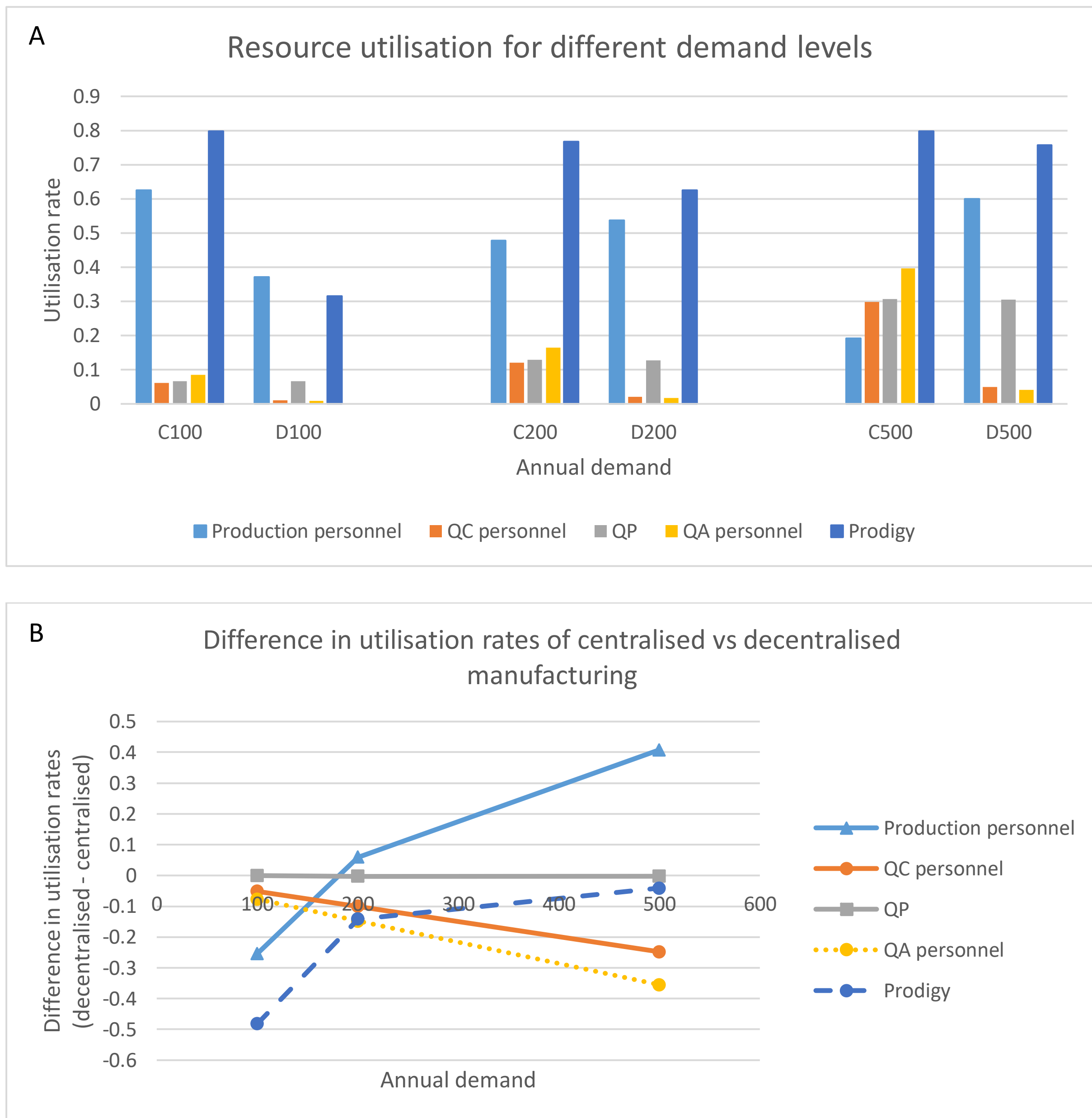


Figure 3.3 Resource utilisation in centralised and decentralised schemes. A: Resource utilisation comparison at 3 demand levels; B: Difference in utilisation rates between centralised and decentralised manufacturing for labour and manufacturing equipment.

3.3.2 System performance under demand stress

As introduced earlier, demand stress is defined as unanticipated increase in demand which exceeds the planned capacity. This section considers the change in cost and resource utilisation as demand stress increases.

3.3.2.1 Cost per treatment

The cost per treatment decreases initially as the system handles more treatments and hence the overall cost can be shared amongst more treatments (Figure 3.4). As demand stress becomes greater, at 50% demand stress, in the centralised scheme, the per treatment cost increased by 1.8%, 2.6% and 11.5% for low, mid and high demand levels respectively; whereas for the decentralised scheme, the per treatment cost decreased for low and mid demand levels by 11.6% and 8.3% and increased for high demand levels by 5.3%.

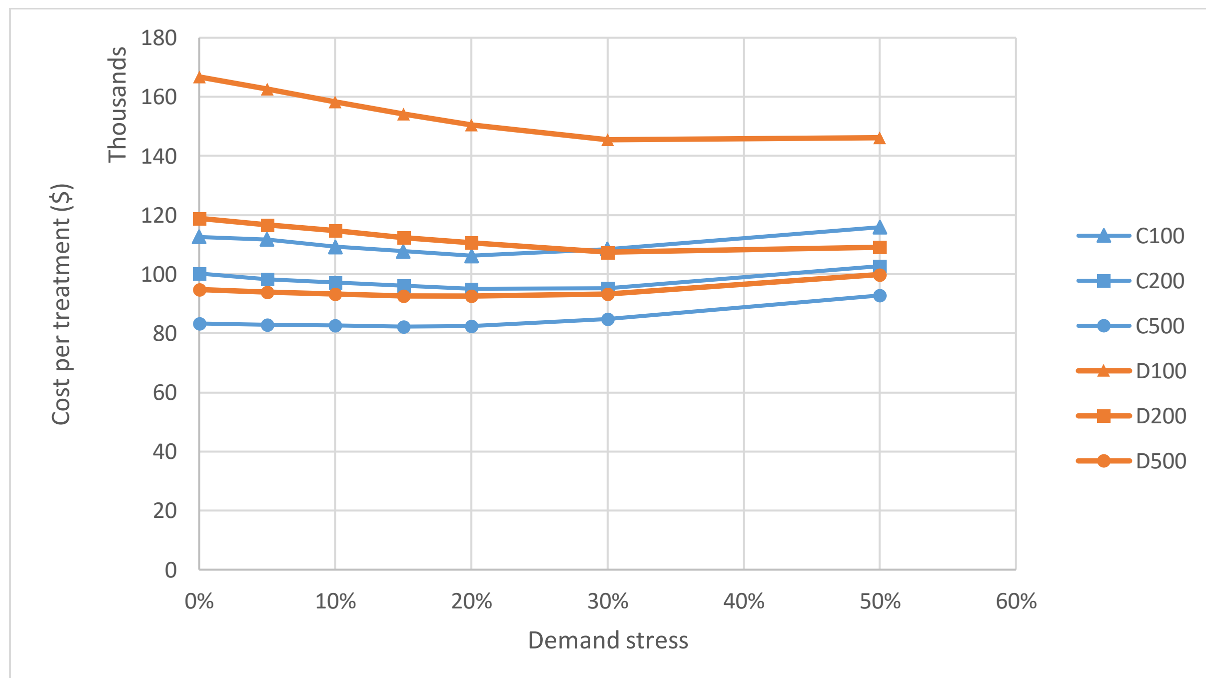


Figure 3.4 Cost per treatment as demand stress increases for centralised (blue) and decentralised (orange) manufacturing. Triangle, square and circle markers correspond to annual demand of 100, 200 and 500 treatments, respectively.

It is shown that when subject to greater demand stress, the difference in the per-treatment cost for decentralised and centralised systems is reduced. This is due to the insufficient manufacturing capacity causing wait queues and resource occupation at the hospitals (Figure 3.5). The turning point corresponds with the resource utilisation and throughput to be discussed in the following section.

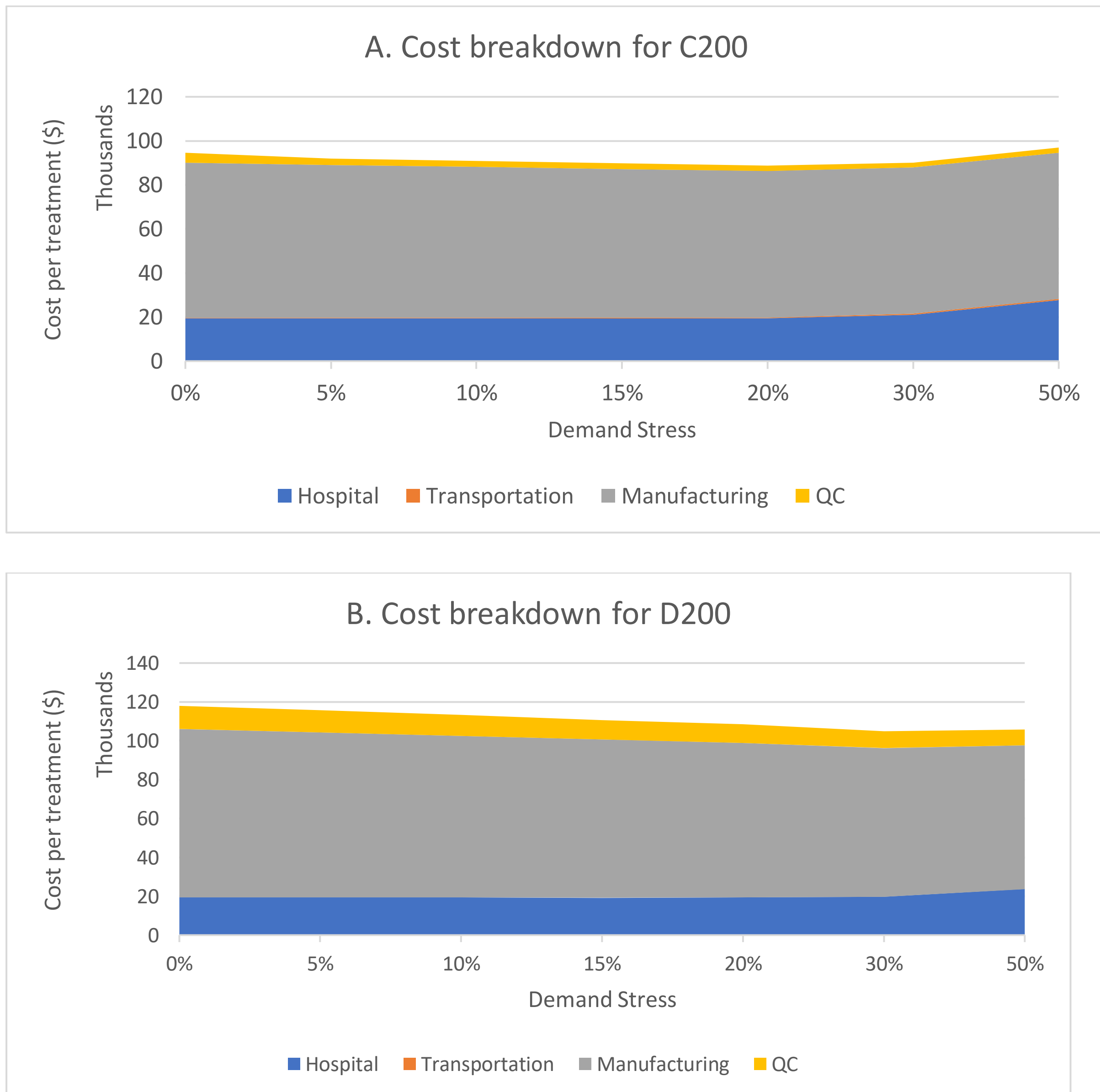


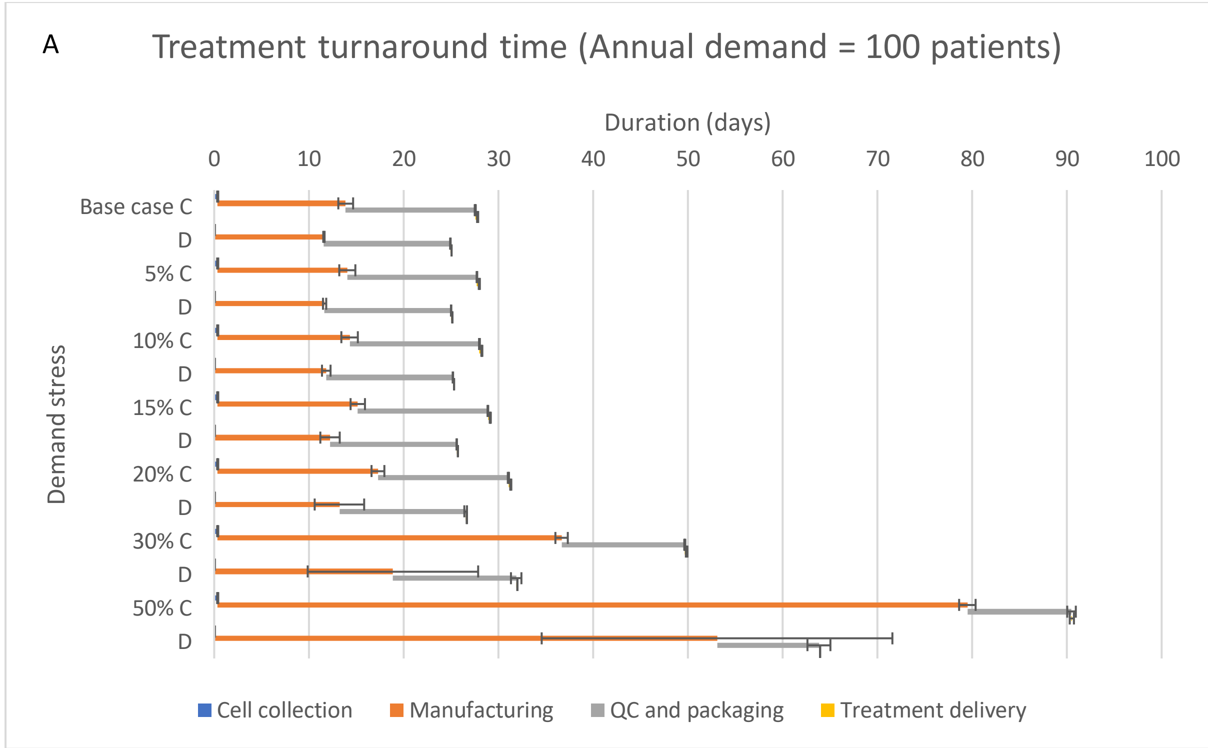
Figure 3.5 Cost breakdown for annual demand 200 patients per year. (A) Centralised; (B) Decentralised

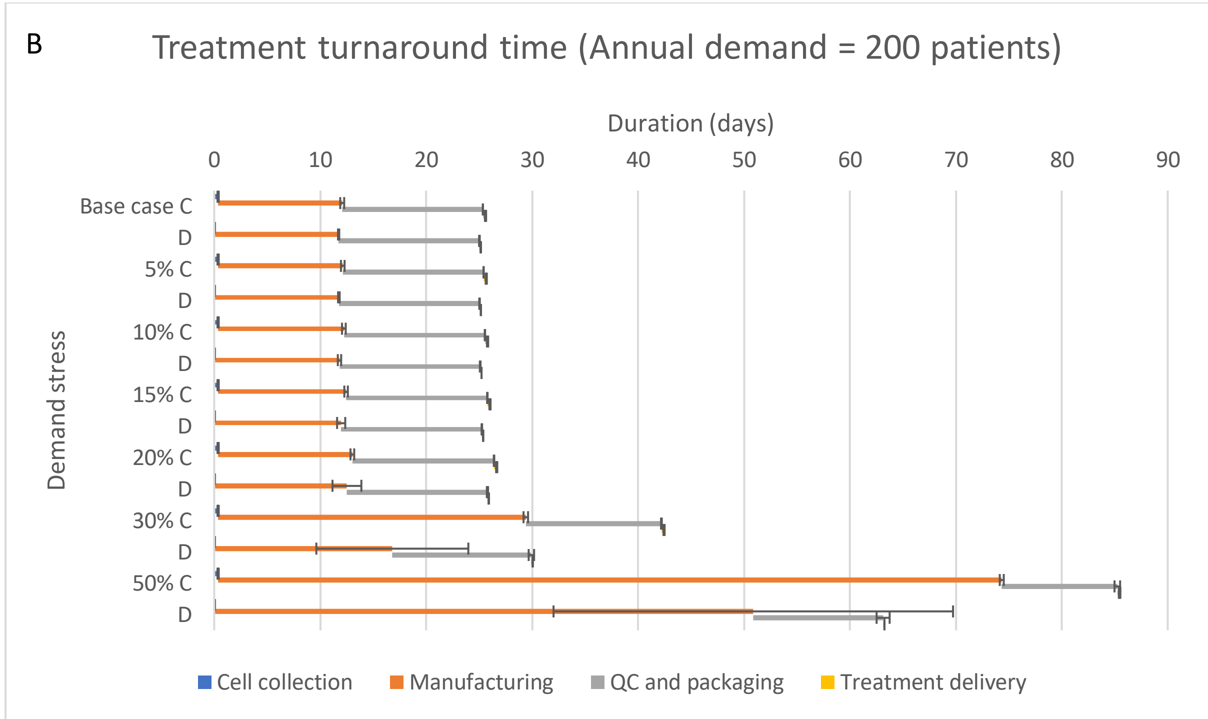
3.3.2.2 Turnaround time per treatment

With the proximity of patients and manufacturing facility, the need for cryopreservation and cold chain transportation in the decentralised setting is reduced and hence the overall duration for decentralised manufacturing is generally shorter than that for centralised manufacturing (Figure 3.6). The duration of around 24-30 days for the entire process from raw material collection to final delivery is consistent with the average time for Gilead's Yescarta (26-29 days) [151].

At high demand stress, whilst the hospitals take a similar amount of time to process each individual patient, the manufacturing facility is unable to cope with the incoming material, which is predicted in the simulation to cause long queues and long waiting times. In reality, hospitals need to liaise with manufacturing facilities to ensure capacity before the cell collection process to ensure that the cells maintain good viability and the patients receive treatments in a timely manner. This also highlights the importance of patient scheduling. Cryopreservation of patient cells is done to allow more flexibility in the collection and delivery scheduling as implemented in this model.

It is also noted, that the decentralised scheme has greater standard deviation values for the manufacturing turnaround time as demand stress increases (Figure 3.6). This is due to the assumption of different hospitals having different numbers of patients coming at various inter-arrival times. With greater demand fluctuations, the manufacturing equipment constraint can cause fluctuations of supply at individual facilities.


A
Treatment turnaround time (Annual demand = 100 patients)
Duration (days)
0
10
20
30
40
50
60
70
80
90
100
Base case C
D
5% C
D
10% C
D
15% C
D
20% C
D
30% C
D
50% C
D
Demand stress
Cell collection
Manufacturing
QC and packaging
Treatment delivery


B
Treatment turnaround time (Annual demand = 200 patients)
Duration (days)
0
10
20
30
40
50
60
70
80
90
Base case C
D
5% C
D
10% C
D
15% C
D
20% C
D
30% C
D
50% C
D
Demand stress
Cell collection
Manufacturing
QC and packaging
Treatment delivery

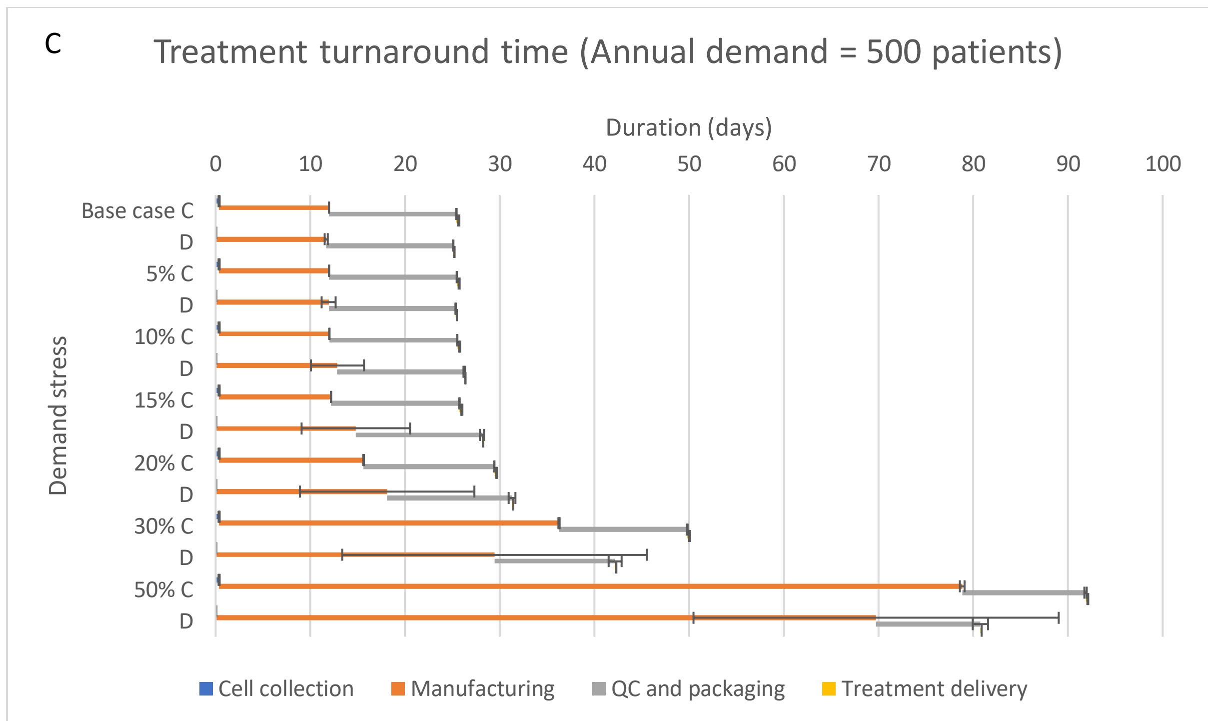


Figure 3.6 Duration breakdown for centralised vs decentralised manufacturing at various annual demands. (A) 100 treatments per year; (B) 200 treatments per year; (C) 500 treatments per year.

3.3.2.3 System Throughput and resource utilisation

For centralised manufacturing, sharing of resources meant the overall manufacturing capacity (number of equipment and shift patterns) can be more tightly designed to meet the particular demand level. Consequently, as shown in Figure 3.7A-F, the centralised scheme can cope with less demand fluctuations. For lower nominal annual demand levels (Figure 3.7A, B), the drop-in system throughput is due to over-utilisation of equipment as demand stress increases from 20% to 30%. For higher nominal demand level (Figure 3.7C), the quality control facilities start to become a constraint and hence the drop in system throughput occurred at lower demand stress (between 10-20%).

For the decentralised scheme, for low demand level (Figure 3.7D, E), the drop in system throughput only occurred between 30-40% while for high demand level (Figure 3.7F), the drop in system throughput occurred much earlier. This is due to the better utilisation of resources at higher demand decentralised scheme as shown in the previous section (Figure 3.3).

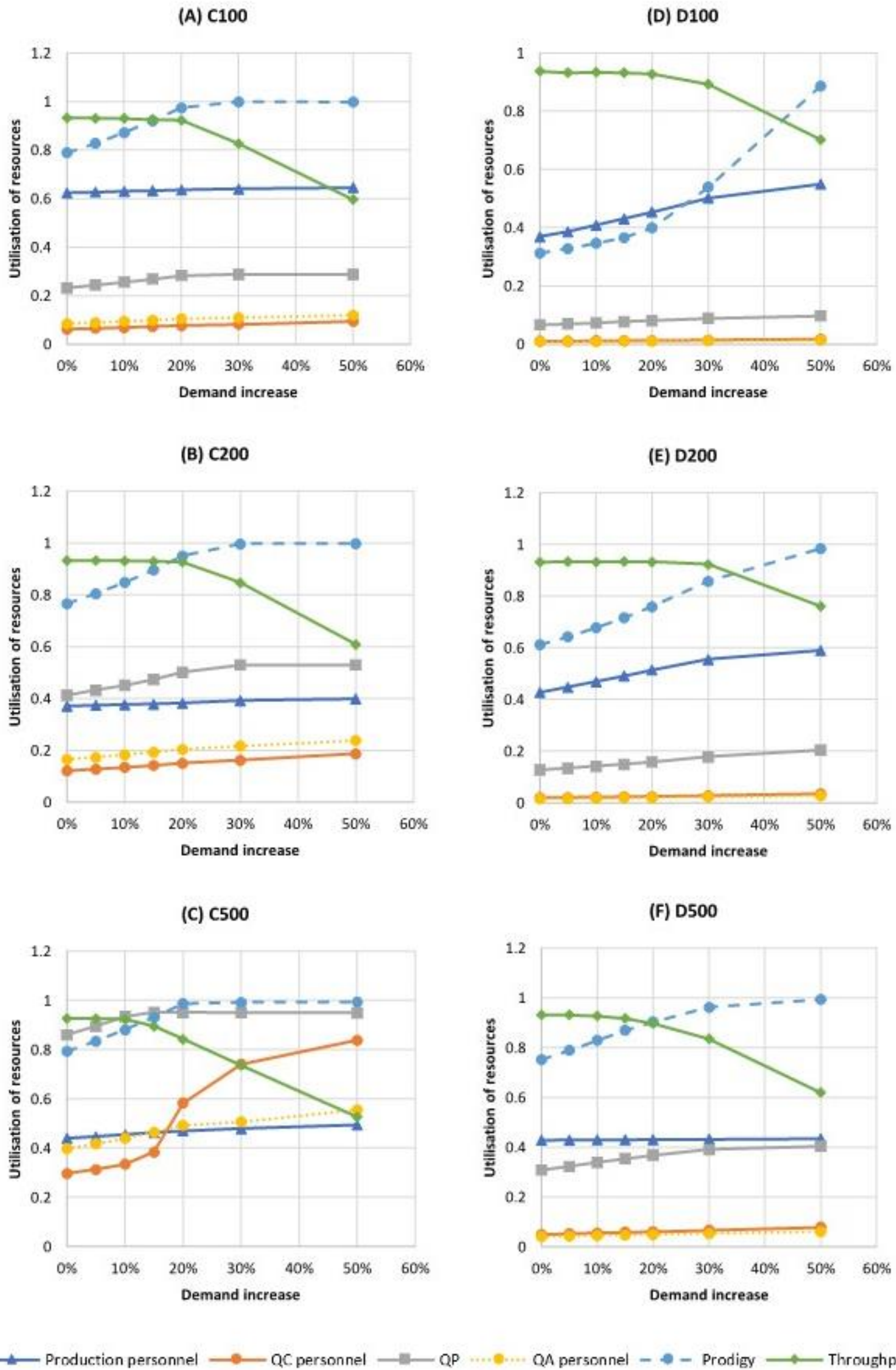


Figure 3.7 Resource utilisation with demand stress. A-C: Centralised manufacturing for annual demand of 100, 200 and 500 treatments per year; D-F: Decentralised manufacturing for annual demand of 100, 200 and 500 treatments per year.

3.4 Discussion

3.4.1 Operational pain points for autologous cell therapy manufacturing

One of the most critical steps in the production of CAR-T therapy is genetic modification and cell processing. In currently active clinical trials registered on clinicaltrials.gov that have reported their gene-editing method, 167 out of 179 trials employ a lentiviral or retroviral vector. The currently approved products Kymriah and Yescarta employ lentiviral and retroviral vectors respectively. In Table 3.5, it is shown that raw material and consumables costs are consistently significant costs, of which the reagents for lentiviral transduction costs account for over one-third of the raw material costs. Improvement in large-scale virus production processes [152], [153] and cheaper CAR-gene insertion technologies such as electroporation and CRISPR/Cas systems can greatly lower the per unit treatment cost. Quality control has shown to be a bottleneck for the delivery time for CAR-T treatments [154], [155]. The current pharmacopoeia requirement for sterility testing takes around 14 days for incubation [156], [157], although regulatory authorities such as US FDA and EMA allow use of sterility test results from 3 days pre-harvest, the QC process still take over 10 days to complete (Figure 3.6).

Currently approved CAR-T products are cryopreserved for improved flexibility in scheduling, shipping delays [116]. However, as CAR-T products consist of live cells, the quality of the product (viability of cells) may be compromised while being refrigerated or cryopreserved where the freeze-thaw cycle have quality implications on the cells [158]. A point-of-care manufacturing approach allows better access to patients and less logistics delays and can thus allow fresh and better quality products to be used on patients [159].

Under circumstances where the benefits of providing a treatment that has not been fully tested outweighs the risks, it may be possible for the product to be used before completion

of sterility testing. Under such circumstances, the rationale should be detailed in the risk assessment and strategies to assure sterility such as testing of media or intermediate products should be considered [126]. Innovation in shortening the sterility testing turnaround time has shown promising results, reducing the length of test to 2 days [160].

Due to the autologous nature of CAR-T therapies, there are multiple handover points where mix-ups can occur. From the simulation results, due to the limited number of total treatments, the effect of mix-ups (estimated based on blood bag mix-up probabilities [149]) was shown to be minimal. In reality, regulatory authorities impose strict track-and-tracing requirements to ensure full proof of chain of identity [126]. On top of this, sensitive patient data is subject to HIPAA (US) or GDPR (EU) regulations [161]. Streamlining data management and proper handling of patient data have proven to be a challenge in CAR-T delivery [162].

The QC bottleneck has led to various discussions over the possibility of release by exception. Release by exception means to release a product automatically if the production process had no deviations from the characterised and documented manufacturing process [163]. This can potentially shorten the turnaround time of autologous cell therapies by over 50%. To facilitate release by exception, better in-process sensors by capturing the critical process parameters are required and other in-process testing methods such as Raman spectroscopy for monitoring molecular profiles and cell microenvironment will be of great importance [164].

3.4.2 Operational pain points for decentralised manufacturing

This hypothetical case study serves to understand whether there is a case for point-of-care manufacturing of CAR-T products within the UK.

Due to the niche indications and low demand levels, the general utilisation rates of facilities can be low as shown in the D100 scenario where resources were under-utilised and

hence the per treatment cost was very high. Moreover, quality control testing equipment costs are shared amongst a very small number of treatments, making the system economically not viable.

At higher demand levels, decentralised manufacturing proved more and more cost competitive as shown in Table 3.5. The difference in resource utilization between the centralised and decentralised scenario reduce as demand increases, allowing equipment and personnel to be better utilised at local facility levels (Figure 3.3). As shown by the greater standard deviation in treatment turnaround time for the decentralised scenario (Figure 3.6), better scheduling of patient demand at hospitals and hence job dispatching can allow more efficient resource and equipment investment and utilisation within each decentralised facility. At lower demand levels for the decentralised manufacturing scheme, each hospital only has one integrated processing platform (Miltenyi Prodigy), hence equipment failure can have a greater impact on manufacturing. However, it is noted that the common practice for equipment maintenance in GMP setting for direct system impact equipment is to have a 24-hour service replacement contract in place. The replacement equipment will have to go through the installation and operational qualification (IQ/OQ) and a deviation report for equipment change should be raised. Subject to risk assessment of individual facilities, they may need additional performance validation prior to being used.

In this case study, the end-to-end process is assumed to be completed in the United Kingdom. Harrison et al looked at the impact of offshore manufacturing, including the evaluation of resource cost discrepancies [165]. It is also important to note that import and export processes across borders can add to the time required for the overall treatment. Extra personnel work hours may have to be allocated to preparing associated paperwork for Human Tissue Act compliance (for equivalent in other countries) [166]. Such extensions could well

alter the comparison between the centralised and decentralised schemes. In addition, extra costs incurred due to transhipment are not considered.

3.4.3 Merits of decentralised manufacturing

Within the UK, as transportation networks are well established, the effect of decentralisation has a relatively low impact on the overall turnaround time of treatments (Figure 3.6). However, when looking at regional centres where cell products may have to go through import and export procedures and airfreight, the impact of transportation, transhipment, and associated costs with maintaining the ultra-cold chain during transportation will be more apparent.

If autologous CAR-T treatments are approved for less niche indications such as solid tumours [167], the overall demand level for autologous treatments will be increased greatly. The effect of having greater flexibility and communication between the hospital and facility was not simulated in this study but was previously cited as one of the key merits of the decentralised paradigm [168]. As there is no need for freezing and thawing for products produced at the point-of-care, this can allow better quality product, better communication between patient’s medical team and the manufacturer and an overall more streamlined treatment experience.

3.4.4 Using discrete event simulation for comparing centralised and decentralised manufacturing

As shown in this study, discrete event simulation combined with scenario analysis allows the granularity of resource allocation to be studied. It could be particularly useful in planning parallel GMP production activities and understanding the production personnel requirement for optimisation.

Scenario analysis allowed the study of various input variables for process optimisation for finding the process pain points and bottlenecks. Another interesting scenario is the cost of underutilisation. Underutilisation suggests overestimation of demand, misplaced investments and higher cost of goods per treatment. However, underutilisation was not considered in this study since the cases were designed per base case demand benchmarked against the demand-side (NHS) estimate).

3.4.5 Limitations

This article provides insights on the operational pain points of centralised and decentralised manufacturing paradigms using closed, automated equipment to tightly control the manufacturing process and ensure comparability across facilities. Product quality impacts introduced in cell collection, freeze-thaw cycle of raw material and the reduced need of transportation are considered to a certain extent in the turnaround time attribute, which however is not able to capture all important aspects of production quality in this operation simulation model.

The per treatment cost ($C_{treatment}$) can be overestimated as cost of treatments that are still being processed at the cut-off time of one year are included in the total cost (Eq 3.11). The ramp-up period was considered relatively insignificance over the simulation duration of a year in this work and therefore not modelled specially. However, consideration of this period can become important for shorter simulations.

As cost data for commercialised products are not publicly available, the model could not be validated with real world data. However, the results were benchmarked with other published models and have shown comparable results.

3.5 Conclusions

This article employed discrete event simulation to investigate and compare operational issues of centralised and decentralised manufacturing of autologous CAR-T therapies. As shown by the simulation, centralised manufacturing is a preferred option for lower demand levels (annual demand of 100-200 patients per year) due to better utilisation of resources which in turn provides cost savings. However, as the anticipated demand increases, the per-treatment cost between centralised and decentralised schemes converges, and the decentralised model becomes more comparable cost-wise. The decentralised model shows greater demand stress resilience and, as the demand level increases, resource utilisation improves within individual facilities and provides opportunity for economies of scale. Quality control lies on the critical path for both centralised and decentralised schemes, more investigation in the potential of release by exception based on risk-benefit assessment should be conducted to shorten the time needed for testing.

Considering both cost and treatment turnaround time, point-of-care manufacturing does not show great advantages over centralised manufacturing due to the relative short amount of time for product transportation required within the country. However, further studies on cross-border product manufacturing and treatment delivery may show greater promise for decentralised manufacturing.

Appendix 3.1 Distribution of treatment centres in the United Kingdom

Name	Type	Location	
		x-coordinate	y-coordinate
Catapult Cell and Gene Therepy	Manufacturing centre	-0.200701298	51.8851217
Great Ormond Street Hospital	Treatment centre	-0.1207462	51.5218626
University College London Hospital	Treatment centre	-0.1229515	51.5219385
King's College Hospital	Treatment centre	-0.0943969	51.4679288
University Hospitals Bristol NHS Foundation Trust	Treatment centre	-2.5944794	51.4599695
The Christie NHS Foundation Trust	Treatment centre	-2.2304081	53.4299659
Royal Manchester Children's Hospital	Treatment centre	-2.2249666	53.4601835
Manchester Royal Infirmary	Treatment centre	-2.2261188	53.462879
Queen Elizabeth Hospital	Treatment centre	-1.944448	52.450565
Great North Children's Hospital	Treatment centre	-1.6179465	54.979611
Newcastle Freeman Hospital	Treatment centre	-1.5929456	55.0030284

Appendix 3.2: Cost and production duration data

2a. Cost data in USD

$$Cost\ per\ year = Capital\ cost * depreciation\ factor$$

Resource type	**Resource Name**	**Cost per year**	**Cost per hour**	**Cost per use**	**Cost per day**	**Cost per item**
Consumables	Liquid nitrogen			10		
Consumables	Liquid nitrogen		0.5			
Consumables	Sepax consumables kit			100		
Consumables	Mycoplasma detection kit					31.55
Consumables	Clinimacs reagent					2156.76
Consumables	Leukapheresis kit					2000
Consumables	Expansion media				28	
Consumables	Transduction kit					627.9
Consumables	T-cell activation kit					2156.76
Consumables	Prodigy kit					3179
Consumables	Aseptic gowning					7.5
Equipment	Shipping container	63.5				
Equipment	Sepax	5000				
Equipment	Clinimacs Prodigy	20000				
Equipment	Barcode reader	120				
Equipment	Peltier block	180				
Equipment	Microscope	1100				
Equipment	Vi-cell	6550				
Equipment	Flow cytometer	6550				
Equipment	PCR	5898				
Equipment	ELISA plate reader	5000				
Equipment	Isolator-2 glove	23834				
Equipment	Incubator	2300				
Equipment	Endosafe	1214.5				
Equipment	BacT-alert	3250				
Equipment	Refridgerator	720				
Equipment	Barcode reader	120				
Equipment	Freezer (-20)	720				
Equipment	freezer (-80)	720				
Equipment	Peltier block	180				
Equipment	Isolator-2 glove	23834				

Equipment	CRF (facility)	1600				
Equipment	Cryogenic freezer	3000				
Equipment	Autoclave	28000				
Facility	Annual revalidation	25000				
Facility	Utility cost (per m^2)		0.00588			
Facility	EMS – handheld portable particle counter	300				
Facility	EMS – annual calibration and maintenance cost	5000				
Hospital	Operation theatre cost		1562.03			
Hospital	Emergency and intensive care		125			
Hospital	Lymphodepletion jabs			1562.03		
Personnel	Nurses		30.24			
Personnel	Chief surgeon		167.92			
Personnel	Pharmacist		33.3			
Personnel	Logistics technicians		25			
Personnel	Clinical support worker		28.64			
Personnel	QC personnel	35000				
Personnel	Production personnel	35000				
Personnel	QP	80000				
Personnel	QA personnel	35000				
Transport	Transportation cost		20			

Facility EMS assumptions

The cost of facility environmental monitoring system is dependent on the type of data monitored, number of equipment requiring temperature monitoring (e.g. incubator, fridges), humidity monitoring, pressure and particle monitoring.

As the process modelled is a closed automated system, it is assumed that only temperature and pressure monitoring is required for the Grade D cleanroom. A portable particle sensor is used for monitoring particle count within the Grade D rooms.

An example quote for an EMS system with software, validation documents and system commissioning for a Grade D room with room sensors (temperature and pressure) and temperature sensors for the following 11 equipment is £13,000/$16,000 (provided by Pharmagraph (United Kingdom)) and an installation cost of £2,000/$2,500:

2 x incubators

2 x Fridges

2 x -20 Freezers

2 x -80 Freezers

1 x Controlled rate freezer

2 x Cryofreezer

Ongoing calibration and maintenance cost contract would be around £4,000/$5000 per year. As a rough guide, the "0.6 rule" usually used for production processes scale economies is applied for scaling up the EMS system[169]:

$$EMS\ Capital\ cost = 18500 * (\frac{\#\ of\ equipment}{11})^{0.6}$$

2b. Process duration data

Location	Activity	Value	Unit
Hospital	Leukapheresis	30	minutes
Hospital	Documentation of collected cells	Tr(20,30,45)	minutes
Hospital	Controlled rate freezing of collected cells	Tr(4,5,6)	hours
Hospital	Lymphodepleting therapy (prep)	10	minutes
Hospital	Lymphodepleting therapy (Day 1)	Tr(1,1.5,2)	hours
Hospital	Lymphodepleting therapy (Day 2)	Tr(1,1.5,2)	hours
Hospital	Lymphodepleting therapy (Day 3)	Tr(1,1.5,2)	hours
Hospital	Lymphodepleting therapy (Day 4)	Tr(1,1.5,2)	hours
Hospital	Product preparation before transplant	Tr(1,1.5,2)	hours
Hospital	Transplant	Tr(1,1.5,2)	hours
Transportation	Transportation	(Dependent on location)	hours
Manufacturing	Visual inspection	Tr(0.1,0.2,0.5)	hours
Manufacturing	Batch record creation	Tr(0.1,0.2,0.5)	hours
Manufacturing	Patient cell sample prep	Tr(0.1,0.2,0.5)	hours
Manufacturing	Patient cell thaw	Tr(0.5,0.75,1)	hours
Prodigy	Prodigy set up	30	minutes
Prodigy	Tubing set priming	30	minutes
Prodigy	Sample and reagent prep for Prodigy	30	minutes
Prodigy	T cell selection	Tr(1.5,2,2.5)	hours
Prodigy	Activation (program)	20	minutes
Prodigy	T cell activation	Tr(0.5,0.75,1)	days
Prodigy	Transduction (program)	10	minutes
Prodigy	Transduction	Tr(0.9,1,1.1)	days
Prodigy	Sampling post-transduction	Tr(0.2,0.35,0.5)	hours
Prodigy	Expansion check	10	minutes
Prodigy	Expansion	9	days
Prodigy	Sampling in expansion phase	Tr(0.2,0.35,0.5)	hours

Prodigy	Formulation (program)	15	minutes
Prodigy	Formulation	2	hours
Prodigy	Remove product	15	minutes
Prodigy	Remove kit	15	minutes
Manufacturing	Controlled rate freezing of product (prep)	10	minutes
Manufacturing	CRF of product	Tr(4,5,6)	hours
Manufacturing	Batch record check	Tr(1,2,3)	hours
Manufacturing	QP sign off	Tr(1,2,3)	hours
QC	Virology screening (prep)	Tr(1.5,2,2.5)	hours
QC	Virology screening	Tr(11,12,13)	hours
QC	Virology report documentation	Tr(0.25,0.4,0.5)	hours
QC	Viability, cell count	0.18	hours
QC	Flow cytometry (phenotype)	0.18	hours
QC	Mycoplasma PCR (prep)	Tr(0.4,0.5,0.6)	hours
QC	Mycoplasma PCR	Tr(2,2.5,3)	hours
QC	Mycoplasma PCR (report)	Tr(0.25,0.4,0.5)	hours
QC	ELISA (surface protein testing)	2	hours
QC	Sterilty testing sample prep on agar	Tr(0.3,0.5,0.7)	hours
QC	Sterilty testing (incubator)	Tr(13.9,14,14.1)	days
QC	Sterility testing report	Tr(0.15,0.2,0.25)	hours
QC	Endosafe	Tr(0.4,0.5,0.75)	hours

Appendix 3.3: Definitions of terms introduced in equations

$\mathrm{A}_{\mathrm{CNC}}$	Number of required air changes per hour for CNC cleanroom
A_D	Number of required air changes per hour for Grade D cleanroom
c_{gown}	Cost per aseptic gown ($)
c_{HVAC}	Air change cost per m3 per hour ($)
C_{CNC}	Capital cost per m^2 of CNC clean rooms($)
C_D	Capital cost per m^2 of Grade D clean rooms ($)
$C_{treatment}$	Cost per treatment ($)
d	Depreciation factor (over 10 years)
$D_{m,CNC}$	Depth of manufacturing equipment in CNC areas (m)
$D_{m,D}$	Depth of manufacturing equipment in Grade D areas (m)
$D_{qc,CNC}$	Depth of QC equipment in CNC areas (m)
E	Capital/equipment cost per year ($)
E_h	Total hospital equipment cost ($)
$E_{m,D}$	Total manufacturing equipment in Grade D cleanroom cost ($)
$E_{m,CNC}$	Total manufacturing equipment in CNC cleanroom cost ($)
$E_{qc,CNC}$	Total QC equipment in CNC cleanroom cost ($)
E_t	Total transportation equipment cost ($)
F_H	Facility costs for hospitals per year ($)
F_M	Facility cost for manufacturing per year ($)
F_{QC}	Facility cost for QC per year ($)
$f_{m,CNC}$	Manufacturing floor space Controlled not classified (CNC)
$f_{m,D}$	Manufacturing floor space (Grade D) (m^2)
$f_{qc,CNC}$	QC floor space Controlled not classified (CNC)
g	GMP working space multiplier
h_t	Transportation hours per year (h)
h_m	Height of cleanroom (m)
h_{OT}	Operating theatre cost per hour ($)
H_{OT}	Hours spent in an operating theatre (h)
Lf	Lang factor for cell therapy facilities

L_h	Hospital labour costs per year ($)
$L_{h,nurse}$	Hours worked by nurses per year (h)
h_{nurse}	Hourly rate of nurses ($)
$L_{h,pharmacists}$	Hours worked by pharmacists per year (h)
$h_{pharmacists}$	Hourly rate of pharmacists ($)
$L_{h,doctor}$	Hours worked by doctors per year (h)
h_{doctor}	Hourly rate of doctors ($)
$L_{h,support}$	Hours worked by support staff per year (h)
$h_{support}$	Hourly rate of support staff ($)
L_t	Transportation labour cost per year ($)
L_{lt}	Hours worked by logistics technician per year (h)
h_{lt}	Hourly rate of logistics technician ($)
L_m	Manufacturing labour costs per year ($)
L_p	Annual salary of production personnel ($)
L_{QC}	Annual salary of QC personnel ($)
L_{QA}	Annual salary of QA personnel ($)
L_{QP}	Annual salary of QP ($)
M	Maintenance costs per year ($)
M_m	Maintenance costs for manufacturing per year ($)
M_{qc}	Maintenance costs for QC ($)
ms	Maintenance and service rate
$n_{m,D}$	Number of equipment for manufacturing in Grade D areas
$n_{m,CNC}$	Number of equipment for manufacturing in CNC areas
$n_{qc,CNC}$	Number of equipment for quality control in CNC areas
R	Raw material costs per year ($)
R_h	Raw material cost for processes in hospital per year ($)
$R_{m,D}$	Raw material cost for manufacturing processes in Grade D cleanroom per year ($)
$R_{m,CNC}$	Raw material cost for manufacturing processes in CNC cleanroom per year ($)

$R_{qc,CNC}$	Raw material cost for QC processes in CNC cleanroom per year ($)
R_t	Raw material cost for transportation per year ($)
s_p	Number of shifts of production personnel per day
s_{QC}	Number of shifts of QC personnel per day
s_{QA}	Number of shifts of QA personnel per day
s_{QP}	Number of shifts of QP per day
TR	Transportation cost per year ($)
TR_t	Transportation cost per hour ($)
TC	Total cost ($)
$T_{treatment}$	Total number of treatment
v	Annual revalidation cost (HEPA recertification) ($)
$W_{m,CNC}$	Width of manufacturing equipment in CNC areas (m)
$W_{m,D}$	Width of manufacturing equipment in Grade D areas (m)
$W_{qc,CNC}$	Width of QC equipment in CNC areas (m)

Appendix 3.4: Patient arrival schedule Triangular distribution of number of days in between patient arrival

4a. Annual demand of 100 patients

Hospital	1			2			3			4			5		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	20.0	48.0	32.0	30.0	50.0	44.0	24.0	40.0	36.0	20.0	40.0	30.0	30.0	80.0	48.0
5%	19.0	45.6	30.4	28.5	47.5	41.8	22.8	38.0	34.2	19.0	38.0	28.5	28.5	76.0	45.6
10%	18.0	43.2	28.8	27.0	45.0	39.6	21.6	36.0	32.4	18.0	36.0	27.0	27.0	72.0	43.2
15%	17.0	41.0	27.2	25.5	42.5	37.4	20.4	34.0	30.6	17.0	34.0	25.5	25.5	68.0	40.8
20%	16.0	38.4	25.6	24.0	40.0	35.2	19.2	32.0	28.8	16.0	32.0	24.0	24.0	64.0	38.4
30%	14.0	33.6	22.4	21.0	35.0	30.8	16.8	28.0	25.2	14.0	28.0	21.0	21.0	56.0	33.6
50%	10.0	24.0	16.0	15.0	25.0	22.0	12.0	20.0	18.0	10.0	20.0	15.0	15.0	40.0	24.0

Hospital	6			7			8			9			10		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	30.0	46.0	38.0	30.0	48.0	40.0	24.0	54.0	42.0	20.0	50.0	26.0	20.0	52.0	40.0
5%	28.5	43.7	36.1	28.5	45.6	38.0	22.8	51.3	39.9	19.0	47.5	24.7	19.0	49.4	38.0
10%	27.0	41.4	34.2	27.0	43.2	36.0	21.6	48.6	37.8	18.0	45.0	23.4	18.0	46.8	36.0
15%	25.5	39.1	32.3	25.5	40.8	34.0	20.4	45.9	35.7	17.0	42.5	22.1	17.0	44.2	34.0
20%	24.0	36.8	30.4	24.0	38.4	32.0	19.2	43.2	33.6	16.0	40.0	20.8	16.0	41.6	32.0
30%	21.0	32.2	26.6	21.0	33.6	28.0	16.8	37.8	29.4	14.0	35.0	18.2	14.0	36.4	28.0
50%	15.0	23.0	19.0	15.0	24.0	20.0	12.0	27.0	21.0	10.0	25.0	13.0	10.0	26.0	20.0

4b. Annual demand of 200 patients

Hospital	1			2			3			4			5		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	10.0	24.0	16.0	15.0	25.0	22.0	12.0	20.0	18.0	10.0	20.0	15.0	15.0	40.0	24.0
5%	9.5	22.8	15.2	14.3	23.8	20.9	11.4	19.0	17.1	9.5	19.0	14.3	14.3	38.0	22.8
10%	9.0	21.6	14.4	13.5	22.5	19.8	10.8	18.0	16.2	9.0	18.0	13.5	13.5	36.0	21.6
15%	8.5	20.4	13.6	12.8	21.3	18.7	10.2	17.0	15.3	8.5	17.0	12.8	12.8	34.0	20.4
20%	8.0	19.2	12.8	12.0	20.0	17.6	9.6	16.0	14.4	8.0	16.0	12.0	12.0	32.0	19.2
30%	7.0	16.8	11.2	10.5	17.5	15.4	8.4	14.0	12.6	7.0	14.0	10.5	10.5	28.0	16.8
50%	5.0	12.0	8.0	7.5	12.5	11.0	6.0	10.0	9.0	5.0	10.0	7.5	7.5	20.0	12.0

Hospital	6			7			8			9			10		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	15.0	23.0	19.0	15.0	24.0	20.0	12.0	27.0	21.0	10.0	25.0	13.0	10.0	26.0	20.0
5%	14.3	21.9	18.1	14.3	22.8	19.0	11.4	25.7	20.0	9.5	23.8	12.4	9.5	24.7	19.0
10%	13.5	20.7	17.1	13.5	21.6	18.0	10.8	24.3	18.9	9.0	22.5	11.7	9.0	23.4	18.0
15%	12.8	19.6	16.2	12.8	20.4	17.0	10.2	23.0	17.9	8.5	21.3	11.1	8.5	22.1	17.0
20%	12.0	18.4	15.2	12.0	19.2	16.0	9.6	21.6	16.8	8.0	20.0	10.4	8.0	20.8	16.0
30%	10.5	16.1	13.3	10.5	16.8	14.0	8.4	18.9	14.7	7.0	17.5	9.1	7.0	18.2	14.0
50%	7.5	11.5	9.5	7.5	12.0	10.0	6.0	13.5	10.5	5.0	12.5	6.5	5.0	13.0	10.0

4c. Annual demand of 500 patients

Hospital	1			2			3			4			5		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	4.0	9.6	6.4	6.0	10.0	8.8	4.8	8.0	7.2	4.0	8.0	6.0	6.0	16.0	9.6
5%	3.8	9.1	6.1	5.7	9.5	8.4	4.6	7.6	6.8	3.8	7.6	5.7	5.7	15.2	9.1
10%	3.6	8.6	5.8	5.4	9.0	7.9	4.3	7.2	6.5	3.6	7.2	5.4	5.4	14.4	8.6
15%	3.4	8.2	5.4	5.1	8.5	7.5	4.1	6.8	6.1	3.4	6.8	5.1	5.1	13.6	8.2
20%	3.2	7.7	5.1	4.8	8.0	7.0	3.8	6.4	5.8	3.2	6.4	4.8	4.8	12.8	7.7
30%	2.8	6.7	4.5	4.2	7.0	6.2	3.4	5.6	5.0	2.8	5.6	4.2	4.2	11.2	6.7
50%	2.0	4.8	3.2	3.0	5.0	4.4	2.4	4.0	3.6	2.0	4.0	3.0	3.0	8.0	4.8

Hospital	6			7			8			9			10		
Triangular Distribution	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely	min	max	Most likely
Base Case	6.0	9.2	7.6	6.0	9.6	8.0	4.8	10.8	8.4	4.0	10.0	5.2	4.0	10.4	8.0
5%	5.7	8.7	7.2	5.7	9.1	7.6	4.6	10.3	8.0	3.8	9.5	4.9	3.8	9.9	7.6
10%	5.4	8.3	6.8	5.4	8.6	7.2	4.3	9.7	7.6	3.6	9.0	4.7	3.6	9.4	7.2
15%	5.1	7.8	6.5	5.1	8.2	6.8	4.1	9.2	7.1	3.4	8.5	4.4	3.4	8.8	6.8
20%	4.8	7.4	6.1	4.8	7.7	6.4	3.8	8.6	6.7	3.2	8.0	4.2	3.2	8.3	6.4
30%	4.2	6.4	5.3	4.2	6.7	5.6	3.4	7.6	5.9	2.8	7.0	3.6	2.8	7.3	5.6
50%	3.0	4.6	3.8	3.0	4.8	4.0	2.4	5.4	4.2	2.0	5.0	2.6	2.0	5.2	4.0

Chapter 4 Capacity planning and product portfolio optimisation

This chapter presents the submitted article:

Lam C, Meinert E, Yang A, Cui Z. Impact of fast-track regulatory designations on strategic commercialisation decisions for autologous cell therapies. *Regenerative medicine* (submitted)

Among all authors who contributed to the article, CL conceived, designed and implemented the model and wrote the manuscript. EM, AY and ZC supervised the study and revised the manuscript.

Summary

Moving up a level from operational decisions, this chapter looks into the tactical decisions of capacity planning and portfolio management with a detailed look at the impact of regulatory designations relevant to autologous cell therapies for unmet medical needs.

Autologous cell therapies come with unique commercialisation challenges associated with high cost of goods, stringent product transport requirements, difficult coordination between hospitals and facilities and limited product shelf-life. To ensure adequate manufacturing capacity is available to meet the growing demands of autologous cell therapies, appropriate decisions are required on capital investment and strategic product and process development. As more and more autologous cell therapies are being approved to treat indications with unmet medical needs, regulatory authorities around the world have introduced fast-track regulatory programs such as Breakthrough Therapy Designation in the United States and PRIME Designation in the European Union. The introduction of fast-track regulatory programs has increased significantly the speed-to-market of cellular therapeutic products.

This chapter describes an optimisation methodology with a mixed-integer linear programming (MILP) model formulation for selecting the timing, location and scale for facility investment. This is in concurrence with product portfolio selection, with the objective to maximise the net present value (NPV) of candidate autologous cell therapies in a specific geographical setting under different regulatory programs.

Applying the model to the UK, an illustrative example was used to understand the impact of fast-track designations on commercialisation of autologous cell therapies. The study shows that fast track designations can allow a 25% earlier breakeven and 42-86% higher NPV over a 20-year time horizon depending on the upfront investment funding availability. However, upfront investments are required 2.5 years earlier. These designations can also reduce the sensitivity of the portfolio to selling price, manufacturing costs and demand fluctuations, highlighting the opportunities in commercialising autologous cell therapies in the current regulatory environment.

4.1 Introduction

Autologous cell therapies are a unique class of products where tissues/cell originate from the patient and are returned to the patient for therapeutic purposes. A previously published study examined three autologous interventions (Epicel, Provenge and Carticel) and summarised the premarket and post-market challenges of commercialising cell therapies, citing unclear regulatory environment and long developmental timelines as the main premarket challenges and manufacturing and supply chain challenges as two key post-market challenges [170]. More specifically, these challenges are manifested in three aspects.

Firstly, as the products are living cells, they are very sensitive to environmental changes and therefore to ensure safety and quality of the product, cold or ultra-cold supply chain has to be considered. Distribution logistics can have a massive impact on the formulation of the product and has to be considered early in the product development cycle [171]. The unique requirement for autologous cell therapy products to be produced on-demand with cell material originating from patients presents new capacity and supply chain complications that have proven to be commercially challenging [23]. Specific to autologous therapies, the geographical constraint and sometimes, trade-off for quality, has led to more interest in decentralised manufacturing [172].

Secondly, managing the cost of goods and marketing cost is a key contributing factor to commercial success. Lipsitz et al have outlined the cost of good (COG) planning roadmap for manufacturing of cell therapies from cell sourcing to patient administration [173]. An interesting challenge faced in the commercialisation of Dendreon, one of the first immunotherapy products for prostate cancer, was the financial implications of substantial upfront investment in specialised GMP production facilities. The lag in treatment adoption and the expensive underutilised facilities caused massive amounts of debts and eventual

market failure [170]. Given the requirement for GMP-compliant facilities to be in place and listed for market authorisation, the lead strategy towards capacity planning (i.e. capacity added in anticipated of increase in demand) can become a huge burden for resource-constrained companies seeking to commercialise cell therapies.

Thirdly, autologous cell therapies are specific to the patient, which means manufacturing cannot be scaled up using larger-scale equipment and has to be scaled out to produce a single batch of therapy per patient. This not only diminishes the effect of traditional economies of scale but also presents risks in mix-ups and cross-contamination [50].

For pharmaceutical product development, process development for manufacturing scale-up and production planning take place alongside clinical trials to prepare for mass production and market roll-out. In drug development, the critical path for new medicinal products proposed by the FDA, manufacturing scale-up and production planning are often only considered in later phases of clinical trials [174]. When applying for market authorisation, the proposed manufacturing sites should be listed and must be GMP-compliant. Setting up GMP-compliant facilities is time-consuming and capital-intensive [175], but for the product to attain maximal economic returns during the market exclusivity period (only 20 years from the filing date of the patent), the GMP-compliant manufacturing capacity has to be available when the product is market-ready, whether through contracting out or building own facilities.

The capacity planning problem has been a long-standing one in the pharmaceutical industry due to the uncertainties around product development, high upfront investment costs and highly regulated industry landscape. These challenges make the optimisation of capacity planning for pharmaceuticals different from other industries such as agrochemicals. Ineffective capacity planning can lead to serious capacity crunches such as that faced by the monoclonal antibody (mAb) industry in the 1990s, which were estimated to have caused

around $3-$4 billion in total revenue loss due to insufficient supply of products [176], [177]. Papageorgiou et al studied the optimisation of investment strategies for product development and introduction of active pharmaceutical ingredient (API) [178] and others have looked into similar problems under uncertain clinical trial outcomes, market pressures and regulations [179]. Liu used a MILP approach to simultaneously optimise the global supply chain for pharmaceuticals considering costs, responsiveness and customer service levels [180]. For biopharmaceutical facility planning, Siganporia et al have formulated a discrete-time MILP model to optimise in-house and contract manufacturing decisions and to study the adoption of fed-batch and continuous perfusion culture processes [33]. More recently, Wang et al studied the CAR-T supply chain to maximise the overall net present value and minimise average response time of patients under demand distribution uncertainties [88]. Simulation studies looking into demand resilience and reagent supplies conducted by Lam et al and Wang et al [89], [181] have discussed the operational challenges for autologous cell therapies. However, these existing models have not addressed the impact of unique regulatory pathways for autologous cell therapies on strategic commercialisation decisions such as timing for capital investment and portfolio considerations.

With the maturation of advanced therapeutic medicinal products (ATMPs) as a drug modality and more and more products moving from bench to market, regulatory authorities around the world have evolved to address to put forward clearer regulatory guidelines and strategies to reduce the developmental timelines. Regulatory authorities around the world have introduced frameworks to allow faster access to these treatments for life-threatening diseases such as blood cancers and genetic disorders [182]–[184]. These policies have been shown to accelerate the commercialisation of ATMPs and have been generally well-accepted and well-adopted (Table 4.1).

With the introduction of accelerated approval processes, the clinical development duration can reduce from 6-7 years (full-fledged phase 1, phase 2, phase 3 clinical trial) to 2-3 years (small scale clinical trials with surrogate end-points) [185], which requires the industrialisation timeline for process development and capacity planning to be managed accordingly. Therefore, the industry needs to re-evaluate the outsourcing and investment strategies for securing manufacturing capacities to benefit fully from accelerated approval.

This study aims to develop a mathematical model for investigating capacity planning decisions to maximise the net present value (NPV) of an autologous cell therapy portfolio. In particular, an illustrative example comparing ‘fast-track’ and standard approval processes is conducted to assess the implications of the former on the timing for capital investment in cell therapy manufacturing facilities, the scale and location of facilities of different scales (smaller decentralised facilities vs larger centralised facilities) and product portfolio.

Table 4.1 Early-access designations in the US, EU, Japan and China

Country / Regulatory body	Regulatory pathway (Year of introduction)	Implication	Qualifying criteria						Example cell/gene therapy product that used this designation
			Serious life-threatening disease	Orphan patient population	Unmet medical need	Superior to existing treatment	Pediatric indications	Regenerative Medicine	
US FDA	Priority review (1992)	Review decision within 6 months $2.7million FDA user fee + $2.4 million usual user fee [186]	√			√			Novartis: Kymriah; Exelixis: Cabometyx; Eisai: Lenvatinib
	Accelerated approval (1992)	Approval based on effect on a predictive surrogate endpoint or an intermediate clinical endpoint [187]	√			√			Pfizer: bosutinib
	Fast track (1998)	Option for rolling NDA/BLA submission [187]	√		√				Renova: RT-100 AC6 gene transfer (Ad5.hAC6); DNAtrix therapeutics: DNX-2401
	Breakthrough therapy (2012)	NDA/BLA data submitted as they are accumulated (rolling review); Most reviewed in 60 days or less, limited types of submissions require 90 days (FDA) [187]	√			√			Juno & Celgene: JCAR017 Adaptimmune & GSK: NY-ESO-1c259T Bluebird & Celgene: bb2121
	Expedited access pathway (2015)	For de novo requests, determination in less than 120 days; Reduces premarket data requirements [187]	√		√				Avita: Recell
	Orphan drug designation (1983)	Approval in 6 months [187]		√					Atara Bio: ATA129 Astellas Pharmaceuticals: ASP2215

	Rare Pediatric Disease Priority Review (2014)	Sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. [187]	√	√					Enzyvant: RVT-802
	RMAT designation (2017)	Increased meeting opportunities with FDA (like Breakthrough therapy); Priority review (initial assessment of the BLA reduced from 10 months to 6 months) [187]	√		√			√	Kiadis Pharma: ATIR101; Asteria: AST-OPC1
EU EMA	Accelerated assessment (2004) [188]	Reduce review timeframe from 210 days to up to 150 days			√				Alynylam Pharmaceuticals: patisiran
	Orphan drug designation (2000) [188]	Fee reduction; Eligible for conditional marketing authorisation; 10 year market exclusivity	√	√					Edison Pharmaceuticals: EPI-743 Astellas Pharmaceuticals: ASP2215
	Marketing authorization under exceptional circumstances (2005) [188]	Authorization without comprehensive data on efficacy and safety		√					
	Conditional marketing authorization (2006) [188]	Earlier authorization based on less complete clinical data	√	√	√				
	Adaptive pathway (2015) [188]	Scientific advice by authority, compassionate use, conditional approval mechanism		√	√				Atara Bio: ATA129

	PRIME(2016)[188]	Identify potential for accelerated assessment earlier in development; More scientific advice and support; Early rapporteur appointment; Dedicated contact person within EMA.			√				Juno & Celgene: JCAR017 Adaptimmune & GSK: NY-ESO-1c259T Bluebird & Celgene: bb2121
Japan PDMA	Priority review[189]	9 months instead of 12 months	√						Glecaprevir/Pibrentasvir (G/P), AbbVie
	Orphan designation (1993) [189]	Administrative and scientific advices, preferential protocol assistance, grant aid for research expenses, authorization for tax deduction, reduction of application fee, extension of re-examination period		√	√				Edison Pharmaceuticals: EPI-743
	Conditional & Time-limited approval (2014) [189]	Earlier authorization based on less complete clinical data	√		√			√	
	SAKIGAKE Forerunner review assignment (2015)[190]	Eligible for rolling review; Shorten consultation on clinical trials time from 2 months to 1 month; Review time from 12 months to 6 months [191]	√			√			Ono pharmaceutical & Bristol-Myers Squibb: Opdivo; Astellas Pharmaceuticals: ASP2215
China	Accelerated and conditional approval (Draft issued in 2017)[192]	Grant conditional approval for meds that treat life-threatening conditions where significant unmet medical needs exist, if early- or mid-stage data can predict the drugs' clinical benefits; cover orphan meds already approved in foreign countries, even those without any trial data from China.	√	√	√				

4.2 Method

This study considers strategic commercialisation challenges such as product portfolio and capacity planning decisions for autologous cell therapies simultaneously. This section describes the problem and the rationale of modelling and presents the mathematical descriptions.

4.2.1 Problem statement

A holistic approach that simultaneously considers product portfolio, capacity planning and equipment procurement is needed to address the challenges facing the commercial development of autologous cell therapies. The problem is summarised in Table 4.2:

Table 4.2 Summary of model assumptions and outputs

Given:	Determine:
- Set of potential products and the time horizon for planning - Forecasted demand levels at different hospital locations - Forecasted selling price of each product - Manufacturing cost, process duration and equipment requirement of each product - Set of location for hospitals and facilities - Set of facility scale (pilot, small, medium, large) - Two types of facilities (contract, new build) - Construction lead-times and capital investment - Contract negotiation time duration and costs - Fixed cost for facilities and operating cost - Fixed number of equipment available at contract manufacturers - Interest rate	- Set of products selected - Facility investment schedule - Optimal facility location - Optimal facility scale - Optimal engagement of facility type over the time horizon - Equipment procurement schedule for each built facility over the time horizon

The goal is to optimise the expected NPV of a company developing these products.

4.2.2 Model formulation

A multi-period uniform time discretisation mixed-integer linear programming (MILP) problem is formulated with 1-year discretisation intervals. Specific to the nature of autologous cell therapies, some key features include parallel closed automated processing (scale-out manufacturing); total product consumption (product generated from patients return to patients at the same location); location, facility scale (pilot, small, medium, large) and type (contract or newbuild) specific considerations. Previous published models have considered the treatment delivery response time [88] which is an important operational level decision for autologous cell therapies, but this model focusses on strategic decisions on portfolio, capacity planning and investment, paying particular attention on the impacts of regulatory programmes.

The formulation is presented in detail as follows.

4.2.2.1 Notations

Indices

P	Product (*P1, P2, P3, …, Pp*)
m	Product manufacturing process (complex, simple)
f	Location of facility (London, Bristol, Newcastle, Edinburgh)
h	Location of hospital (London, Bristol, Newcastle, Edinburgh)
Ft	Facility type (contract, newbuild)
Fs	Facility scale (pilot, small, medium, large)
t	Time periods (years)

Sets

CP	Set of complex products
SP	Set of simple products
CT	Time periods over which clinical trials occur (years)
Mkt	Time periods over which the product is on market (years)

Parameters

$Dd_{m,t}^{P,h}$	Annual Demand of product *P* at hospital *h* requiring process *m* at year t
CD_t^P	Annual demand for all complex products
SD_t^P	Annual demand for all simple products
$Price_t^P$	Price of product *P* in year *t* (thousand USD), $t \in Mkt$
φ	Funding available (thousand USD)
Facility	
σ_{Fs}	Facility footprint for facility scale *Fs* (m^2)
Inv_{Fs}^f	Investment cost of facility at location *f* and scale *Fs* (thousand USD)
$\tau f_{Ft,Fs}^f$	Set-up time of facility at location *f,* type *Ft,* scale *Fs* (thousand USD)
Ctc_f	Contract cost of engaging contract facility at *f* (thousand USD)
$FC_{Fs,Ft}^f$	Annual facility fixed cost for facility at location *f,* type *Ft,* scale *Fs* (thousand USD)
$\sigma_{support,Fs}$	Footprint of utilities and support equipment (m^2)
$C_{support,Fs}$	Capital Cost of utility equipment (thousand USD)
$\sigma_{core,Fs}$	Footprint of core equipment for facility scale *Fs* (m^2)
$C_{core,Fs}$	Capital cost of Core equipment for facility scale *Fs* (thousand USD)
$\sigma_{QC,Fs}$	Footprint of QC equipment space for facility scale *Fs* (m^2)
$C_{QC,Fs}$	Capital cost of QC equipment for facility scale *Fs* (thousand USD)
$\sigma_{eq,m,Fs}$	Production equipment floor space for process *m* (m^2)
$C_{eq,m,Fs}$	Capital cost of production equipment for process *m* (thousand USD)
$maxps_{Fs}$	Max production space for facility of scale *Fs*
M	Maximum operating days in each time period
$Opcost$	Facility operating cost per square meter per year (thousand USD)
Inv_{Fs}^f	Investment cost of a facility at location f and scale Fs
Cost of goods	
$VCCOG^P$	Manufacturing variable cost of goods of product *P* (thousand USD)
Out_{Ft}	Outsource penalty of facility type *Ft*
Sp_{Fs}	Scale penalty of facility scale *Fs*
Lp_f	Location penalty of facility location *f*

$COG^{P,f}_{Fs,Ft}$	Cost of goods of product *P* at facility location *f*, type *Ft*, scale (thousand USD)
d^{f}_{h}	Distance between facility at *f* and hospital at *h* (in miles)
tc	Transport cost per mile (USD)
tr^{f}_{h}	Transport cost per treatment (USD)
Pt^{P}	Process turnaround time for product *P* (days)
δ_t	Discount factor at year *t*

Variables

FI_t	Investment cost at year *t*
$Ctrt_t$	Contract cost at year *t*
$EqInvCost_t$	Production equipment investment cost at year *t*
$FEqInvCost_t$	Fixed equipment (support, core and QC) investment cost at year *t*
$EqP^{m}_{f,Ft,Fs,t}$	Number of equipment for process *m* purchased for facility at *f* of scale *Fs* at year *t*
$EqNo^{m}_{f,Ft,Fs,t}$	Number of equipment available for process *m* at facility location *f*, type *Ft*, scale *Fs* at year *t*
$EqCapacity^{Complex}_{f,Ft,Fs,t}$	Annual maximum operational days of available complex equipment for producing complex products
$EqCapacity^{Simple}_{f,Ft,Fs,t}$	Maximum operational days of available simple equipment for producing simple products
$Fixop_t$	Fixed operating costs at year *t*
$TrtF^{Complex}_{f,Ft,Fs,t}$	Complex treatments produced at facility location *f*, type *Ft*, scale *Fs* at year *t*
$TrTF^{Simple}_{f,Ft,Fs,t}$	Simple treatments produced at facility location *f*, type *Ft*, scale *Fs* at year *t*
$TrTH^{P}_{h,t}$	Product *P* delivered at hospital *h* in year *t*
TTH^{P}_{t}	Total treatment *P* delivered in all hospitals at year *t*
TTP^{P}_{t}	Total treatment *P* produced in all facilities at year *t*
$\varepsilon^{P}_{f,Ft,Fs,h,t}$	Total treatment *P* delivered at hospital *h* from facility location *f*, type *Ft*, scale *Fs* at year *t*

$Sales_t^P$	Total sales of product *P* at year *t* (in USD)
$Transport_t$	Total transportation cost at year *t* (USD)
$TCOG_t$	Total COG at year *t* (USD)
$TRev_t$	Total revenue at year *t* (USD)
$cflow_t$	Total cashflow at year *t* (USD)
NPV	Net present value over time horizon (USD)

Binary Variables

$Fac_{Ft,Fs,t}^f$	Facility investment decision of facility at location *f*, type *Ft*, scale *Fs* at year *t*
$A_{Ft,Fs,t}^f$	Facility availability at year *t*
V^P	Product selection decision

4.2.2.2 Mathematical descriptions

The cost and constraints equations are organised into facility level, equipment level, product level and capital level with the overall objective to maximize the NPV over the time horizon.

4.2.2.2.1 Facility-level constraints and costing

Facility availability constraint

Contract manufacturing facilities (CMO)

It is assumed that at every location, a pilot-scale CMO facility is available to be engaged at the start of the time horizon for planning. Contracting out manufacturing to CMOs requires no upfront capital investment, but it involves contract negotiations for the price, intellectual property ownership and exclusivity which require significant technical and legal expertise [193]. Hence, an upfront cost for contract negotiation (Ctc_f) is required, as well as a contract negotiation period ($\tau f_{contract,pilot}^f$). The contract facilities are assumed to have a fixed number of equipment for complex and simple processes ($EqNo_{f,contract,pilot,t}^{Ppt}$).

Newbuild facilities

Purpose-built facilities with equipment purchases based on the required processes take a longer time to set up. The time required to set up facilities is represented by $\tau f^{f}_{Ft,Fs}$. A binary variable $A^{f}_{Ft,Fs,t}$, assigned to represent the availability of a facility of type *Ft* and scale *Fs*, is equal to 1 if the facility has been built at location f at year *t*.

$Fac^{f}_{Ft,Fs,t}$, representing facility investment decisions, is set to 1 if the decision to invest has been made at time *t*, but this facility becomes available (and starts to contribute to production output) only after it has been set up completely (Eq *4.1*):

$$A^{f}_{Ft,Fs,t} \leq A^{f}_{Ft,Fs,t-1} + Fac^{f}_{Ft,Fs,t-\tau f^{f}_{Ft,Fs}} \qquad \text{Eq 4.1}$$

Contract facility upfront cost

As explained in Eq *4.1*, if a contract facility is engaged at year *t*, the binary variable $Fac^{f}_{contract,pilot,t}$ is assigned to be 1. An upfront cost of engaging a contract facility will be incurred (once the negotiation is concluded) to account for contract negotiation costs or retainer contract costs (upfront contract cost even if nothing is produced) (Eq *4.2*).

$$Ctrt_t = \sum_{f} Fac^{f}_{contract,Fspilot,t-\tau f^{f}_{contract,pilot}} * Ctc_f \qquad \text{Eq 4.2}$$

Newbuild facility investment cost

The investment cost of a facility at location f and scale Fs is given by Inv^{f}_{Fs}, which includes design and construction costs, basic cleanroom hardware (cleanroom panels), land costs and qualification and validation costs. If the decision of building a facility is made at year *t* (i.e. $Fac^{f}_{newbuild,Fs,t} = 1$), the facility investment cost (FI_t) is given by Eq *4.3*.

$$FI_t = \sum_{f} \sum_{Ft} \sum_{Fs} Fac^{f}_{Ft,Fs,t} * Inv^{f}_{Fs} \qquad \text{Eq 4.3}$$

Fixed facility costs and fixed operating costs

Fixed facility costs include the rental and land cost of the facility ($FC_{Ft,Fs}^{f}$) and the fixed operating costs ($Fixop_t$) are the fixed operating costs of running the heat, ventilation and air-conditioning (HVAC) of the facility (*Eq 4.4*). The fixed operating costs is given by the cost of air changes per m^2 ($Opcost$) multiplied by the footprint of facility (σ_{Fs}) which is scale dependent.

$$Fixop_t = \sum_{f}\sum_{Ft}\sum_{Fs}(A_{Ft,Fs,t}^{f} * (\sigma_{Fs} * Opcost + FC_{Ft,Fs}^{f})) \quad \textit{Eq 4.4}$$

4.2.2.2.2 Equipment-level constraints and costing

Equipment availability constraint

Closed processes are assumed for each facility to allow parallel production of treatments for different patients within the same cleanroom with a Grade C/D background and reduced risks of cross-contamination. Shared space and equipment are assumed within a facility to account for equipment common for all types of processes. A facility is divided into 4 main spaces as shown in the illustrative facility schematic shown in Figure 4.1.

The support footprint ($\sigma_{support,Fs}$) accounts for airlocks between cleanrooms and corridors, changing rooms, waste management, utilities and HVAC areas (heat, ventilation and air conditioning). QC footprint ($\sigma_{QC,Fs}$) accounts for the area required for QC equipment. Core equipment footprint ($\sigma_{core,Fs}$) accounts for the area required for core equipment such as filling lines, incubators and cold storage facilities. These spaces are dependent on the scale of the facility, i.e. the bigger the facility the more support space is required. The remaining space in the facility is given by *Eq 4.5*a and can be used to accommodate production equipment.

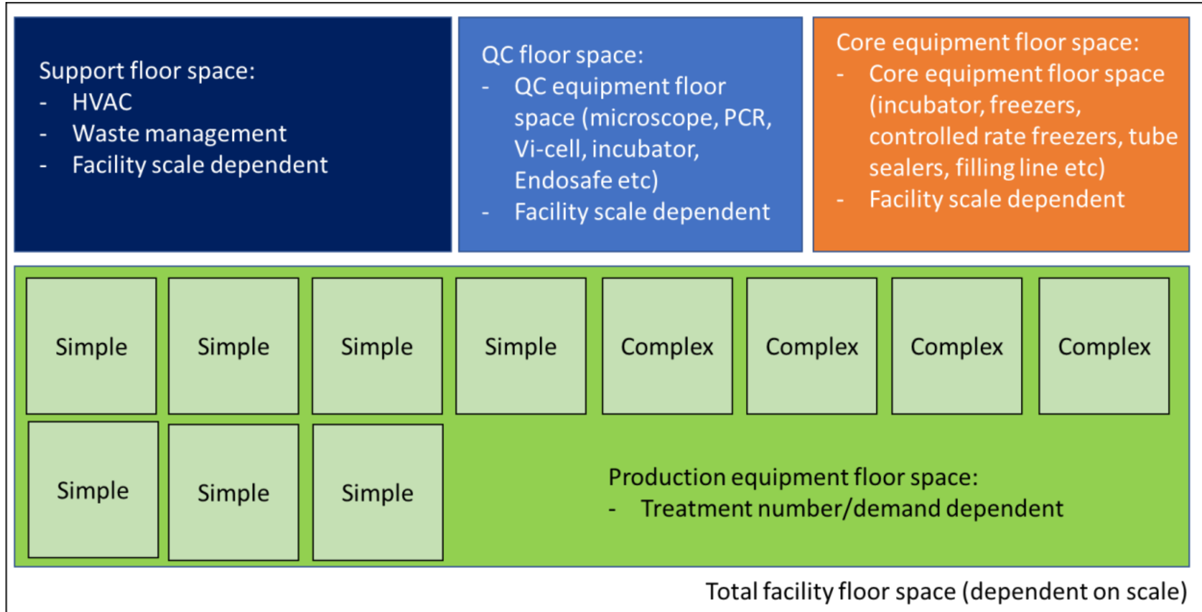


Figure 4.1 Facility floor plan schematic

Production equipment footprint ($\sigma_{eq,m,Fs}$) is dependent on the number of equipment to support the quantity of products P produced using process m. The number of production equipment that can be accommodated in an available facility is constrained by *Eq 4.5*b.

The number of equipment at a given facility is limited by the space available in the chosen scale of the facility. Four facility scales (*Fs*) are considered: pilot, small, medium and large. Within the facility with a footprint of σ_{Fs} depending on scale *Fs*, supporting space, quality control area and core equipment must be present.

$$maxps_{Fs} = \sigma_{Fs} - \sigma_{support,Fs} - \sigma_{core,Fs} - \sigma_{QC,Fs} \qquad \text{Eq 4.5a}$$

$$maxps_{Fs} * A^{f}_{Ft,Fs,t} \geq \sum_{m} (EqNo^{m}_{f,Ft,Fs,t} * \sigma_{eq,m,Fs}) \qquad \text{Eq 4.5b}$$

Equipment available at given year t ($EqNo^{m}_{f,Ft,Fs,t}$) is the number of equipment available in the previous year plus the equipment purchased during the period ($EqP^{m}_{f,Fs,t}$). It is assumed that the equipment purchased the year before will stay in the facility for the lifetime of the facility (*Eq 4.6*) and therefore the equipment purchased must be a positive integer (*Eq 4.7*).

$$EqNo^{m}_{f,newbuild,Fs,t} = EqNo^{m}_{f,newbuild,Fs,t-1} + EqP^{m}_{f,newbuild,Fs,t} \qquad \text{Eq 4.6}$$

$$EqP^{m}_{f,newbuild,Fs,t} \geq 0 \qquad \text{Eq 4.7}$$

Equipment investment cost

Support, core and QC equipment are essential for any product or process and are therefore assumed to be purchased when the investment on a newbuild facility occurs.

Support equipment refers to HVAC, utilities and environmental monitoring system-related equipment, and the capital cost is dependent on facility scale ($C_{support,Fs}$). Core equipment costs ($C_{core,Fs}$) refers to costs of equipment core to all processes such as filling lines, incubators and cold storage facilities (Appendix 4.2 (1)). QC equipment costs ($C_{QC,Fs}$) refers to costs of equipment for product quality control, the list of commonly used are listed in Appendix 4.2 (2). The fixed equipment (support, core and QC) investment cost at year t ($FEqInvCost$) is given by Eq 4.8.

Production equipment can be purchased at any point after the completion of the facility and as demand arises. Therefore, the equipment investment cost at a certain year ($EqInvCost_t$) is given by the number of equipment purchased that year multiplied by the capital cost of the production equipment (Eq 4.9).

$$FEqInvCost_t = \sum_{f} \sum_{Fs} Fac^{f}_{newbuild,Fs,t} * (C_{support,Fs} + C_{core,Fs} + C_{QC,Fs}) \qquad \text{Eq 4.8}$$

$$EqInvCost_t = \sum_{f} \sum_{Fs} \sum_{m} C_{eq,m,Fs} * EqP^{m}_{f,newbuild,Fs,t} \qquad \text{Eq 4.9}$$

4.2.2.2.3 Product-level constraints

Product type and demand

The types of cell therapy products can be generalised into simple and complex, where simple products require a simple process to produce (i.e. expansion process without genetic modifications) and complex products require a complex process to produce (i.e. require

genetic modifications through viral transduction). The annual product demand at each hospital ($Dd_{m,t}^{P,h}$) is assumed to be a known parameter. Only products authorised for market use are allowed to be sold at the expected price ($Price_t^P$); products in clinical trials are not reimbursed and are costed as developmental costs.

Eq 4.10 and *Eq 4.11* aggregate respectively the total demand for each complex (CD_{te}^P) and simple product (SD_{te}^P) across all hospitals at location *h*.

$$CD_t^P = \sum_h Dd_{Complex,t}^{P,h} \qquad Eq\ 4.10$$

$$SD_t^P = \sum_h Dd_{Simple,t}^{P,h} \qquad Eq\ 4.11$$

4.2.2.2.4 Product production and cost of goods

Equipment capacity constraint

The number of products produced cannot exceed the maximum capacity of the facility and its available equipment. Complex products can only be produced using complex equipment (*Eq 4.12*) and simple products can only be produced using simple equipment (*Eq 4.13*).

$$\sum_P TrtF_{f,Ft,Fs,t}^{Complex} * Pt_P \leq EqNo_{f,Ft,Fs,t}^{Complex} * M \qquad \forall\ P \in CP \qquad Eq\ 4.12$$

$$\sum_P TrtF_{f,Ft,Fs,t}^{Simple} * Pt_P \leq EqNo_{f,Ft,Fs,t}^{Simple} * M \qquad \forall\ P \in SP \qquad Eq\ 4.13$$

The variable cost of good ($VCCOG^P$) is the total fundamental cost of producing each treatment, including the raw material, consumable, labour costs. A penalty cost multiplier is introduced to consider economies of scale, outsource and location penalties on the variable cost of good ($VCCOG^P$).

Whilst scale-out manufacturing is a more common approach for autologous cell therapies, better utilization of human resources and equipment allows a certain degree of

economies of scale[50]. Therefore, a scale penalty (Sp_{Fs}) is used to account for scale-related cost savings. The scale penalty is benchmarked against findings from Chapter 3.

For outsourcing, successful contract manufacturers generally operate at 20-30% profit margins[194], hence an outsource penalty cost multiplier (Out_{Ft}) is used to simulate the additional costs incurred. A location penalty multiplier (Lp_f) is used to account for areas where the costs of labour is more expensive, e.g. London.

$COG_{Fs,Ft}^{P,f}$ refers to the cost per treatment of product P at facility F of type Ft and scale Fs and this is computed using Eq 4.14.

$$COG_{Fs,Ft}^{P,f} = VCCOG^{P} * Out_{Ft} * Sp_{Fs} * Lp_f \qquad \textit{Eq 4.14}$$

4.2.2.2.5 Complete product consumption constraint

As a feature of autologous cell therapies, all products manufactured must be used at the hospitals where the initial demand arose, therefore the total number of treatments delivered at hospitals equals to the total number of the treatments produced at the facilities (*Eq 4.15*). The total number of treatments delivered at hospital *h* equals the total number of treatments produced that are delivered to the hospital (*Eq 4.16*). The total number of treatments produced at a certain facility equals the total number of treatments demanded at all hospitals produced at the facility (*Eq 4.17*).

$$TTP_t^P = TTH_t^P = \sum_h TrtH_{h,t}^P = \sum_f \sum_{Ft} \sum_{Fs} TrtF_{f,Ft,Fs,t}^P \qquad \textit{Eq 4.15}$$

$$TrtH_{h,t}^P = \sum_f \sum_{Ft} \sum_{Fs} \varepsilon_{f,Ft,Fs,h,t}^P \qquad \textit{Eq 4.16}$$

$$TrtF_{f,Ft,Fs,t}^P = \sum_h \varepsilon_{f,Ft,Fs,h,t}^P \qquad \textit{Eq 4.17}$$

4.2.2.2.6 Transportation costs

For autologous therapies, transportation between facilities and hospitals is an important cost to consider as the raw material originates from patients and must finally be delivered to the same patient at the same hospital. Transportation cost per treatment from the hospital at h to the facility at f and back (tr_h^f) is given by the transportation cost per mile (tc) multiplied by the return distance between the hospital and facility ($d_h^f * 2$) (*Eq 4.18*).

$$tr_h^f = tc * d_h^f * 2 \qquad \textit{Eq 4.18}$$

The total transportation cost ($Transport_t$) incurred in year t is given by the total number of treatment delivered from hospital at h to facility at lf at year t ($\varepsilon_{f,Ft,Fs,h,t}^P$) (*Eq 4.19*).

$$Transport_t = \sum_P \sum_f \sum_{Ft} \sum_{Fs} \sum_h \varepsilon_{f,Ft,Fs,h,t}^P * tr_h^f \qquad \textit{Eq 4.19}$$

4.2.2.2.7 Clinical trial and sales constraint

For the optimisation model to decide which product to invest in and produce, a binary variable (V_p) is used, where V_p equals 1 if the product is selected. The two time periods considered are the clinical trial phase and market phase. All facility and equipment costs are the same throughout the two time periods, except sales and revenue are only generated during the market phase.

Since the planning objective to maximise overall NPV, it may decide not to produce products to its maximum demand. However, to ensure that products are produced for clinical trial phases, product demand during clinical trial phases must be met despite the products not fetching any reimbursements (*Eq 4.20*).

$$TrtH_{h,t}^{P} = \sum_{m} Dd_{m,t}^{P,h} * V_p \qquad \forall\, t \in CT \qquad Eq\ 4.20$$

The number of treatments of product P delivered at the hospital at location h cannot exceed the demand of the product at the same hospital when the product is on market (*Eq 4.21*).

$$TrtH_{h,t}^{P} \le \sum_{m} Dd_{m,t}^{P,h} * V_p \qquad \forall\, t \in Mkt \qquad Eq\ 4.21$$

4.2.2.2.8 Product Sales and Revenue

The annual sales of each product at year t is given by the total treatments multiplied by the price of the product ($Price_{te}^{P}$) (*Eq 4.22*). The product can only be sold when it receives its market authorisation; before then the selling price equals zero (Eq 4.23).

$$Sales_{Mkt}^{P} = \sum_{P} \sum_{f} \sum_{Ft} \sum_{Fs} \sum_{h} \varepsilon_{f,Ft,Fs,h,t}^{P} * Price_{t}^{P} \qquad \forall t \in Mkt \qquad Eq\ 4.22$$

$$Sales_{t}^{P} = 0 \qquad \forall t \in CT \qquad Eq\ 4.23$$

The total revenue is given by the summation of all sales of developed products (*Eq 4.24*).

$$TRev_t = \sum_{P} Sales_{t}^{P} \qquad Eq\ 4.24$$

4.2.2.2.9 Objective function and overall capital constraint

During the development phase, the total amount of capital is limited by the investment capital raised. Therefore, the summation of the cash flows during the development phase is limited by the funding available (φ) (*Eq 4.25*).

$$\varphi \le \sum_{t} cflow_{CT} \qquad \forall\, t \in Mkt \qquad Eq\ 4.25$$

A discount factor (δ_t) is used for discounting future investments or cash flows into current values using the interest rate (r) (Eq 4.26).

$$\delta_t = \frac{1}{(1+r)^t} \qquad Eq\ 4.26$$

Over the time horizon, it is assumed that the objective of the company is to maximise its financial returns through optimising its capacity investment strategies based on the product development portfolio, e.g. prioritizing products that will bring the most financial returns whilst minimizing capital expenses. The cash flow in a certain year is given by the incomes minus the costs incurred in the year (*Eq 4.27*).

Cash flow ($cflow_t$) is the total revenue ($TRev_t$) minus the facility investment (FI_t), contract set-up ($Ctrt_t$), equipment procurement (Fixed, $FEqInvCost_t$ and production equipment $EqInvCost_t$), fixed operating costs ($Fixop_t$), total variable cost of goods ($TCOG_t$) and transportation costs ($Transport_t$) (*Eq 4.27*).

$$cflow_t = TRev_t - FI_t - Ctrt_t - FEqInvCost_t - EqInvCost_t - Fixop_t - TCOG_t - Transport_t \qquad Eq\ 4.27$$

The overall objective of this model is to maximize the net present value of the product portfolio. The summation of discounted cashflows at each year gives the expected NPV over the time horizon (*Eq 4.28*).

$$NPV = \sum_t cflow_t * \delta_t \qquad Eq\ 4.28$$

4.2.2.2.10 Model formulation summary

The model formulation is summarised as follows:

Eq	Mathematical Formulation	Description
Objective function		
4.24	$TRev_t = \sum_P Sales^P_t$	Total revenue
4.27	$cflow_t = TRev_t - FI_t - Ctrt_t - FEqInvCost_t - EqInvCost_t - Fixop_t - TCOG_t - Transport_t$	Cash flow
4.28	$NPV = \sum_t cflow_t * \delta_t$	Maximise total NPV
Constraints		
4.1	$A^f_{Ft,Fs,t} \le A^f_{Ft,Fs,t-1} + Fac^f_{Ft,Fs,t-\tau f^f_{Ft,Fs}}$	Newbuild facility investment and costs
4.3	$FI_t = \sum_f \sum_{Ft} \sum_{Fs} Fac^f_{Ft,Fs,t} * Inv^f_{Fs}$	
4.4	$Fixop_t = \sum_f \sum_{Ft} \sum_{Fs} (A^f_{Ft,Fs,t} * (\sigma_{Fs} * Opcost + FC^f_{Ft,Fs}))$	
4.2	$Ctrt_t = \sum_f Fac^f_{contract,Fspilot,t-\tau f^f_{contract,pilot}} * Ctc_f$	Contract facility cost
4.5a	$maxps_{Fs} = \sigma_{Fs} - \sigma_{support,Fs} - \sigma_{core,Fs} - \sigma_{QC,Fs}$	Equipment footprint constraint
4.5b	$maxps_{Fs} * A^f_{Ft,Fs,t} \ge \sum_m (EqNo^m_{f,Ft,Fs,t} * \sigma_{eq,m,Fs})$	
4.6	$EqNo^m_{f,newbuild,Fs,t} = EqNo^m_{f,newbuild,Fs,t-1} + EqP^m_{f,newbuild,Fs,t}$	Equipment purchase and cost
4.7	$EqP^m_{f,newbuild,Fs,t} \ge 0$	
4.8	$FEqInvCost_t = \sum_f \sum_{Fs} Fac^f_{newbuild,Fs,t} * (C_{support,Fs} + C_{core,Fs} + C_{QC,Fs})$	
4.9	$EqInvCost_t = \sum_f \sum_{Fs} \sum_m C_{eq,m,Fs} * EqP^m_{f,newbuild,Fs,t}$	
4.10	$CD^P_t = \sum_h Dd^{P,h}_{Complex,t}$	Demand constraint
4.11	$SD^P_t = \sum_h Dd^{P,h}_{Simple,t}$	
4.12	$\sum_P TrtF^{Complex}_{f,Ft,Fs,t} * Pt_P \le EqNo^{Complex}_{f,Ft,Fs,t} * M \quad \forall\ P \in CP$	Equipment capacity constraint
4.13	$\sum_P TrtF^{Simple}_{f,Ft,Fs,t} * Pt_P \le EqNo^{Simple}_{f,Ft,Fs,t} * M \quad \forall\ P \in SP$	

4.14	$COG^{P,f}_{Fs,Ft} = VCCOG^{P} * Out_{Ft} * Sp_{Fs} * Lp_{f}$		COG per treatment
4.15	$TTP^{P}_{t} = TTH^{P}_{t} = \sum_{h} TrtH^{P}_{h,t} = \sum_{f}\sum_{Ft}\sum_{Fs} TrtF^{P}_{f,Ft,Fs,t}$		Total product consumption constraint
4.16	$TrtH^{P}_{h,t} = \sum_{f}\sum_{Ft}\sum_{Fs} \varepsilon^{P}_{f,Ft,Fs,h,t}$		
4.17	$TrtF^{P}_{f,Ft,Fs,t} = \sum_{h} \varepsilon^{P}_{f,Ft,Fs,h,t}$		
4.18	$tr^{f}_{h} = tc * d^{f}_{h} * 2$		Transportation Cost
4.19	$Transport_{t} = \sum_{P}\sum_{f}\sum_{Ft}\sum_{Fs}\sum_{h} \varepsilon^{P}_{f,Ft,Fs,h,t} * tr^{f}_{h}$		
4.20	$TrtH^{P}_{h,t} = \sum_{m} Dd^{P,h}_{m,t} * V_{p}$	$\forall\ t \in CT$	Clinical trial material produced for all selected products
4.21	$TrtH^{P}_{h,t} \leq \sum_{m} Dd^{P,h}_{m,t} * V_{p}$	$\forall\ t \in Mkt$	Product demand constraint
4.22	$Sales^{P}_{Mkt} = \sum_{P}\sum_{f}\sum_{Ft}\sum_{Fs}\sum_{h} \varepsilon^{P}_{f,Ft,Fs,h,t} * Price^{P}_{t}$	$\forall t \in Mkt$	Product sales only for products on market
4.23	$Sales^{P}_{t} = 0$	$\forall t \in CT$	
4.25	$\varphi \leq \sum_{t} cflow_{CT}$	$\forall\ t \in Mkt$	Funding availability constraint

4.2.3 Model application on an illustrative case study

The mathematical model was implemented within the General Algebraic Modelling System (GAMS) 26.2 and the problem was solved using the CPLEX solver. Two scenarios of a UK based case study, with fast-track (FT) and without fast-track designations (NFT), are solved to illustrate the proposed mathematical model. The main advantages of fast-track regulatory schemes (detailed in Table 4.1) are shorter review times, quicker approvals and conditional market authorisations. In this study, this is reflected by the shorter product development timeline and the early “takeoff” of the product demand levels (Figure 4.3).

The time horizon for this study is taken to be 20 years, reflecting the typical patent exclusivity period before the entrance of generic products [195]. In this model, a discrete-

time formulation is used, i.e. time horizon is discretised into 1-year time intervals. As single-use closed automated systems are assumed to be used at scale, the changeover time is assumed to be negligible in the time horizon of 20 years. Figure 4.2 shows the product development timeline of orphan/unmet medical need products versus the typical drug development timeline.

The number of products and manufacturing capacity investment is limited by the availability of funding (φ). The model optimises the product portfolio based on the amount of funding available. Benchmarking against typical series A-C funding rounds, available funding ranges from $10m to $200m [196].

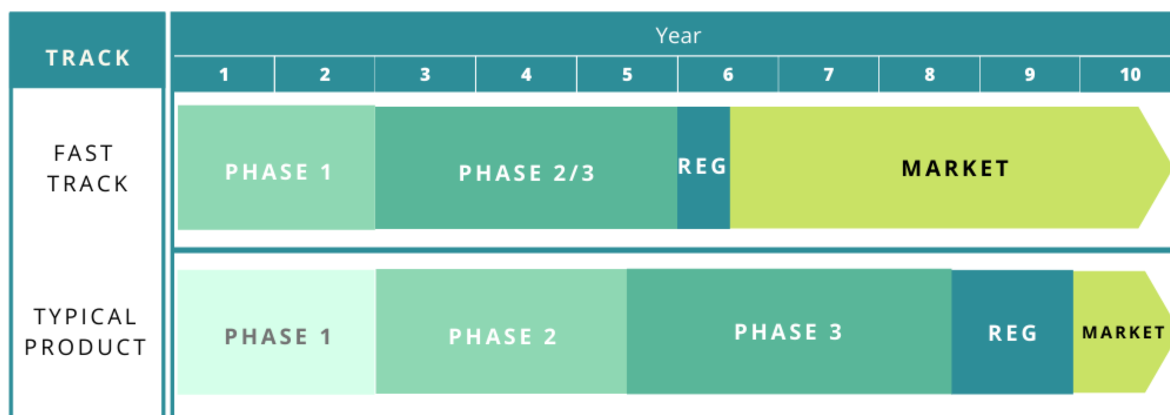


Figure 4.2 Product development timeline of orphan/unmet medical need products vs typical timeline

4.2.3.1 Product portfolio and demand scenario

A hypothetical product portfolio can be found in Table 4.3. The demand level of cell therapy products are categorised into niche and mass, where niche products are targeted at orphan diseases with a small patient population (e.g. late-stage rare blood cancers such as acute lymphoblastic leukaemia) and mass products are targeted at a larger patient population (e.g. solid tumours, cartilage). A list of products, their estimated demand and price base on NICE and NHS estimates for five indications are shown in Table 4.3. It is assumed that only

products authorised for market use are allowed to be sold and products in clinical trials are not reimbursed.

In this study, four geographical locations are assumed for hospital and facility locations for illustrative purposes, namely London, Bristol, Newcastle and Edinburgh. The distance between the locations (d_h^f) can be found in Table 4.4, and the location influences the cost of manufacturing (*Eq 4.14*) and the transportation costs (*Eq 4.18*).

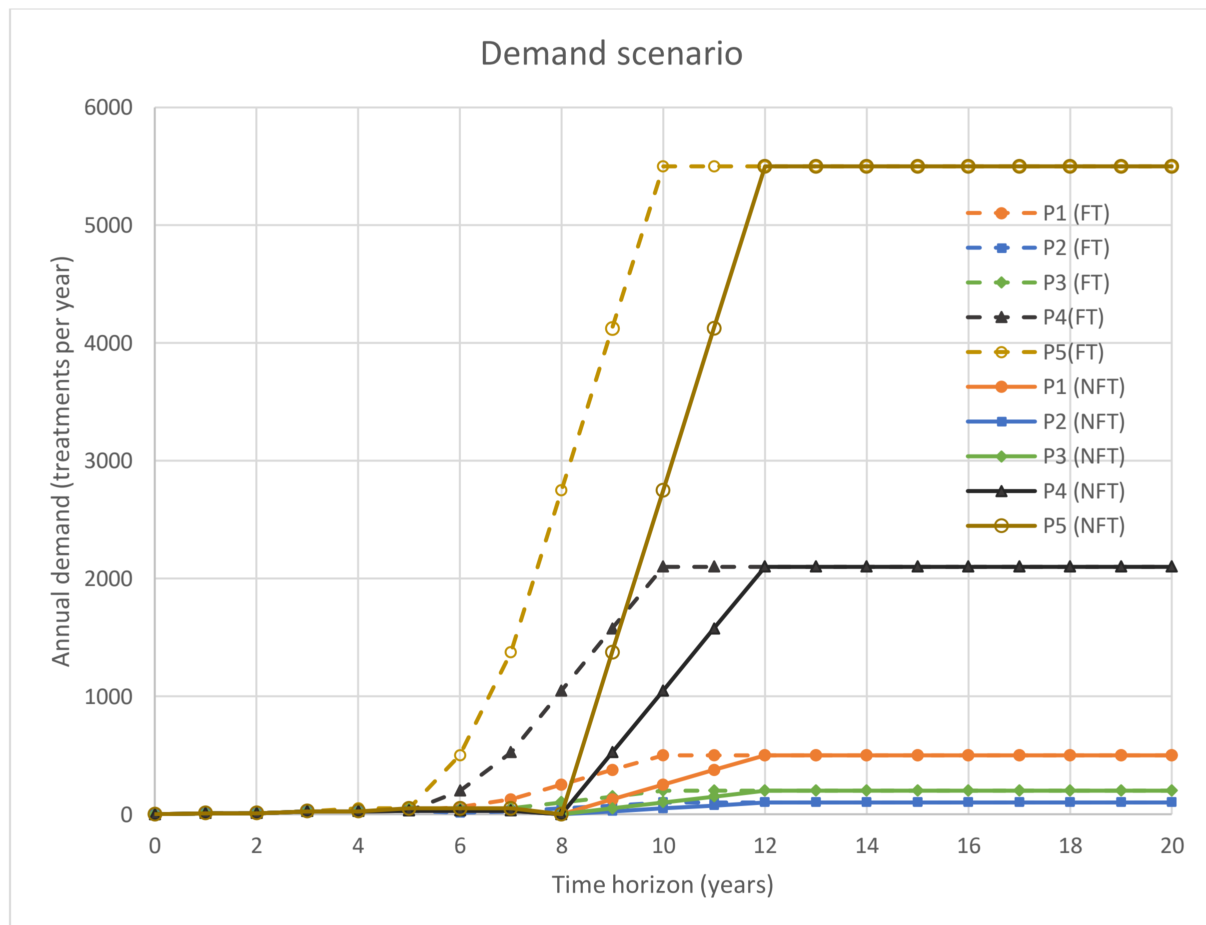


Figure 4.3 Forecasted demand level for products over 20 years. Dotted lines refer to the scenario with fast-track designations, solid lines refer to the scenario without fast-track designations.

Table 4.3 Hypothetical product data

Product, P	Clinical Indication	Annual UK demand	Selling Price $Price_t^P$ ($)	Process type, m	Cost per treatment, $COG_{Fs,Ft}^{P,f}$ ($)	Process duration, Pt^P (days)
P1	Cartilage transplantation [197]	500	20,000	Simple	3,000	20
P2	Limbal stem cell deficiency [198]	100	100,000	Simple	10,000	14
P3	Refractory Large B-Cell Lymphoma [148]	200	475,000	Complex	60,000	20
P4	Multiple Myeloma [199]	2100	276,000	Complex	40,000	14
P5	Stage IV Breast cancer [200], [201]	5500	200,000	Complex	45,000	14

Table 4.4 Distance between cities in miles

	London	**Bristol**	**Edinburgh**	**Newcastle**
London	-	118	402	282
Bristol	118	-	373	295
Edinburgh	402	373	-	120
Newcastle	282	295	120	-

The national product demand for both scenarios, with fast-track designations and without fast-track designations, are distributed amongst the four locations at a ratio of 4:2:2:2. After market approval, a 'ramp-up' period is assumed to simulate the time needed for a mature sales level to be reached [202], Figure 4.3 shows the forecasted demand level for each product.

The problem is defined such that the capacity planning decision will be made at the initial year under the assumption that products will be successful in clinical trials. The exact product demand for each product in various hospital location in each year within the time horizon is given in Appendix 4.1.

4.2.3.2 Facility and equipment assumptions

The facility assumptions are shown in Table 4.5. According to Airgate Engineering (Hong Kong), a cleanroom design and construction company based in Hong Kong, support space accounts for around 40% of the whole facility for small facilities and 20% for larger ones. Floor space occupied by core, QC and production equipment is calculated by summation of individual equipment footprint which is estimated by the equipment size specified in manufacturer manuals plus 1 meter of working space allowed around each equipment. Appendix 4.2 shows the list of equipment included and their size and floorspace requirement.

Table 4.5 Facility parameters

Facility type, Ft	Contract		Newbuild		
Facility scale, Fs	Pilot	Pilot	Small	Medium	Large
Floorspace, σ_{Fs} (m^2)	N/A	120	300	1000	3000
Support floorspace, $\sigma_{support,Fs}$ (m^2)	N/A	30	120	250	600
Core equipment floorspace, $\sigma_{core,Fs}$(m^2)	N/A	42	42	84	168
QC floorspace, $\sigma_{QC,Fs}$(m^2)	N/A	25	25	25	50
Support equipment cost, $C_{support,Fs}$ (thousand USD)	N/A	280	300	350	400
Core equipment cost, $C_{core,Fs}$ (thousand USD)	N/A	510	630	660	800
QC equipment cost, $C_{QC,Fs}$ (thousand USD)	N/A	421	421	842	1684
Contract negotiation costs, Ctc_f (thousand USD)	25	N/A	N/A	N/A	N/A
Facility Investment cost, Inv^f_{Fs} (thousand USD)	N/A	2800	6000	12000	20000
Set-up time, $\tau f^f_{Ft,Fs}$ (years)	0.5	2	3	3.5	4
Equipment # (Simple), $EqNo^{Simple}_{f,contract,pilot,t}$	5	N/A	N/A	N/A	N/A
Equipment # (Complex), $EqNo^{Complex}_{f,contract,pilot,t}$	3				
Facility fixed cost (thousand USD)	25	100	150	200	300
Outsource penalty cost multiplier (Out_{Ft})	1.2	N/A	N/A	N/A	N/A
Scale penalty multiplier (Sp_{Fs})	1.2	1.2	1.15	1.1	1

Table 4.6 Additional parameters

Definition and symbol of parameter	Value of parameter
Contract negotiation costs, Ctc_f (thousand \$USD)	25
Contract negotiation duration, $\tau f^f_{contract,pilot}$ (years)	0.5
Interest rate, r (%)	10
Time horizon, t (years)	20
Transportation cost per mile (\$USD)	1
Maximum operating days, M (days)	292
Facility operating cost, $Opcost$ (thousand \$USD per m^2 per year)	1.5
Location penalty multiplier (Lp_f) London Other locations	 1.1 1
Funding available, φ (million \$USD)	27

Other model parameters are provided in Table 4.6.

.

4.2.3.3 Sensitivity analysis

The main barriers to cell therapy commercial adoption identified by Davies et al are reimbursement, manufacturing and cost-effectiveness [203] and distribution logistics is another important challenge mentioned by Dodson et al [170]. To better analyse the effect of commercialization challenge-related parameters on the NPV and the robustness of the investment plan, a sensitivity analysis of the following parameters is conducted (Table 4.7).

Table 4.7 Sensitivity analysis parameters

Commercialisation challenge	Model Parameter
Funding availability	Funding available (φ)
Reimbursement	Product selling price ($Price_t^P$)
	Product demand uptake ($Dd_{m,t}^{P,h}$)
Manufacturing	Variable COG of product ($VCCOG^P$)
	Process turnaround time ($Pt(P)$)
Logistics	Transport cost per mile (tc)

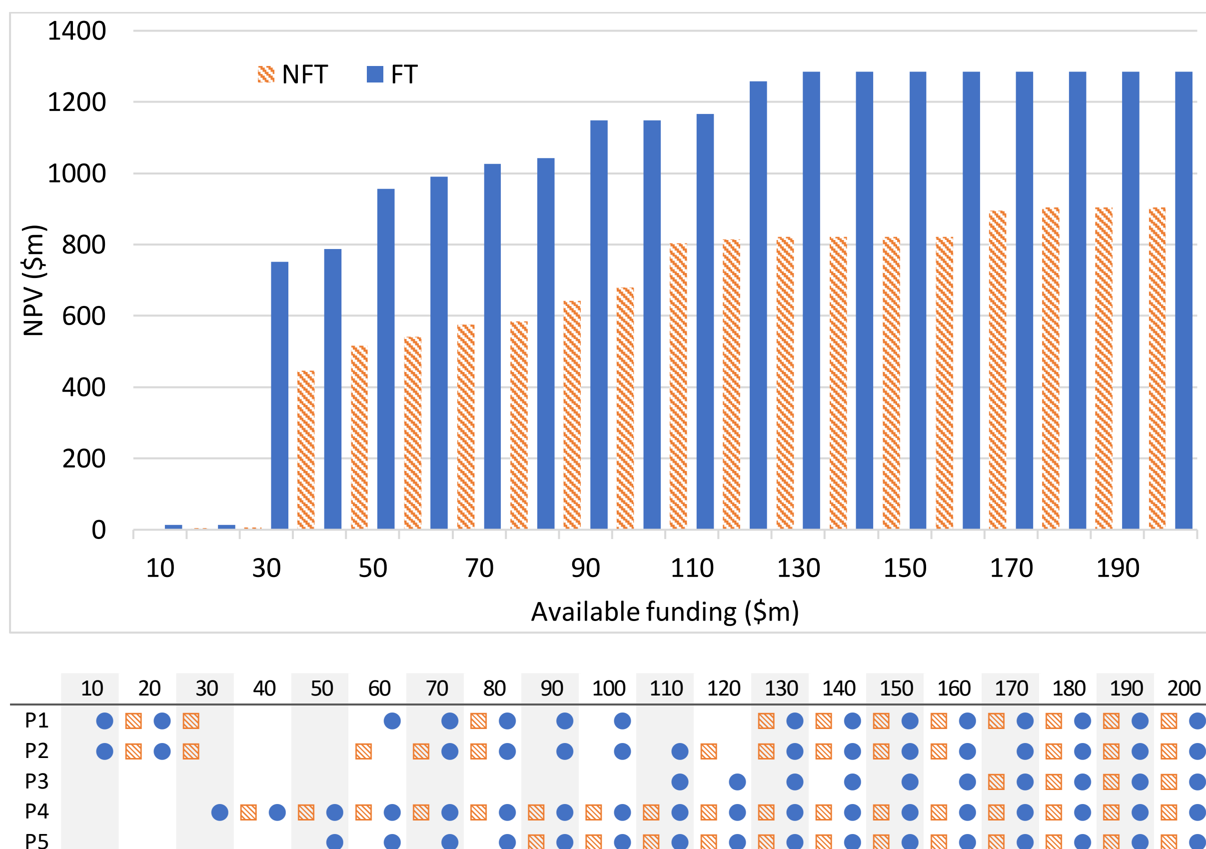
4.3 Results

4.3.1 Product selection decision

The set of 5 candidate products represents the characteristics of a variety of currently commercialized autologous products. P1 represents a moderate demand product with an indication with a relatively low reimbursement price. P2 illustrates the case of a niche demand product with a higher reimbursement price. P3 represents a niche product for a high-value indication. P4 and P5 finally represent high demand products for high-value indications. Two scenarios are compared, fast-track (FT) and without fast-track designations (NFT).

Figure 4.4A shows the changes in NPV and product portfolio selected with increasing available funding (Figure 4.4B). For both scenarios, with a limited amount of funding, P1 and

P2 are selected. P1 and P2 require cheaper upfront equipment investments and lower variable cost of goods but fetches a lower selling price. With a higher amount of investment funds, complex products with higher annual demands (P4, P5) are preferred. Although the selling price of these products is relatively lower compared to P3, the market size is much greater and delivers a greater overall return. With funding above \$40m, the NPV for scenario FT is consistently higher than that of scenario NFT, by a range from 40% (φ = \$180-200m) to 86% (φ = \$50m).



	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200
P1	FT	NFT, FT	NFT			FT	FT	NFT, FT	FT	FT			NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT
P2	FT	NFT, FT	NFT			NFT	NFT, FT	NFT, FT	FT	FT	FT	NFT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	FT	NFT, FT	NFT, FT	NFT, FT
P3											FT	FT	FT	FT	FT	FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT
P4			FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT
P5					FT	FT	FT	FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT	NFT, FT

Figure 4.4A NPV of the product portfolio with increasing funding available for the scenario with fast-track designations and without. Figure 4.4B Table showing the products selected for development and scale-up manufacturing, where orange represents scenario NFT and blue represents scenario FT.

A more in-depth analysis of the discounted NPV over 20 years for an investment funding constraint of \$120m shows that the breakeven for scenario FT occurs at year 7.5,

approximately 2.5 years earlier than the scenario without fast-track schemes. This represents a 25% reduction in the time to achieve breakeven of investments (Figure 4.5).

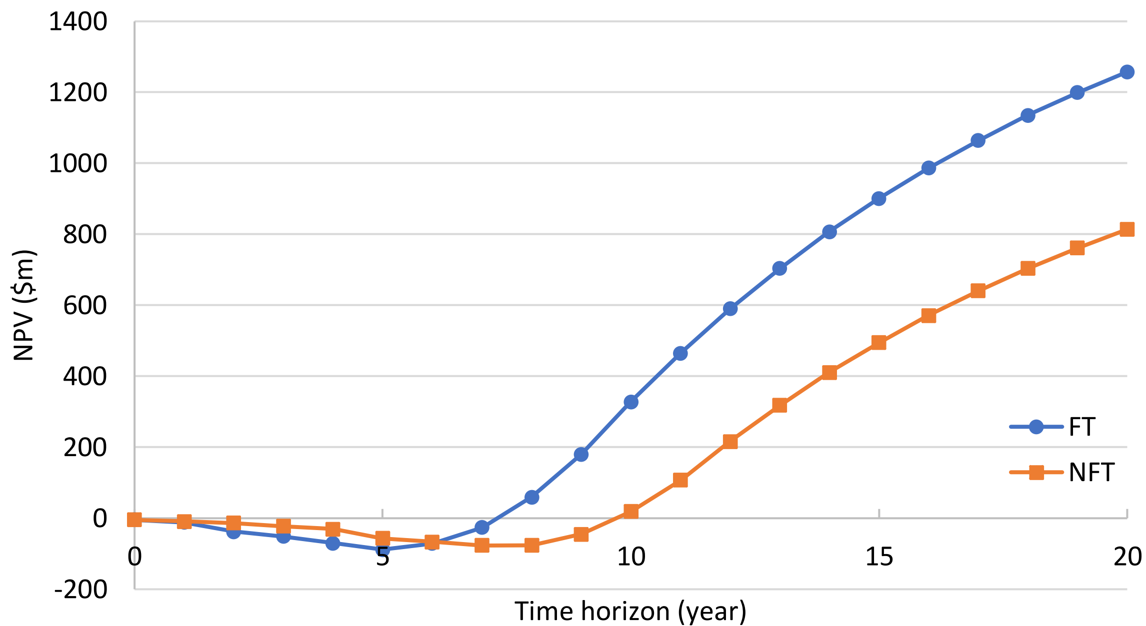


Figure 4.5 NPV over time horizon for investment funding constraint of $120m

4.3.2 Facility investment decision schedule

Further analysis with φ = $120m is considered, where for both scenarios four products are selected to be developed and manufactured.

The facility investment and equipment purchase decision schedule are shown in Figure 4.6. For both scenarios, contract manufacturing facilities are engaged at base year to produce clinical trial materials and disengaged once the newbuild pilot facility is available. As the clinical trial demand for all chosen products is forced to be completely satisfied, both scenarios invested in newbuild facilities early in the time horizon. Once newbuild facilities are available, contract facilities are no longer engaged. Further, as shown in Figure 4.7, as the number of treatment increases, the model favours manufacturing in the largest available facility.

A. Fast track			Year te																				
Facility			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
London	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					
Bristol	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					
Newcastle	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					
Edinburgh	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					

B. No Fast track			Year te																				
Facility			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
London	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					
Bristol	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					
Newcastle	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					
Edinburgh	Contract	Pilot																					
	Newbuild	Pilot																					
		Small																					
		Medium																					
		Large																					

Figure 4.6 Facility investment schedule over time horizon for $\varphi = \$120m$ A: Fast track scenario, B: no fast-track scenario (red blocks show the decision to build/engage, green blocks show period when the facility is available).

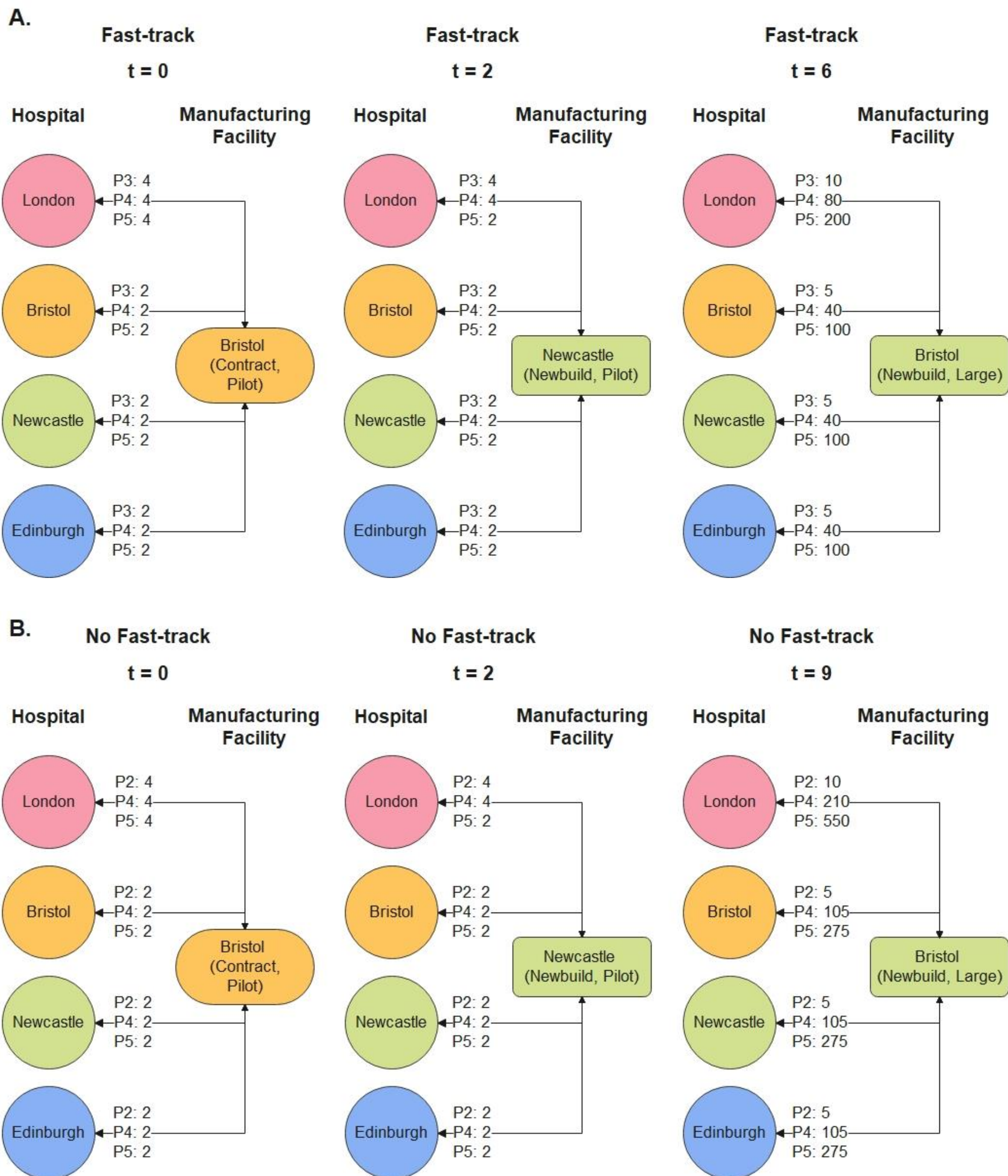


Figure 4.7 Hospital-Manufacturing facility product distribution network for $\varphi = \$120m$.

Comparing the two scenarios, the decision to invest in a larger centralized facility (built at Bristol, Figure 4.6) came in earlier at year 2 on in the FT scenario rather than year 5 in the NFT scenario, and correspondingly larger upfront investment is incurred earlier (Figure 4.8). In terms of the total facility and equipment capital investment costs, those of scenario FT are 2% higher than scenario NFT. Due to the long construction and validation lead-times of

facilities, it is noted that for the fast-track option, the investment decisions to build a large newbuild facility is made at year 2, which is 3 years earlier for the NFT scenario, highlighting the high capital risk nature of commercialization of autologous cell therapies, especially with the crunched timeline.

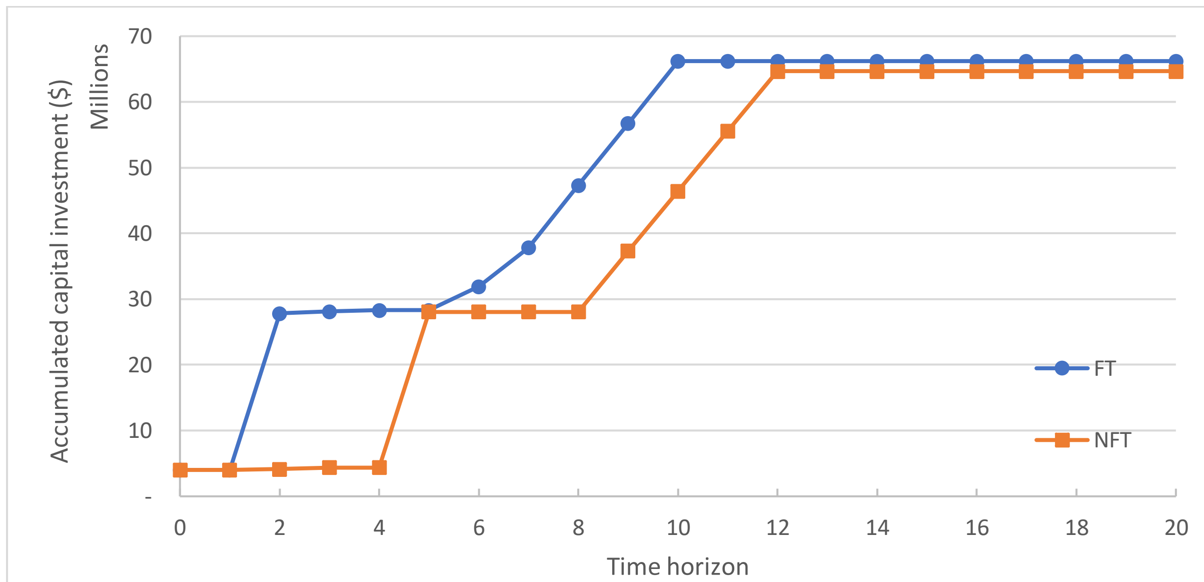


Figure 4.8 Facility and equipment capital investment for scenario FT and NFT over 20 years

4.3.3 Product distribution

Due to more expensive manufacturing and higher upfront investment, although the demand is higher in London (40% of total demand), the optimized model does not suggest building a facility in London and its local demand is satisfied by other facilities. For both scenarios, at the terminal year, the products are produced centrally at the large facility built in Bristol where production benefits from economies of scale (no scale penalty at large scale) and cheap location (no location penalty).

4.3.4 Sensitivity analysis

To understand the sensitivity of the NPV to market and manufacturing uncertainties and the robustness of the product selection robustness, the input parameters listed in Table

4.7 were varied +/- 20%. A sensitivity analysis was conducted for capital investment funding of $120m.

As the model allows for simultaneous optimization of product selection and capacity planning, changes in the input parameters have an impact on both product selection and facility investment decisions and in turn the NPV over the time horizon (Table 4.8). The product selection decision is more robust in scenario FT with fewer changes in the product portfolio. This, in turn, impacts facility investment and equipment investment decisions.

For scenario NFT, product P4 is selected for all cases, whilst for scenario FT, product P3 and P4 are selected for all cases. Fast-track designations make the decision to develop and produce niche, high-value products (P3, P4) more resistant to uncertainties and without FT designations, niche, very high-valued products (P3) are not chosen.

Table 4.8 Product selection portfolio with changes in input parameters (A) NFT, (B) FT

A	Product characteristics			Without fast track														
	Demand	Indication value	Process type	VCCOG			Product Demand			Selling price			Transportation Cost			Process Turnaround time		
				-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%
P1	Moderate	Low	Simple															
P2	Niche	Moderate	Simple															
P3	Niche	Very High	Complex															
P4	High	High	Complex															
P5	Very High	High	Complex															

B	Product characteristics			With fast track														
	Demand	Indication value	Process type	VCCOG			Product Demand			Selling price			Transportation Cost			Process Turnaround time		
				-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%
P1	Moderate	Low	Simple															
P2	Niche	Moderate	Simple															
P3	Niche	Very High	Complex															
P4	High	High	Complex															
P5	Very High	High	Complex															

For both scenarios, product demand changes and transportation costs fluctuations made no impact on the product portfolio. For both scenario, lower selling price deselects P5 (a very-high-demand, high-valued complex product) and favours instead simple products (P1, P2).

For both scenarios, the overall NPV is most sensitive to the selling price, followed by the manufacturing variable cost of goods and finally the product demand; the sensitivity to the transportation cost and the process turnaround time is minimal (Figure 4.9). Transportation only accounts for around 0.1-0.2% of the total cost and hence its changes have very little impact on the overall cost and NPV. Scenario NFT is more sensitive to negative changes in both price and manufacturing variable costs than scenario FT.

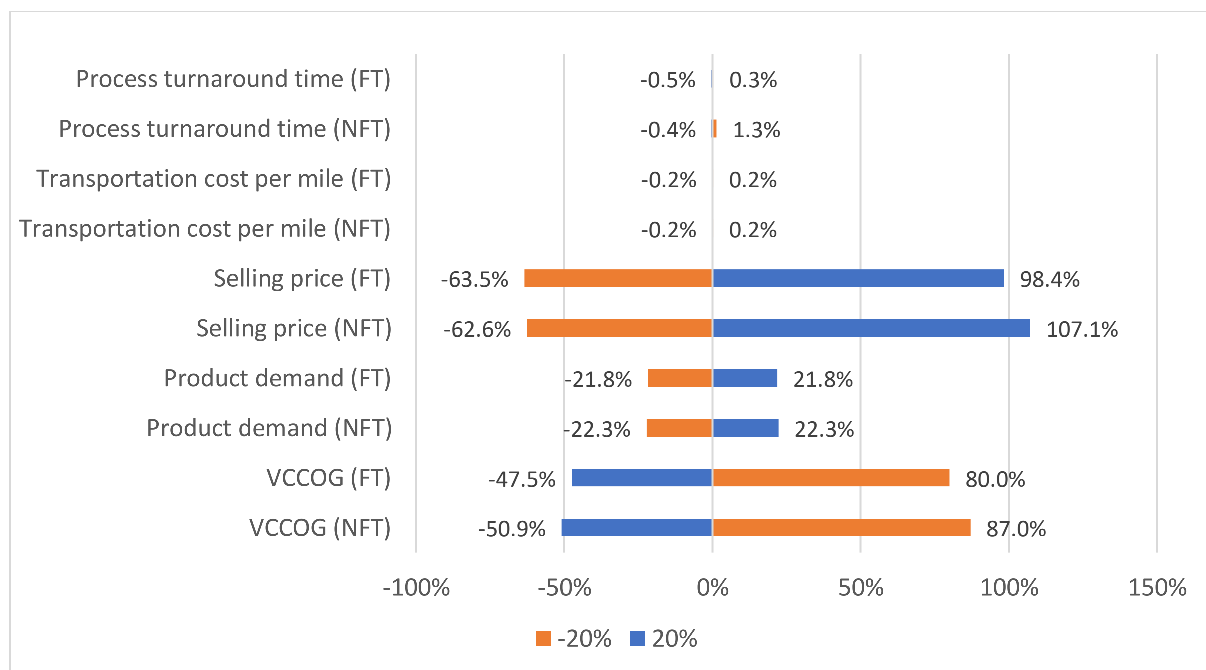


Figure 4.9 Sensitivity of NPV to parameter changes

With a decrease in selling price and an increase in manufacturing variable costs, for both scenarios, the optimal portfolio deselected P5 which has a greater product demand but has a lower profit margin. This shows the importance of maintaining profit margins for high demand products. With the decrease in selling price and either increase or decrease in

manufacturing variable costs, for both scenarios, P1 is selected. Although the profit margin for P1 is smaller, the barrier of commercialisation P1 is also lowest as shown by the low required funding as shown in Figure 4.4.

4.4 Discussion

This work proposed a problem formulation specific to a challenge faced by manufacturers seeking to commercialise autologous cell therapies considering the recent introduction of fast-track regulatory schemes and the autologous nature of these therapies. Using the United Kingdom as an illustrative example, we have shown the impact of fast-track regulatory designations on capacity planning and investment decisions.

Specific to the unique challenges of commercialising autologous cell therapies, this model addressed scale-out, geographical constraints, long-term capacity investment decisions and the unique regulatory routes of these therapies.

4.4.1 Opportunities and challenges of fast-track regulatory schemes for autologous cell therapies

Fast-track regulatory designations can allow companies to achieve breakeven years earlier and higher NPV over the time horizon (Figure 4.5). This is consistent with the observations by Capital Cell, an online investment platform for healthcare and biotechnology in Europe, which concluded that fast-track therapeutics provide lower exit times and higher valuations [204]. A review of the value of companies holding Breakthrough Therapy Designations also shows that such designations add significant value to the company [205].

However, with the crunched development timeline, large upfront investments for manufacturing would be incurred earlier. This can have great risk implications especially for small-medium enterprises seeking to commercialise clinical-stage autologous cell therapy products. Secondly, with a small amount of clinical data, the risk of the marketed product may

be higher. A review on fast-tracked products withdrawn cited lack of efficacy, adverse events and safety issues as the main reasons for withdrawal [206]. Further analysis looking into the trade-off between developmental risks and speed-to-approval can be critical in instilling patient and commercial confidence in such therapies.

4.4.2 Strengths and Limitations of the model

This model considers common product-market characteristics, manufacturing scale-out instead of scale-up to simultaneously optimise strategic commercialisation decisions such as product portfolio selection, facility and equipment selection for autologous cell therapies. The impact of the introduction of fast-track schemes for therapies targeting unmet medical need is considered in a comparative scenario analysis exercise. However, although the model results are consistent with real world findings, it is impossible to replicate the scenario in real-life and validate the results generated by the model.

To illustrate the impact of regulatory incentives, the MILP model is applied to a UK specific example to demonstrate the applicability of the model. With further extensions including tax and trading structures, the model can be applied for simultaneous facility planning and product portfolio selection for a wider region. Also, cross-national regulation harmonisation is a challenge faced by the regenerative medicine industry [207]. A limitation of the model is that the costs of patents and intellectual property rights are not considered. IP licensing is a cost that can be significant in the product development process [208]. However, this is considered out of scope for analysing the impact of fast-track regulatory schemes on product portfolio selection and overall project NPV. Another limitation is that clinical trial failure is not accounted for. However, whilst it is unrealistic to assume that each product will be successful in clinical trials, the model can serve as a decision aid for companies that need to produce capacity investment plans for internal planning and capital raising

purposes. Future extensions to the model will consider stochasticity in product demand and probabilities of failures in clinical trials.

The model proposed is a deterministic model and a sensitivity analysis was conducted to address the parametric uncertainties. Future work could explore more sophisticated approaches such as stochastic programming.

4.5 Conclusion

In this paper, we have described and modelled the unique challenges and opportunities for capacity planning and investment strategies for autologous cell therapies in a mixed-integer linear programming model. An illustrative example comparing fast-track regulatory schemes and typical developmental timelines in the United Kingdom with a hypothetical set of products was used to demonstrate the applicability of the model. The results were validated against real-world observations in relevant investments.

The results show that with fast-track designations, whilst upfront investments are incurred earlier, the NPV breakeven occurs around 25% earlier with an overall NPV improvement of 42-86% depending on the investment funding available. Products with higher value indications are preferred where sufficient investment funding is in place.

The scenario with fast-track designations, in general, is less sensitive to changes in model parameters. The sensitivity analysis shows a greater than proportionate impact of selling price and manufacturing variable cost of goods on the NPV over the 20-year time horizon for both scenarios. A 20% lower selling price causing over 60% lower NPV and a 20% higher variable manufacturing costs can cause over 80% lower NPV in the scenario with fast-track designations and over 100% in the scenario without such designations, showing a need for further research into more robust reimbursement, manufacturing cost management and pricing strategy.

Overall, this study highlights the opportunities in commercializing autologous cell therapies with the introduction of favourable regulatory programmes. The modelling approach and the results may facilitate the industry in making product portfolio, capital raising and capacity investment decisions.

Appendix 4.1 Case study parameters

Product (P) demand at location h at year t (with fast track)

		Phase 1		Phase 2/3			Reg	Ramp up			Market demand
Year (t)	base	1	2	3	4	5	6	7	8	9	10-20
P1.London	0	4	4	10	12	12	24	50	100	150	200
P1.Bristol	0	2	2	5	6	6	12	25	50	75	100
P1.Newcastle	0	2	2	5	6	6	12	25	50	75	100
P1.Edinburgh	0	2	2	5	6	6	12	25	50	75	100
P2.London	0	4	4	10	12	12	5	10	20	30	40
P2.Bristol	0	2	2	5	6	6	2	5	10	15	20
P2.Newcastle	0	2	2	5	6	6	2	5	10	15	20
P2.Edinburgh	0	2	2	5	6	6	2	5	10	15	20
P3.London	0	4	4	10	16	16	10	20	40	60	80
P3.Bristol	0	2	2	5	8	8	5	10	20	30	40
P3.Newcastle	0	2	2	5	8	8	5	10	20	30	40
P3.Edinburgh	0	2	2	5	8	8	5	10	20	30	40
P4.London	0	4	4	10	12	12	80	210	420	630	840
P4.Bristol	0	2	2	5	6	6	40	105	210	315	420
P4.Newcastle	0	2	2	5	6	6	40	105	210	315	420
P4.Edinburgh	0	2	2	5	6	6	40	105	210	315	420
P5.London	0	4	4	10	20	20	200	550	1100	1650	2200
P5.Bristol	0	2	2	5	10	10	100	275	550	825	1100
P5.Newcastle	0	2	2	5	10	10	100	275	550	825	1100
P5.Edinburgh	0	2	2	5	10	10	100	275	550	825	1100

Product (P) demand at location h at year t (without fast track)

		Phase 1		Phase 2		Phase 3			Reg	Ramp up			Market demand
Year (t)	base	1	2	3	4	5	6	7	8	9	10	11	12-20
P1.London	0	4	4	10	10	12	12	12	0	50	100	150	200
P1.Bristol	0	2	2	5	5	6	6	6	0	25	50	75	100
P1.Newcastle	0	2	2	5	5	6	6	6	0	25	50	75	100
P1.Edinburgh	0	2	2	5	5	6	6	6	0	25	50	75	100
P2.London	0	4	4	10	10	12	12	12	0	10	20	30	40
P2.Bristol	0	2	2	5	5	6	6	6	0	5	10	15	20
P2.Newcastle	0	2	2	5	5	6	6	6	0	5	10	15	20
P2.Edinburgh	0	2	2	5	5	6	6	6	0	5	10	15	20
P3.London	0	4	4	10	10	16	16	16	0	20	40	60	80
P3.Bristol	0	2	2	5	5	8	8	8	0	10	20	30	40
P3.Newcastle	0	2	2	5	5	8	8	8	0	10	20	30	40
P3.Edinburgh	0	2	2	5	5	8	8	8	0	10	20	30	40
P4.London	0	4	4	10	10	12	12	12	0	210	420	630	840
P4.Bristol	0	2	2	5	5	6	6	6	0	105	210	315	420
P4.Newcastle	0	2	2	5	5	6	6	6	0	105	210	315	420
P4.Edinburgh	0	2	2	5	5	6	6	6	0	105	210	315	420
P5.London	0	4	4	10	10	20	20	20	0	550	1100	1650	2200
P5.Bristol	0	2	2	5	5	10	10	10	0	275	550	825	1100
P5.Newcastle	0	2	2	5	5	10	10	10	0	275	550	825	1100
P5.Edinburgh	0	2	2	5	5	10	10	10	0	275	550	825	1100

Appendix 4.2 Equipment

(1) Core equipment cost and size

Core equipment	Equipment cost (USD)	Equipment width (m)	Equipment depth (m)	Floorspace requirement (m^2)
Isolator with filling line	188,000	2.80	1.10	8
TFF	80,000	1.80	0.80	5
Tube Welder	18,700	0.20	0.34	2
Tube Sealer	13,500	0.07	0.34	1
Refrigerator	7,200	0.77	0.83	3
Freezer (-20 °C)	7,200	0.77	0.83	3
Freezer (-80 °C)	7,200	0.77	0.83	3
Cryogenic freezer	30,000	0.88	1.04	4
Controlled rate freezer	16,000	0.81	0.52	3

(2) QC equipment cost and size

QC Equipment	Equipment cost (USD)	Equipment size(w)	Equipment size (d)	Floorspace requirement (m^2)
Microscope	11,000	0.21	0.36	1.64
Vi-cell	65,500	0.91	0.62	3.09
Flow cytometer	65,500	0.91	0.62	3.09
PCR	58,950	0.50	0.50	2.25
ELISA plate reader	50,000	0.42	0.46	2.07
Isolator-2 glove	238,340	1.30	0.90	4.37
Incubator	23,000	1.67	0.92	5.13
Endosafe	12,145	0.20	0.25	1.50
BacT-alert	32,500	0.60	0.50	2.40

Chapter 5 Market-specific valuation model for advanced therapies considering commercialisation barriers

This chapter presents an unsubmitted manuscript:
Lam C, Meinert E, Yang A, Cui Z. Valuation model considering commercialisation barriers for advanced therapies.
Among all authors who contributed to the article, CL conceived, designed and implemented the model and wrote the manuscript. EM, AY and ZC supervised the study and revised the manuscript.

Summary

Chapter 3 and Chapter 4 have discussed the operational and tactical problems of supply chain and capacity planning. However, other market barriers and uncertainties have not yet been addressed. In addition, the NPV approach used in Chapter 4 does not consider the risks of clinical trial failure and market-specific risks. The barriers of commercialising these advanced therapies have been extensively analysed and previous models as discussed in Chapter 3 have addressed it through stochastic modelling approaches. However, these barriers have not been systematically reflected in the commonly used valuation techniques for biotechnology investments such as risk-adjusted net present value (rNPV).

In this work, we propose to implement an adaptive neuro-fuzzy inference strategy (ANFIS) to consider the effect of ambiguous commercialisation barriers on peak market penetration and market ramp-up time. Fuzzy-based models using linguistic terms provide a systematic method of capturing ambiguous qualitative concepts. Commercialised products in various markets are evaluated and used to train and test the ANFIS model. The implemented ANFIS network models showed strong correlation between predicted and actual data sets, implying reasonably good predictive abilities despite the small dataset.

To demonstrate the applicability of the model, four hypothetical scenarios are considered: autologous with and without orphan designation, allogeneic with and without orphan designation in four different markets. The rNPV study shows which markets are more likely to be profitable and further sensitivity analysis indicates which markets are most sensitive to commercialisation uncertainties.

This approach offers a systematic way of incorporating uncertainties and learnings from previously commercialised products into the conventional rNPV approach. Due to the small number of commercialised autologous therapies on the market, this study included data outside the thesis scope to overcome the severe issue of data availability and the general approach presented in this chapter can be applied to not only autologous therapies but also other ATMPs.

5.1 Introduction

Over the last two decades, more and more advanced therapeutic medicinal products (ATMPs) have been commercialised. However, due to obstacles such as strict regulatory requirements in clinical use, manufacturing, pricing arrangements and user (patient and clinician) sentiments, the commercial success of these products has been limited. Different markets have different characteristics in acceptance of innovative medicines and different methods of assessing cost-effectiveness and reimbursement methods. For instance, the main considerations for pricing, reimbursement and market access in 5 of the major economies in Europe (UK, Germany, France, Italy, Spain) were identified to be treatment cost, size of the patient population, clinical benefit measured, in contrast to an appropriate comparator and healthcare budget constraints considered as most important in countries where public healthcare is less well-funded [209]. In general, the market potential of an ATMP may be affected by a range of factors, which are considered below.

Safety and efficacy data from local patients are required by regulatory authorities in key markets such as the USA, EU, China, India, Japan and Korea [210]. This factor, when combined with the niche indications of some of the autologous cell therapies, makes clinical trial enrolment difficult. New guidelines issued by the Chinese National Medical Products Administration (NMDA) in 2020 states that they may accept overseas clinical trial data if they are authentic and reliable provided that racial sensitivity analyses are conducted. For orphan indications where treatment options are scarce, clinical trial data from outside of China may be 'partially accepted' as conditional trial data and further validity and safety data can be collected after drug listing [211], making it more attractive for orphan medications to enter the market.

A previous study looked at the impact of manufacturing process decisions on the cost of goods of allogeneic stem cell therapies and analysed the operational and economic performance of different manufacturing platforms under different demand scenarios [108]. However, while manufacturing issues and costs have been cited as an important barrier to commercialisation, more factors contribute to the less-than-satisfactory uptake of advanced therapies.

Specific to ATMPs with the promise of a one-off treatment but lacking long-term efficacy data, uncertainties around reimbursement and generating adequate data to prove long-term clinical superiority at market launch may be difficult. The reimbursement mechanism is different in various markets [212]. In the US, reimbursement is via insurance and intermediaries while in most EU countries, national healthcare agencies carry out health technology assessments (HTA) to evaluate the cost-effectiveness and carry out negotiations with drug companies. In Japan, approved drugs are automatically covered and reimbursed by the National Health Insurance (NHI) system. In Canada, Canadian Agency for Drugs and

Technologies in Health (CADTH) conducts thorough and objective evaluations of the clinical, economic, patient, and clinician evidence on drugs. While performance-based payment structures have been raised by companies and various reimbursement agencies as a potential mitigation measure, the cost of implementing such agreements may incur greater costs in the long run due to the increased frequency of monitoring [213]. In addition, the pricing and cost-effectiveness for some advanced therapies have been heavily scrutinised, with some estimating the incremental cost for each quality life-year gained way above national HTA thresholds, resulting in therapies not getting reimbursed [214], ultimately resulting in commercial failures.

In addition, overestimation of market demand and uptake has been a costly mistake for some companies. For instance, high upfront capital investment and GMP maintenance cost have been cited as important reasons for Provenge's commercial failure [215]. More recently, overestimation of gene therapy demand was cited as one of Novartis' reasons for shutting down their facility in Colorado [216].

5.1.1 NPV calculations and project valuations

Net present value is a widely accepted valuation tool for product portfolios, projects, technologies, and assets. For high-risk endeavours such as drug development programs, risks adjustments are crucial in informing investment decisions which are often high capital in nature. Risk-adjusted NPV (rNPV) takes into account cash inflows (revenues) and outflows (costs), time (through discount factor) and the relevant success rate(s) for each stage of development [217]. Recently, Woo et al. analysed datasets from clinical trial success rates to improve the risk-adjusted approach for biopharmaceutical valuations [218]. A cell therapy specific NPV tool has been proposed [219], but since then more ATMP products have been commercialised and the challenges and opportunities in the commercialisation of ATMPs are

better understood. For new and complex drug modalities, where the commercialisation risks are high, post-approval risks specific to commercialisation such as clinical adoption, insufficient long-term safety data should be considered to reflect cell therapy-specific challenges. These uncertainties are difficult to quantify and reflect in NPV models, and fuzzy logic can be a systematic way of incorporating these ambiguous variables for a more usable model.

5.1.2 Adaptive neuro-fuzzy inference system (ANFIS)

Fuzzy logic was first introduced by Zadeh as a method to aid decision-making based on ambiguous data [100] and the adaptive neuro-fuzzy inference system (ANFIS) was further proposed to map human knowledge into the rule base and database of a fuzzy inference system in form of fuzzy if-then rules [220]. Combining both neural networks and fuzzy logic principles, ANFIS corresponds to a set of fuzzy IF-THEN rules that estimate nonlinear functions through learning from data. It offers a method of incorporating real-world observations and understanding to process imprecise and vague information [220].

ANFIS has been applied in various time series prediction and forecasting problems to aid decision-making. In tourism, it has been applied to forecasting tourist arrival for planning demand and infrastructure needs. In the energy field, it has been applied to manage the demand and supply of energy in smart grid [101]. ANFIS is also extensively used for the optimisation of investment decisions (net present value and internal rate of return) of wind farm projects [221], mining projects [222] and even real estate valuation [223]. Other applications include aiding manager’s decisions in food product development and market strategy with predictions of development success and market demand [224] and forecasting the entrepreneurial success of industrial organisations [225].

In the biomedical field, it has been used for predicting disease progression with the use of clinical records and patient physiological parameters to predict renal failure progression and take effective actions [226]. More recently, it was applied in the detection of COVID-19 through image texture analysis[227] and forecasting of COVID-19 cases in China [228].

For pharmaceutical market entry, a market due diligence should first be conducted to evaluate the barriers to entry. The market analysis on the consumer approval processes should include consumer preferences, perceptions, and reimbursement (country income level, pricing controls) and the national regulatory requirements (additional clinical trial and approval processes), and market infrastructure for the distribution of the product. Using Mamdani fuzzy logic to consider uncertainties and ambiguity in marketing strategy, perceived value and competition, Haji et al. proposed a method of addressing new product pricing challenges [229].

With the uncertainties and market barriers for advanced therapies, it is difficult to accurately predict the market performance of a new product. With the high cost of market entry, especially with the high upfront investment in manufacturing capacity and establishment of clinical partners, learning from past innovative product launches and better strategies for the evaluation of market entry decisions is critical, which however has not been supported by a systematic approach. In this chapter, a fuzzy risk-adjusted NPV (rNPV) based valuation model is developed which is capable of aggregating empirical past product launch data with expert understanding of barriers in commercialisation as a way to simultaneously consider the barriers to commercialisation of cell therapies and market entry to aid market entry decisions. A database based on current marketed innovative products in various

markets and their market performances is constructed and used to train the artificial neural network for the prediction of market performance of advanced therapies in different markets.

5.2. Method

A deterministic rNPV model is first considered, and variables related to barriers in cell therapy commercialisation are fuzzified in order to capture the ambiguities and uncertainties. This section will describe the calculation and modelling approach used.

5.2.1 System boundary

For this study, we consider a 20-year horizon from the commencement of Phase 1 clinical trial such that the costs and risks during the clinical development phase can be considered. Geographically, we consider the market of a specific region, which is typically a country.

5.2.2 Model structure

The model is divided into two modules: ANFIS-based fuzzy logic module and risk-adjusted NPV module (Figure 5.1). Firstly, the ANFIS modules are trained using the commercialised product database. The rule bases generated from the model are then used to predict the market performance of the product, namely peak market penetration and ramp-up duration with a given set of fuzzy variables. Peak market penetration represents the maximum percentage of patient base to adopt the drug if commercialised and ramp-up duration represents the estimated time required for a product to reach peak penetration. These variables are subsequently used for further rNPV calculations with other market-specific and indication-specific parameters.

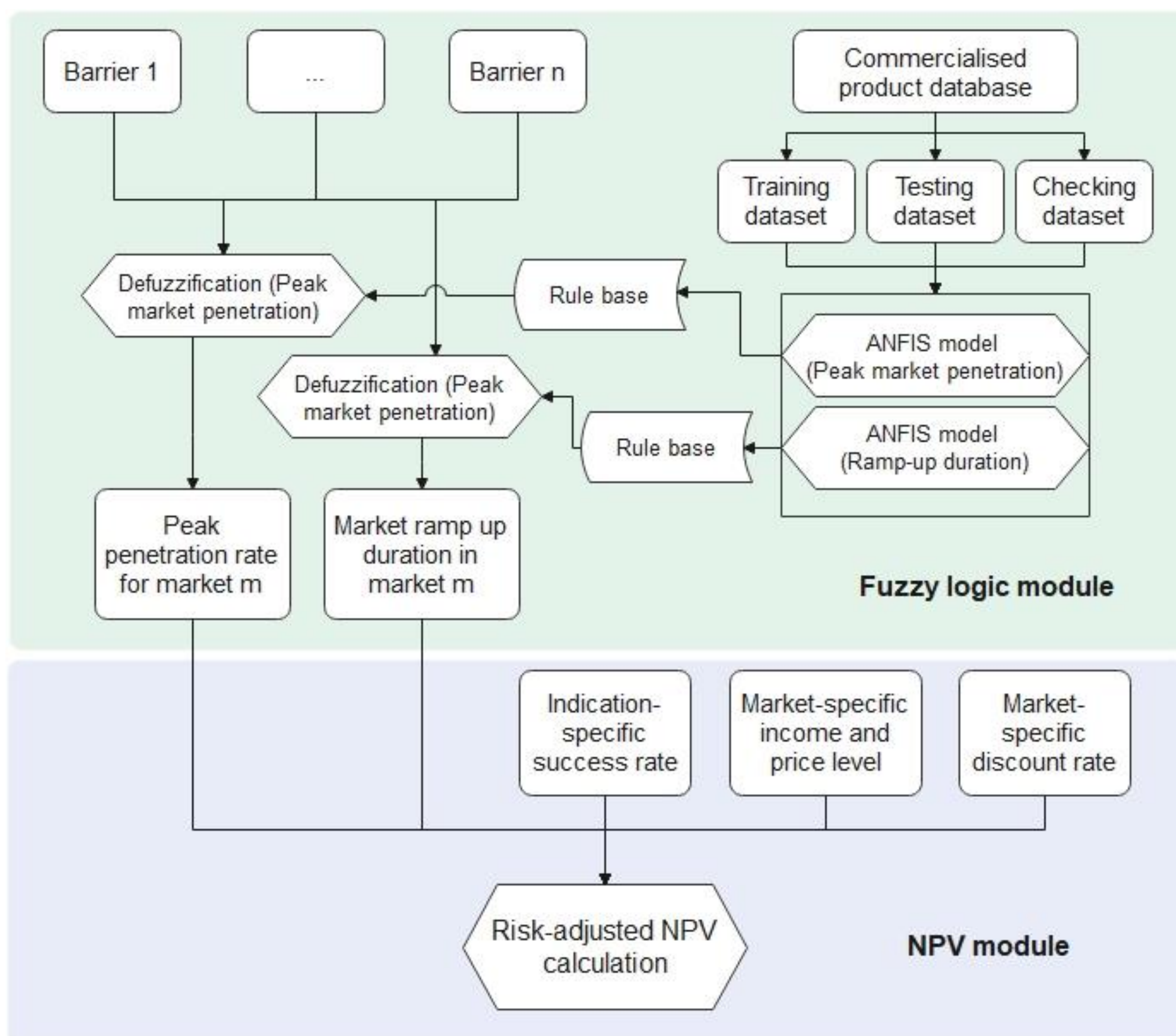


Figure 5.1 Model structure

5.2.3 ANFIS model implementation

The ANFIS model is implemented using the MATLAB R2020a Fuzzy Logic Toolbox (Mathworks, Massachusetts, United States).

5.2.3.1 Step 1: Define the input and output variables of the system.

The main barriers to the commercialisation of cell therapies have been extensively discussed in literature [22], [203] and the inputs are selected based on published literature and experts' opinion. Ten market barriers are identified as inputs of the system (Table 5.1)

and the output variables are two indicators of the market performance of the product, namely peak market penetration and time-to-peak sales.

Table 5.1 Commercialisation barriers linguistic variables and fuzzy scoring framework

Barrier	Linguistic values	Description
Usability: Difficulties in use of products in clinical environment	Difficult	Difficult-to-use product, e.g. long turnaround time, multiple hospital visits
	Medium	Moderately easy-to-use product
	Easy	Easy-to-use product, procedure can be completed in out-patient setting
Infrastructure: Clinical and manufacturing facilities for use and production of products	Poor	Few eligible hospitals, poor supply chain networks, poor manufacturing conditions
	Fair	Some eligible hospitals, Fair supply chain networks, Good manufacturing conditions
	Excellent	Many eligible hospitals, Good supply chain networks, Excellent manufacturing conditions
Regulation: Complexity of regulatory approval processes	Difficult	Difficult regulatory approval processes in the market. No fast-track designations for orphan drugs. High requirements for additional data.
	Moderate	Fair regulatory approval processes and requirements
	Simple	Fast-track designations and fast turnaround time for regulatory approval processes
Cost effectiveness: Cost weighed against demonstrated benefit	Low	Incremental per QALY cost exceed market threshold
	Moderate	Incremental per QALY cost equal or slightly exceed market threshold, but the cost can be reimbursed via special routes
	High	Incremental pre QALY cost below market threshold
Safety: Safety data from clinical trials for the product	Low	Poor safety data and serious adverse events
	Moderate	Moderate safety data and some adverse events
	High	Strong safety data and little adverse events
Market competition: Product uniqueness and applicable market	Saturated	There are many other products for the indication
	Fair	There are a few products for the indication
	Unmet	There are no other products for the indication
Production indication:	Ultra-niche	Orphan drug status, ultra-niche disease

Product indication orphan status	Niche	Orphan drug status
	Mass	For a mass patient population
Efficacy: Efficacy data from clinical trials	Numerical input	Reported value in clinical trial
Manufacturing issues: Difficulties in manufacturing, quality, scale-up and cost	High	Complex product and production processes, occurrence of out-of-specification batches, very expensive to produce
	Moderate	Moderately difficult to produce
	Low	Easy to produce and easy to scale-up/out, minimum manipulation, cheap to produce
Reimbursement: Reimbursement tracks within the market	Difficult	The market does not reimburse the treatment, e.g. HTA agencies reject the product, insurance companies do not reimburse the product. Negative decision by national HTA bodies.
	Moderate	The market reimburses the treatment through special routes or partial reimbursement via insurance companies. Restricted or conditional decision by national HTA bodies.
	Easy	The market reimburses the treatment fully. Positive decision by national HTA bodies.

5.3.3.2 Step 2: Data collection

Firstly, commercialised advanced therapy products are identified. This includes tissue-engineered products, cell and gene therapy products. The markets considered in this exercise are United States, Canada, EU5 (UK, France, Germany, Spain, Italy), China, Japan, South Korea and Australia. The products and respective assessments in each of the markets can be found in Appendix 5.1.

The products are then assessed in respective markets according to the market barrier criteria (Table 5.1) and the market performance of these products are identified through company reports, HTA agency reports and analyst estimation reports. Together 100 datasets were identified across 28 commercialised regenerative medicine products in 11 countries. Using Chen and Hwang's [230] numerical approximation system, the linguistic terms are

converted into crisp values which are then used as inputs to the neural network. The 3-tiered linguistic terms correspond to the values 0.1667 (Low), 0.5000 (Medium) and 0.8333 (High). The dataset can be found in Appendix 5.1.

5.3.3.3 Step 3: ANFIS model implementation

Together, 100 training data sets with 100 epochs were used to train, test and check the ANFIS model. The data points were randomised in Excel and split into training, testing, and checking datasets with the ratio 70:15:15. The training dataset is used to train the network which tunes the model parameters using the specified input/output training data. A hybrid training algorithm using a combination of backpropagation gradient descent methods to calculate input membership function parameters and the least-square method to calculate the parameters of output function are used in the training process. The testing dataset is used to validate the model being built through predicting responses using the trained model while tuning the model's hyperparameters. Finally, the checking dataset is an independent dataset that is used to provide an unbiased evaluation of the final model fit on the training dataset. For cases where the product was not commercialised in a certain market due to failure to attain local HTA approval, the data point was excluded from the ramp-up duration model. Thirty data points were excluded, and the dataset was split in the ratio of 50:10:10.

The ANFIS model properties are summarised in Table 5.2. Due to the high number of input parameters, subtractive clustering technique was used to reduce the input size and reduce the number of rules generated. Subtractive clustering is a data clustering algorithm that clusters input into a similar group with the same properties using the improved Mountain method of data partitioning which automatically determines the best possible number of clusters for a given input-output dataset [231]. As the Neural Network Toolbox in MATLAB uses a technique called early stopping to prevent overfitting or underfitting, a high epoch

number is chosen. The training process stops when the error on the testing set to increase such that the model with the minimum testing error can be chosen.

To account for the slight difference in the data set, where products not commercialised are not included in the training and testing of the ramp-up duration output variable, peak market penetration and market ramp-up duration are modelled in separate networks using the same ANFIS properties. The IF-THEN rules generated by the model can be found in Appendix 5.3.

Table 5.2 ANFIS properties

Parameter	Description/value
Type of fuzzy inference system	Sugeno
Optimization method for training FIS	Subtractive clustering
Range of influence	0.5
Squash factor	1.25
Accept ratio	0.5
Reject ratio	0.15
Input number	10
Output number	1
Number of input membership functions	47, 47, 47, 47, 47, 47, 47, 47, 47, 47
Optimisation methods	Hybrid
Training epoch number	100

5.3.3.4 Model evaluation

To evaluate the ANFIS models, root mean square error (RMSE) of the training, testing and checking datasets are computed. RMSE is a standard way of measuring error in predictive quantitative models (*Eq 5.1*), where $\hat{y}_1$, $\hat{y}_2$, …, $\hat{y}_n$ are predicted values, y_1, y_2, …, y_n are observed values; and n is the number of observations.

$$RMSE = \sqrt{\sum_{i=1}^{n} \frac{(\hat{y}_i - y_i)^2}{n}} \quad \text{Eq 5.1}$$

5.3.3.5 Sensitivity analysis

To better understand the contribution of the input variables on the model outputs, a sensitivity analysis was carried out. To determine the percentage contribution of each of the input variables, the said input is varied whilst all other input variables are kept constant, and the importance of the variables is ranked. All input variables in the base case are set to be 'average', and for each iteration, one variable is adjusted to 'poor' to better understand the impact of the input on the final peak market penetration and ramp-up duration.

5.2.4 rNPV model

The model builds on existing risk-adjusted NPV models adapted for biotechnology and biopharmaceutical use cases [218], [232] considering uncertainties in the commercialisation of ATMPs.

5.2.4.1 Peak market penetration and market ramp-up duration

Market uptake of medicine is affected by many factors, such as physician adoption, patient behaviour, market acceptance to new drugs, reimbursement etc [203], [233]. The same product can be very different in different markets, e.g. physicians in certain markets may be more inclined to prescribe established drugs and the cost-effectiveness may assume a greater weight in the decision-making process in markets where a centralised drug appraisal mechanism is in place. The peak market penetration (∂) and ramp-up duration (τ) from the ANFIS module are used to compute the market share in a specific market ($M_{m,t}$) (Eq *5.2*) and the projected revenue ($R_{t,m}$) (*Eq 5.6*).

$$t < \tau, M_{m,t} = \frac{\partial}{\tau} t \qquad \textit{Eq 5.2}$$

$$t \geq \tau, M_{m,t} = \partial$$

5.3.4.2 Revenue estimation

A bottom-up approach is used to estimate the revenue in each market [234]. The estimated number of cases in market m at year t ($T_{m,t}$) is given by the total population in market m (W_m) multiplied by annual population growth (g_m) the age-standardised incidence rate for a specific indication(α) and the line of treatment adjustment factor (l) (*Eq 5.3*). The line of treatment adjustment factor is introduced in this model as autologous cell therapies such as CAR-T treatments are usually indicated as the second or third-line treatment due to their high risk and cost [235].

$$T_{m,t} = W_m * (1 + g_m)^{t-1} * \alpha * l \qquad \text{Eq 5.3}$$

Typically, price in different markets depends on their respective income levels, reimbursement mechanisms and competition level. Previous studies have shown a strong correlation between the per capita GDP and drug prices [236]. This is roughly consistent with multi-national autologous cell therapy pricing in recent years (Appendix 5.2).

For simplicity, this model normalises the originator country product selling price (P_m) to the per capita GDP of the other markets (GDP_m) (*Eq 5.4*). Revenue for market m at year t ($R_{t,m}$) is given by the market share in a certain market at year t multiplied by the selling price (Eq *5.6*).

Due to geographical constraints, it is reasonable to assume manufacturing in respective markets through licensing, contract manufacturing or as a new market entrant. However, due to the relative few GMP-compliant automated equipment and raw material suppliers, the difference in cost is likely to be reflected only in labour costs which are around 5% of the total cost of goods (COG) [181], which is normalised to country income level to obtain the market-specific COGs (COG_m) (Eq *5.5*).

$$P_m = P_{m1} * \frac{GDP_m}{GDP_{m1}} \quad \text{Eq 5.4}$$

$$COG_m = COG_{m1} * 0.95 + COG_{m1} * 0.05 * \frac{GDP_m}{GDP_{m1}} \quad \text{Eq 5.5}$$

$$R_{t,m} = (P_m - COG_m) * T_{m,t} * M_{m,t} \quad \text{Eq 5.6}$$

The rNPV formula for a market m ($rNPV_m$) is given by risk-adjusting present-value-discounted net cash flows as shown in *Eq 5.7* [218]. The likelihood of approval given by multiplying the probability of success of all phases (r_{LOA}), probability of success for certain indication at different clinical trial phases (ρ_t) [237], discount rate for different markets ($d_{t,m}$) [238] and the product developmental costs in market before approval such as patent and regulatory costs for different market m at year t ($C_{t,m}$) and are described in Appendix 5.4. The global rNPV ($rNPV_{global}$) is given by summation of the rNPV for all markets for the decision-maker to understand the valuation of the product worldwide.

$$rNPV_m = \sum_t \frac{r_{LOA} R_{t,m}}{(1 + d_{t,m})^t} - \sum_t \frac{\rho_t C_{t,m}}{(1 + d_{t,m})^t} \quad \text{Eq 5.7}$$

$$rNPV_{global} = \sum_m rNPV_m$$

5.2.5 Hypothetical case study

To illustrate the application of the model, two hypothetical products – an autologous and allogeneic CAR-T product for non-Hodgkin’s lymphoma of predefined characteristics (Table 5.3) are introduced and the NPV of each product in different markets is calculated.

Four scenarios are compared: (1) Autologous product without orphan designation, (2) Autologous product with orphan designation, (3) Allogeneic product without orphan designation and (4) Allogeneic product with orphan designation. The costs of goods for the products are benchmarked using previously conducted studies [165], [181].

The linguistic inputs are first converted using the numerical approximation system [230] into crisp values which are then used as inputs to the neural network. The output values are then used as inputs for NPV calculations.

Table 5.3 Hypothetical product characteristics in different markets

	US	EU	China	Australia
Market-specific parameters				
Population, W_m (in million)	328	446	1,398	25.4
Annual population growth, g_m	0.5%	0.2%	0.4%	1.5%
Income level, GNI per capita (USD) (World Bank 2020)	65,760	46,473	10,410	54,910
Stem cell clinic infrastructure [239]	187	24	23	19
Discount rate (early) [238]	19.7%	18.2%	15.1%	15.1%
Discount rate (mid) [238]	16.5%	15.8%	14.0%	14.0%
Discount rate (late stage) [238]	13.7%	13.5%	13.0%	13.0%
<u>Non-orphan</u>				
Tax rate	14.5%	20.0%	16.0% [240]	30.0%
Tax rebate during trials	25.0%	0.00%	0.00%	50.0%
Additional clinical trial requirements if approved elsewhere	N	N	Y Compulsory for Class III medical devices	N
Patent maintenance fees (USD)	5,980	5,000	3,580	1,200
Regulatory fees (in local currency)	BLA: $310,764	Marketing authorisation application: €296,500	First registration: ¥153,600 (domestic)/	Class 2, 3, 4 biological annual charge for

			¥308,800 (imported)	ARTG inclusion: AUS 6,890
		Scientific advice: €89,000	Renewal (every 5 years): ¥40,800	Manufacturing site (annual): AUS 166,800
		Annual fee: €106,300	Annual Clinical trial approval (high-risk devices): ¥43,200	Site inspection fees Item (Annual): $22,300
<u>Orphan incentives</u>				
Tax rate	14.5%	20.0%	3.0%	30.0%
Orphan drug approval fast track policies	Y	Y	Y	Y
Orphan drug authorisation cost reduction	50%	100%	50%	100%
Indication-specific parameters				
Disease prevalence, α_y	0.020%	0.007%	0.015%	0.022%
Probability of success, ρ	Phase 1: 57.1% Phase 2: 40.0% Phase 3: 44.0% Registration to approval: 83.3%			
Product-specific parameters				
Price, P_m (USD)	375,000	265,015	59,364	313,127
Cost of goods, COG_m (USD)				
Autologous	50,000	49,267	47,896	49,588
Allogeneic	5,000	4,927	4,790	4,959
Line of treatment, l	20%	20%	20%	20%

Product commercialisation barriers					
Autologous CAR-T product	Usability	Difficult	Difficult	Difficult	Difficult
	Infrastructure	Excellent	Excellent	Fair	Excellent
	Regulation	Fair	Fair	Difficult	Fair
	Cost-effectiveness	Moderate	Moderate	Low	Moderate
	Safety	High	High	High	High
	Market competition	Moderate	Moderate	Low	Low
	Product indication	Niche	Niche	Niche	Niche
	Efficacy	High	High	High	High
	Manufacturing issues	High	High	High	High
	Reimbursement	Moderate	Moderate	Difficult	Moderate
Allogeneic CAR-T product	Usability	Fair	Fair	Fair	Fair
	Infrastructure	Excellent	Excellent	Fair	Excellent
	Regulation	Difficult	Difficult	Difficult	Fair
	Cost-effectiveness	Moderate	Moderate	Low	Moderate
	Safety	Moderate	Moderate	Moderate	Moderate
	Market competition	Moderate	Moderate	Low	Low
	Product indication	Niche	Niche	Niche	Niche
	Efficacy	High	High	High	High
	Manufacturing issues	High	High	High	High
	Reimbursement	Moderate	Moderate	Difficult	Moderate

5.3. Results

The results section is divided into 3 main parts: (1) ANFIS model performance; (2) Sensitivity analysis and (3) Hypothetical case study.

5.3.1 ANFIS model performance

The properties of the generated ANFIS model are shown in Table 5.4. The RMSE of the models shows prediction errors around ±10% for peak market penetration and ±1 year for ramp-up duration for both the testing and checking data. The generated rule base can be found in Appendix 5.3.

Table 5.4 ANFIS models properties

	Peak Market Penetration	Ramp-up duration
Number of Rules generated	49	33
RMSE (in absolute values)		
Training data	0.061	0.514
Testing data	0.086	0.454
Checking data	0.086	0.572

Figure 5.2 shows the actual and predicted values for peak market penetration, 90% of the data points lie within ±10% of perfect prediction. The R^2 value for the testing data and checking data are 0.916 and 0.910 respectively, indicating a strong correlation between the actual and predicted data. Notably, the outlying data points are the ones with higher market penetration. This may be due to the limited dataset for ultra-niche products where the peak market penetration can be very high, causing the predicted values to be less accurate. Figure 5.3 shows the actual and predicted values for ramp-up duration. 90% of the data points lie within ±10% of perfect prediction, with the R^2 value for the testing data and checking data being 0.988 and 0.974 respectively, indicating a strong correlation in the data sets.

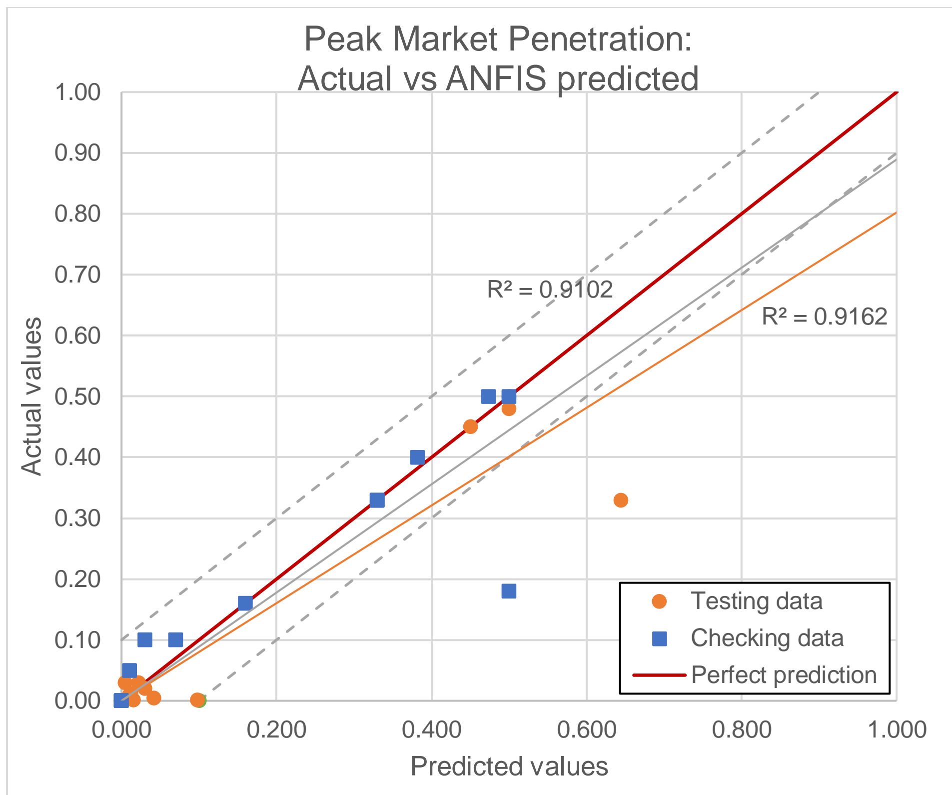


Figure 5.2 Scatter plot showing ANFIS model-predicted and actual peak market penetration values: testing data (square) and checking data (circle), dotted lines show the bounds of ±10% error

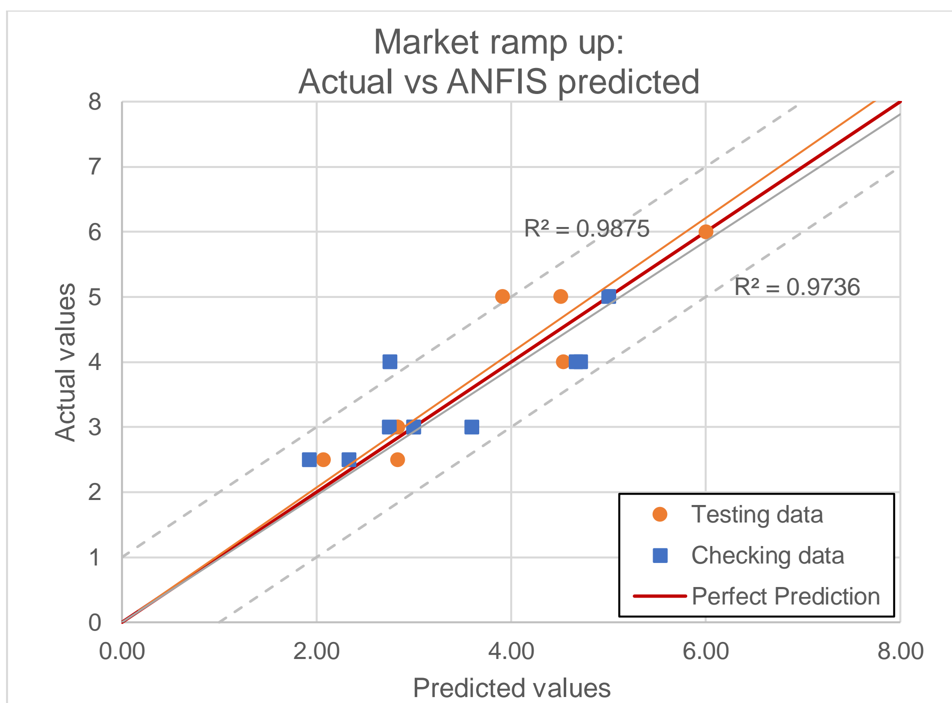


Figure 5.3 Scatter plot showing ANFIS model-predicted and actual market ramp-up duration: testing data (square) and checking data (circle), dotted lines show the bounds of ±10% error

5.3.2 ANFIS model sensitivity analysis

The sensitivity analysis (Table 5.5) shows that niche and autologous products are more likely to achieve higher market penetration while less favourable cost-effectiveness evaluations and reimbursement environment reduce the peak market penetration significantly.

For the ramp-up duration, where the product indication is more niche, the duration it takes to ramp up to peak penetration is lower. All other input variables cause a less-than-proportionate effect on the output.

Table 5.5 Sensitivity analysis of ANFIS models

	Peak market penetration	Ramp-up duration
Usability	385%	1%
Infrastructure	1%	-4%
Regulation	21%	-4%
Cost effectiveness	-51%	-12%
Safety	-5%	-5%
Market competition	-5%	-4%
Product indication	306%	-33%
Efficacy	-21%	-5%
Manufacturing issues	-33%	-5%
Reimbursement	-51%	-1%

5.3.3 Hypothetical case study

The application of the model for the case study follows the flowchart presented in Figure 5.1. Firstly, the peak market penetration and ramp-up duration are computed by the ANFIS model, which are subsequently used as the rNPV model input.

5.3.3.1 ANFIS model output

The product and market characteristics (Table 5.3) are inputted into the ANFIS model and the output for respective markets are computed (Table 5.6).

Due to the lower profit margin after selling price adjustment (*Eq 5.4*) in relatively lower GDP markets (i.e. China), the model showed that it is infeasible for the autologous product to enter the market and a low penetration rate for the allogeneic product. The ramp-up duration is also longer than other markets due to more uncertain market conditions.

Table 5.6 Output variables from ANFIS models

		US	EU	China	Australia
Autologous	Peak market penetration (%)	43.9%	43.9%	0.0%	47.3%
	Ramp-up duration (years)	3.70	3.70	6.43	1.64
Allogeneic	Peak market penetration (%)	40.7%	40.7%	7.7%	46.0%
	Ramp-up duration (years)	2.23	2.23	4.07	2.36

5.3.3.2 rNPV calculation

The rNPV calculated for the 4 scenarios are detailed in Table 5.7. With orphan designations, all target markets have a higher NPV. It is noted that the calculation shows that it is not profitable to commercialise an autologous product in China due to lower profit margins and low market penetration. The overall positive impact of orphan designation was shown to be greater in autologous products than in allogeneic products.

Table 5.7 rNPV for hypothetical scenarios

Scenario	1	2	3	4
Designation	Non-Orphan	Orphan	Non-Orphan	Orphan
Product type	Autologous	Autologous	Allogeneic	Allogeneic
US ($)	1442m	3240m	2060m	3798m
EU ($)	490m	944m	622m	1177m
China ($)	-64m	-47m	66m	217m
Australia ($)	66m	236m	75m	265m
Global NPV ($)	1997m	4420m	4373m	5456m

To evaluate sensitivity of the calculated NPV to the ANFIS model error, the best-case scenario and worst-case scenario are evaluated where the best-case is given by peak market penetration of $\left(\partial + RMSE_{testing}\right)$ and ramp-up duration of $(\tau - RMSE_{testing})$ and the worst-case scenario is given by peak market penetration of $\left(\partial - RMSE_{testing}\right)$ and ramp-up duration of $(\tau + RMSE_{testing})$. The sensitivity analysis of the rNPV to the peak market penetration and ramp-up duration from the ANFIS model (Figure 5.4) shows that China is most sensitive to market uncertainties represented by the ANFIS output variables due to lower profit margins and less favourable market barrier conditions. These risks can be mitigated through employing different market entry modes such as licensing and joint venture. This is also consistent with recent market activities with increasing joint ventures and strategic partnerships in Asia where the regulatory landscape and market channels are less certain [241].

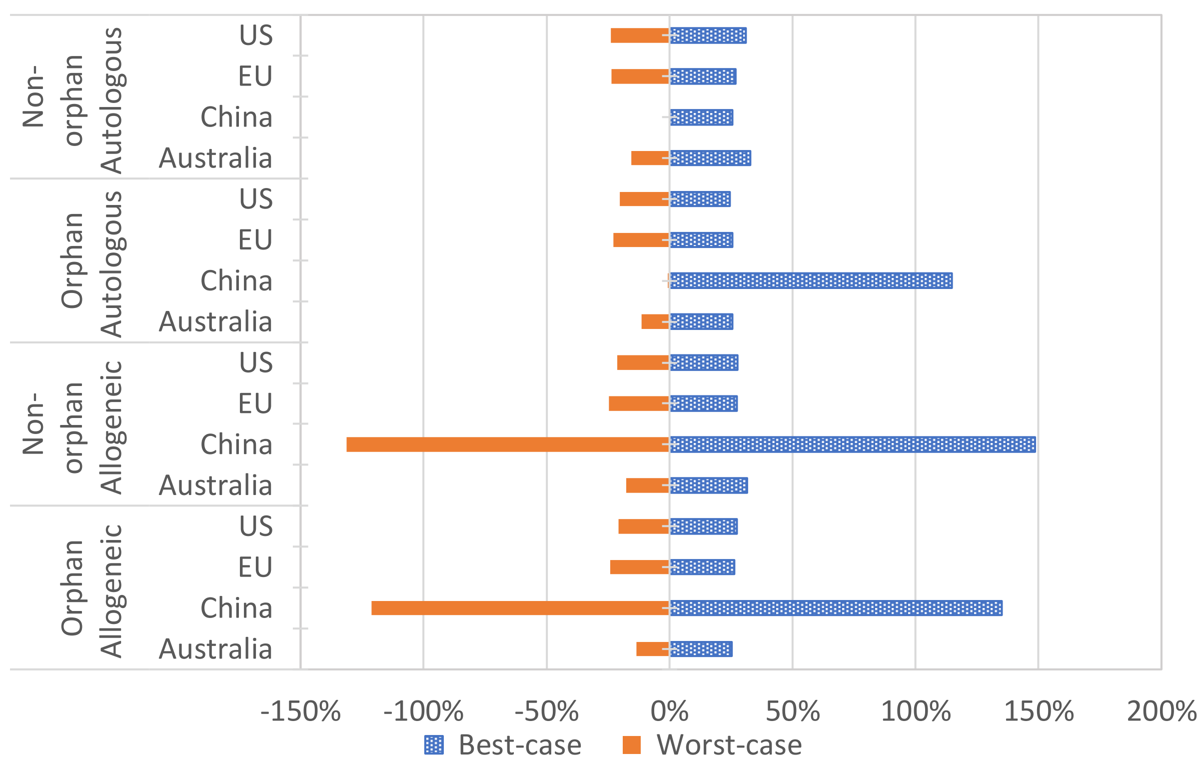


Figure 5.4 Sensitivity of rNPV to peak market penetration and ramp-up duration errors from ANFIS model

5.4. Discussion

The valuation model, illustrated via the hypothetical case study, provides a systematic method of incorporating uncertainties and market barriers into the rNPV calculation that is widely used in the biotech and financial sectors for the valuation of projects and companies.

From the sensitivity analysis (Table 5.5), the key barriers affecting market penetration and ramp-up duration are identified to be usability, nicheness of product indication, cost-effectiveness, reimbursement issues and manufacturing issues. These are loosely consistent with the commercial expert interview findings conducted by Davies et al [242] which cited reimbursement, manufacturing and cost-effectiveness are the top three biggest barriers to adoption. While complex regulatory requirements have frequently been cited as a major barrier to commercialisation [243], [244], in recent years, most countries have clarified their policies and improved their mechanisms in facilitating orphan drug entry and

commercialisation of innovative medical products; one example of this is, China's new policy on expediting orphan drug review to within 3 months [211].

From the model, the NPV of a product in various markets can be derived. This can inform further decisions for companies for market entry strategies. For ATMPs, uncertainties in the long-term safety and efficacy of cell and gene therapies were cited as one of the reasons for companies to shift towards licensing and collaborative agreements instead of upfront mergers and acquisitions [245]. Joint venture companies (JV) are commonly defined as a business arrangement where two or more parties agree to pool resources and share risks and returns through shared ownership of a new entity. This arrangement allows foreign companies to circumvent mandatory local investment laws, gain access to local know-how, market-specific knowledge, local resources and distribution networks, reduce risks and reduce the time required for a new product launch in a foreign country [246]. This in turn mitigates some of the commercialisation uncertainties and barriers. Innovative frameworks for pricing and reimbursement have been introduced. These include (1) risk-sharing agreements (RSAs) between healthcare services and manufacturers, (2) payment-for-performance schemes under which future payments are benchmarked on positive health outcomes for patients or rebates in cases in which the therapy was not as efficacious as expected, (3) pay-over-time schemes where the cost of the therapies is amortised over several years, and (4) risk pools/re-insurance where the risk is shared by multiple insurance companies [247].

Another commercialisation hurdle not considered in this study is the patent landscape. Whilst cell-related patents have been filed and issued around the world (for instance, >100 filed in the United States, China, Australia and Canada for CAR-T [248]), the patentability of autologous cell therapies may be questionable in US and EU patent laws [249], [250]. The

validity of these patents may be a potential challenge that can lead to significant losses in sales and profit [251], causing further uncertainties in the commercialisation landscape.

5.5. Strength and limitations

This valuation model provides a methodology for supporting global commercialisation decisions of advanced therapies which incorporates ambiguous commercialisation barriers into advanced therapy NPV calculation. In particular, ANFIS offers a systematic method for aggregating empirical learnings from currently commercialised products for the prediction of market peak penetration and ramp-up rates through a nonlinear model. Making the fuzzy logic module an extension to the rNPV approach makes the method more usable as rNPV is the most used technique in biopharma valuations.

However, there are a few drawbacks to the model. Firstly, drug pricing in the model is normalised to the country's GDP, but in reality, national health services can negotiate the price of the product. The level of centralisation of local governments and their respective decision-making pathways are quite different especially between centralised HTA models and private insurance models. If more data is available, it would make sense to split up private and public reimbursement models where the cost-effectiveness of a particular drug may be valued differently. Secondly, as ATMPs are still new, there is a limited amount of data especially for recently approved products and use of analyst estimates may skew the results towards more optimistic values. In reality, the linguistic barriers may be perceived differently by each expert. This can be mitigated by having more experts evaluate the product performance in the market. Thirdly, some of the products included in the training database used in this work are very niche and span a period of over 20 years, during which the market and regulatory conditions have changed. Using past products as the training set means the system is backward-looking. Moreover, the rule of thumb for the size of the ANFIS dataset is

for the training set to be at least 50 times the number of adjustable parameters in the neural network [252]. As more products are commercialised, the dataset can be expanded to enhance the reliability and predictive power of the model.

5.6. Conclusion

This work proposes a systematic method of incorporating ambiguous uncertainties and market barriers into the conventional net present value calculation for ATMPs.

A training database for ANFIS was assembled from the information available from existing products. Typical market barriers were analysed and treated as inputs of the ANFIS network to predict the peak market penetration and ramp-up duration of a new product, which in turn feed into the evaluation of the risk-adjusted NPV (rNPV) of a certain ATMP product in different markets. A hypothetical product was used to illustrate the applicability of the approach. The implemented ANFIS network models showed reasonable accuracies. With more products moving into the market, the database for training the model can be expanded to provide more accurate results.

The hypothetical case study has demonstrated the applicability of the model and shown that the rNPV is most sensitive to usability, product indication, cost-effectiveness and reimbursement. The study also demonstrated how the model can be used to estimate rNPV for further commercialisation decisions such as whether or not to enter a market and inform decisions for market entry mode.

Appendix 5.1 Commercialised product dataset

ID	Country	Product	Usability	Infra-structure	Regu-lation	Cost effective-ness	Safety	Market competition	Product indication	Efficacy	Manu-facturing issues	Reimburse-ment	Peak market penetration	Ramp-up duration (years)
1	Australia	Imlygic	Easy	Fair	Moderate	Moderate	Moderate	Fair	Niche	0.30	Low	Moderate	1%	4
2	Australia	Yescarta	Difficult	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Easy	50%	2.5
3	Australia	Luxturna	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	30%	2
4	Australia	MACI	Difficult	Fair	Simple	Moderate	High	Fair	Mass	0.80	Moderate	Moderate	3%	5
5	Australia	Kymriah	Difficult	Excellent	Moderate	Moderate	Moderate	Unmet	Niche	0.75	Moderate	Easy	50%	2.5
6	Canada	Luxturna	Easy	Excellent	Moderate	Low	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	63%	4
7	Canada	Yescarta	Difficult	Excellent	Moderate	Low	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	25%	2.5
8	Canada	Zolgensma	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.66	Moderate	Moderate	30%	4
9	Canada	Kymriah	Difficult	Excellent	Moderate	Moderate	Moderate	Unmet	Niche	0.75	Moderate	Moderate	45%	2.5
10	Canada	Prochymal	Medium	Fair	Moderate	Moderate	Moderate	Unmet	Mass	0.58	High	Difficult	0%	4
11	China	Activskin	Medium	Fair	Difficult	Low	Moderate	Saturated	Mass	0.80	High	Difficult	5%	5
12	China	Gendicine	Easy	Fair	Moderate	Low	Moderate	Unmet	Niche	0.90	Moderate	Difficult	9%	5
13	China	Provenge	Difficult	Poor	Difficult	Moderate	Moderate	Fair	Niche	0.23	High	Moderate	56%	10
14	China	Oncorine	Medium	Fair	Moderate	Low	Moderate	Unmet	Niche	0.79	Moderate	Moderate	0%	4
15	France	Alofisel	Medium	Fair	Moderate	Moderate	Moderate	Fair	Mass	0.52	Moderate	Moderate	3%	5
16	France	Holoclar	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.72	High	Moderate	7%	3
17	France	Imlygic	Easy	Fair	Moderate	Low	Moderate	Fair	Niche	0.30	Low	Difficult	0%	0
18	France	MACI	Difficult	Fair	Moderate	Low	High	Fair	Mass	0.80	Moderate	Difficult	0%	0
19	France	Glybera	Easy	Excellent	Moderate	Low	High	Fair	Ultra niche	0.50	Low	Difficult	0%	0
20	France	Kymriah	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Niche	0.75	High	Moderate	50%	3
21	France	Spherox	Medium	Fair	Moderate	Low	High	Saturated	Mass	0.50	High	Difficult	0%	0

22	France	Zalmoxis	Medium	Fair	Moderate	Low	Moderate	Unmet	Ultra niche	0.51	High	Difficult	0%	0
23	France	Strimvelis	Medium	Fair	Moderate	Low	High	Unmet	Ultra niche	1.00	High	Difficult	0%	0
24	France	Yescarta	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	50%	3
25	France	Luxturna	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	30%	5
26	France	Zolgensma	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.66	Moderate	Moderate	33%	3
27	France	Provenge	Difficult	Fair	Difficult	Low	Moderate	Fair	Niche	0.23	High	Difficult	0%	0
28	Germany	Zolgensma	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.66	Moderate	Moderate	33%	3
29	Germany	Zalmoxis	Medium	Fair	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.51	High	Moderate	1%	3
30	Germany	Holoclar	Difficult	Fair	Difficult	Low	Moderate	Unmet	Ultra niche	0.72	High	Difficult	0%	0
31	Germany	Imlygic	Easy	Excellent	Moderate	Low	Moderate	Fair	Niche	0.30	Low	Difficult	0%	0
32	Germany	Provenge	Difficult	Fair	Difficult	Low	Moderate	Fair	Niche	0.23	High	Moderate	0%	0
33	Germany	Yescarta	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	50%	3
34	Germany	MACI	Difficult	Fair	Moderate	Low	High	Fair	Mass	0.80	Moderate	Moderate	0%	0
35	Germany	Spherox	Medium	Fair	Moderate	Moderate	High	Saturated	Mass	0.50	High	Easy	5%	3
36	Germany	Luxturna	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	50%	1
37	Germany	Alofisel	Medium	Fair	Moderate	Moderate	Moderate	Fair	Mass	0.52	Moderate	Moderate	2%	3
38	Germany	Kymriah	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Niche	0.75	High	Moderate	48%	3
39	Germany	Strimvelis	Medium	Fair	Moderate	Low	High	Unmet	Ultra niche	1.00	High	Difficult	0%	0
40	Germany	Glybera	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.50	Low	Moderate	16%	6
41	Italy	Alofisel	Medium	Fair	Moderate	Low	Moderate	Fair	Mass	0.52	Moderate	Difficult	0%	0
42	Italy	Yescarta	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Difficult	0%	0
43	Italy	Luxturna	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Difficult	0%	0
44	Italy	Glybera	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.50	Low	Moderate	16%	6
45	Italy	MACI	Difficult	Fair	Moderate	Low	High	Fair	Mass	0.80	Moderate	Difficult	0%	0
46	Italy	Zalmoxis	Medium	Fair	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.51	High	Easy	1%	3
47	Italy	Spherox	Medium	Fair	Moderate	Low	High	Saturated	Mass	0.50	High	Difficult	0%	0
48	Italy	Strimvelis	Medium	Excellent	Moderate	Moderate	High	Unmet	Ultra niche	1.00	High	Moderate	33%	1

49	Italy	Provenge	Difficult	Fair	Difficult	Low	Moderate	Fair	Niche	0.23	High	Difficult	0%	0
50	Italy	Imlygic	Easy	Fair	Moderate	Low	Moderate	Fair	Niche	0.30	Low	Difficult	0%	0
51	Italy	Kymriah	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Niche	0.75	High	Moderate	50%	3
52	Italy	Zolgensma	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.66	Moderate	Moderate	33%	3
53	Italy	Holoclar	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.72	High	Easy	10%	3
54	Japan	Heartsheet	Difficult	Fair	Moderate	Moderate	Moderate	Fair	Niche	0.80	High	Moderate	3%	5
55	Japan	Zolgensma	Easy	Excellent	Moderate	High	Moderate	Unmet	Ultra niche	0.66	Moderate	Easy	95%	1
56	Japan	Kymriah	Difficult	Excellent	Moderate	Moderate	Moderate	Unmet	Niche	0.75	Moderate	Moderate	45%	2
57	Japan	JACC	Difficult	Fair	Moderate	Moderate	Moderate	Fair	Mass	0.50	High	Moderate	10%	4
58	Japan	Yescarta	Difficult	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	40%	2
59	South Korea	Hearticellgram	Difficult	Fair	Moderate	Low	Moderate	Fair	Niche	0.50	High	Difficult	3%	5
60	South Korea	Cartistem	Medium	Fair	Moderate	Low	Moderate	Saturated	Mass	0.50	Moderate	Difficult	0%	6
61	South Korea	Cupistem	Difficult	Fair	Moderate	High	Moderate	Fair	Mass	0.75	High	Easy	3%	5
62	Spain	Strimvelis	Medium	Fair	Moderate	Moderate	High	Unmet	Ultra niche	1.00	High	Easy	33%	1
63	Spain	Holoclar	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.72	High	Easy	7%	3
64	Spain	Kymriah	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Niche	0.75	High	Moderate	50%	3
65	Spain	Alofisel	Medium	Fair	Moderate	Moderate	Moderate	Fair	Mass	0.52	Moderate	Moderate	3%	5
66	Spain	Imlygic	Easy	Fair	Moderate	Moderate	Moderate	Fair	Niche	0.30	Low	Easy	1%	5
67	Spain	Spherox	Medium	Fair	Moderate	Low	High	Saturated	Mass	0.50	High	Difficult	0%	0
68	Spain	Provenge	Difficult	Fair	Difficult	Low	Moderate	Fair	Niche	0.23	High	Difficult	0%	0
69	Spain	Yescarta	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	50%	3
70	Spain	Glybera	Easy	Excellent	Moderate	Low	High	Fair	Ultra niche	0.50	Low	Difficult	0%	0
71	Spain	MACI	Difficult	Fair	Moderate	Low	High	Fair	Mass	0.80	Moderate	Difficult	0%	0
72	Spain	Zalmoxis	Medium	Fair	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.51	High	Easy	1%	3
73	Spain	Luxturna	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Difficult	0%	0
74	UK	Alofisel	Medium	Fair	Moderate	Low	Moderate	Fair	Mass	0.52	Moderate	Difficult	0%	0

75	UK	Zynteglo	Medium	Fair	Moderate	Low	Low	Fair	Ultra niche	0.90	Moderate	Difficult	0%	0
76	UK	Strimvelis	Medium	Fair	Moderate	Moderate	High	Unmet	Ultra niche	1.00	High	Easy	100%	1
77	UK	Holoclar	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.72	Moderate	Moderate	6%	5
78	UK	Zalmoxis	Medium	Fair	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.51	High	Moderate	0%	0
79	UK	Glybera	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.50	Low	Difficult	0%	0
80	UK	Provenge	Difficult	Fair	Difficult	Low	Moderate	Fair	Niche	0.23	High	Difficult	0%	0
81	UK	Yescarta	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	50%	2.5
82	UK	Luxturna	Easy	Excellent	Moderate	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	48%	4
83	UK	MACI	Difficult	Fair	Moderate	Low	High	Fair	Mass	0.80	Moderate	Difficult	0%	0
84	UK	Spherox	Medium	Fair	Moderate	Moderate	High	Saturated	Mass	0.50	High	Easy	5%	3
85	UK	Imlygic	Easy	Excellent	Moderate	High	Moderate	Fair	Niche	0.3	Low	Moderate	1%	3
86	UK	Kymriah	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Niche	0.75	High	Moderate	50%	2.5
87	UK	TECARTUS	Difficult	Fair	Moderate	Moderate	Moderate	Fair	Ultra niche	0.87	Moderate	Moderate	18%	2.5
88	UK	Zolgensma	Easy	Excellent	Moderate	Moderate	High	Fair	Ultra niche	0.66	Moderate	Moderate	33%	3
89	US	Apligraf	Medium	Poor	Difficult	Low	Moderate	Saturated	Mass	0.56	High	Moderate	32%	4
90	US	MACI	Difficult	Fair	Moderate	Moderate	High	Fair	Mass	0.80	Moderate	Easy	1%	4
91	US	Provenge	Medium	Fair	Difficult	Low	Moderate	Fair	Niche	0.23	High	Difficult	9%	4
92	US	Kymriah	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Niche	0.75	High	Moderate	50%	2.5
93	US	Yescarta	Difficult	Fair	Difficult	Moderate	Moderate	Unmet	Ultra niche	0.93	Moderate	Moderate	50%	2.5
94	US	TECARTUS	Difficult	Fair	Moderate	Moderate	Moderate	Fair	Ultra niche	0.87	Moderate	Moderate	50%	2.5
95	US	Imlygic	Easy	Excellent	Moderate	Low	Moderate	Fair	Niche	0.30	Low	Easy	1%	5
96	US	Luxturna	Easy	Excellent	Moderate	Low	High	Unmet	Ultra niche	0.93	Moderate	Moderate	20%	3.5
97	US	Carticel	Difficult	Fair	Difficult	Moderate	High	Saturated	Mass	0.50	High	Difficult	1%	7
98	US	Epicel	Medium	Fair	Difficult	Moderate	High	Saturated	Mass	0.87	High	Moderate	1%	5
99	US	Zolgensma	Easy	Excellent	Moderate	Low	High	Fair	Ultra niche	0.66	Moderate	Moderate	58%	2
100	US	Laviv	Difficult	Fair	Moderate	Moderate	High	Saturated	Mass	0.59	High	Difficult	5%	4

Appendix 5.2 Cell therapy pricing in different markets

Product	Approval Country	Approval Date	Price
Provenge	United States	29/04/2010	$ 93,000.00
Provenge	European Union	06/09/2013	$ 61,500.00
Autologous chondrocyte cells (MACI)	European Union (UK)	27/06/2013	$ 21,000.00
Autologous chondrocyte cells (MACI)	United States	13/12/2016	$ 28,650.00
Yescarta	United States	18/10/2017	$ 447,600.00
Yescarta	European Union	23/08/2018	$ 412,460.00
Imlygic	United States	27/10/2015	$ 559,293.00
Imlygic	European Union (Germany)	16/12/2015	$ 316,245.00
Imlygic	Australia	16/11/2018	$ 237,677.00
Kymriah	United States	30/08/2017	$ 570,000.00
Kymriah	European Union (Germany)	27/08/2018	$ 416,481.00
Kymriah	European Union (UK)	27/08/2018	$ 364,948.00
Kymriah	Switzerland	05/09/2018	$ 371,000.00
Kymriah	Australia	19/12/2018	$ 423,898.28
Luxturna	United States	19/12/2017	$ 850,000.00
Luxturna	European Union	23/11/2018	$ 747,747.00

Appendix 5.3 Rules generated by ANFIS model

PeakMarket penetration rule base:

1. If (Usability is Usability) and (Infrastructure is in2cluster1) and (Regulation is in3cluster1) and (Cost-effectiveness is in4cluster1) and (Safety is in5cluster1) and (Market_competition is in6cluster1) and (Product_indication is in7cluster1) and (Efficacy is in8cluster1) and (Manufacturing_issues is in9cluster1) and (Reimbursement is in10cluster1) then (Peak_Market_Penetration is out1cluster1) (1)
2. If (Usability is in1cluster2) and (Infrastructure is in2cluster2) and (Regulation is in3cluster2) and (Cost-effectiveness is in4cluster2) and (Safety is in5cluster2) and (Market_competition is in6cluster2) and (Product_indication is in7cluster2) and (Efficacy is in8cluster2) and (Manufacturing_issues is in9cluster2) and (Reimbursement is in10cluster2) then (Peak_Market_Penetration is out1cluster2) (1)
3. If (Usability is in1cluster3) and (Infrastructure is in2cluster3) and (Regulation is in3cluster3) and (Cost-effectiveness is in4cluster3) and (Safety is in5cluster3) and (Market_competition is in6cluster3) and (Product_indication is in7cluster3) and (Efficacy is in8cluster3) and (Manufacturing_issues is in9cluster3) and (Reimbursement is in10cluster3) then (Peak_Market_Penetration is out1cluster3) (1)
4. If (Usability is in1cluster4) and (Infrastructure is in2cluster4) and (Regulation is in3cluster4) and (Cost-effectiveness is in4cluster4) and (Safety is in5cluster4) and (Market_competition is in6cluster4) and (Product_indication is in7cluster4) and (Efficacy is in8cluster4) and (Manufacturing_issues is in9cluster4) and (Reimbursement is in10cluster4) then (Peak_Market_Penetration is out1cluster4) (1)
5. If (Usability is in1cluster5) and (Infrastructure is in2cluster5) and (Regulation is in3cluster5) and (Cost-effectiveness is in4cluster5) and (Safety is in5cluster5) and (Market_competition is in6cluster5) and (Product_indication is in7cluster5) and (Efficacy is in8cluster5) and (Manufacturing_issues is in9cluster5) and (Reimbursement is in10cluster5) then (Peak_Market_Penetration is out1cluster5) (1)
6. If (Usability is in1cluster6) and (Infrastructure is in2cluster6) and (Regulation is in3cluster6) and (Cost-effectiveness is in4cluster6) and (Safety is in5cluster6) and (Market_competition is in6cluster6) and (Product_indication is in7cluster6) and (Efficacy is

in8cluster6) and (Manufacturing_issues is in9cluster6) and (Reimbursement is in10cluster6) then (Peak_Market_Penetration is out1cluster6) (1)

7. If (Usability is in1cluster7) and (Infrastructure is in2cluster7) and (Regulation is in3cluster7) and (Cost-effectiveness is in4cluster7) and (Safety is in5cluster7) and (Market_competition is in6cluster7) and (Product_indication is in7cluster7) and (Efficacy is in8cluster7) and (Manufacturing_issues is in9cluster7) and (Reimbursement is in10cluster7) then (Peak_Market_Penetration is out1cluster7) (1)

8. If (Usability is in1cluster8) and (Infrastructure is in2cluster8) and (Regulation is in3cluster8) and (Cost-effectiveness is in4cluster8) and (Safety is in5cluster8) and (Market_competition is in6cluster8) and (Product_indication is in7cluster8) and (Efficacy is in8cluster8) and (Manufacturing_issues is in9cluster8) and (Reimbursement is in10cluster8) then (Peak_Market_Penetration is out1cluster8) (1)

9. If (Usability is in1cluster9) and (Infrastructure is in2cluster9) and (Regulation is in3cluster9) and (Cost-effectiveness is in4cluster9) and (Safety is in5cluster9) and (Market_competition is in6cluster9) and (Product_indication is in7cluster9) and (Efficacy is in8cluster9) and (Manufacturing_issues is in9cluster9) and (Reimbursement is in10cluster9) then (Peak_Market_Penetration is out1cluster9) (1)

10. If (Usability is in1cluster10) and (Infrastructure is in2cluster10) and (Regulation is in3cluster10) and (Cost-effectiveness is in4cluster10) and (Safety is in5cluster10) and (Market_competition is in6cluster10) and (Product_indication is in7cluster10) and (Efficacy is in8cluster10) and (Manufacturing_issues is in9cluster10) and (Reimbursement is in10cluster10) then (Peak_Market_Penetration is out1cluster10) (1)

11. If (Usability is in1cluster11) and (Infrastructure is in2cluster11) and (Regulation is in3cluster11) and (Cost-effectiveness is in4cluster11) and (Safety is in5cluster11) and (Market_competition is in6cluster11) and (Product_indication is in7cluster11) and (Efficacy is in8cluster11) and (Manufacturing_issues is in9cluster11) and (Reimbursement is in10cluster11) then (Peak_Market_Penetration is out1cluster11) (1)

12. If (Usability is in1cluster12) and (Infrastructure is in2cluster12) and (Regulation is in3cluster12) and (Cost-effectiveness is in4cluster12) and (Safety is in5cluster12) and (Market_competition is in6cluster12) and (Product_indication is in7cluster12) and (Efficacy is in8cluster12) and (Manufacturing_issues is in9cluster12) and (Reimbursement is in10cluster12) then (Peak_Market_Penetration is out1cluster12) (1)

13. If (Usability is in1cluster13) and (Infrastructure is in2cluster13) and (Regulation is in3cluster13) and (Cost-effectiveness is in4cluster13) and (Safety is in5cluster13) and (Market_competition is in6cluster13) and (Product_indication is in7cluster13) and (Efficacy is in8cluster13) and (Manufacturing_issues is in9cluster13) and (Reimbursement is in10cluster13) then (Peak_Market_Penetration is out1cluster13) (1)
14. If (Usability is in1cluster14) and (Infrastructure is in2cluster14) and (Regulation is in3cluster14) and (Cost-effectiveness is in4cluster14) and (Safety is in5cluster14) and (Market_competition is in6cluster14) and (Product_indication is in7cluster14) and (Efficacy is in8cluster14) and (Manufacturing_issues is in9cluster14) and (Reimbursement is in10cluster14) then (Peak_Market_Penetration is out1cluster14) (1)
15. If (Usability is in1cluster15) and (Infrastructure is in2cluster15) and (Regulation is in3cluster15) and (Cost-effectiveness is in4cluster15) and (Safety is in5cluster15) and (Market_competition is in6cluster15) and (Product_indication is in7cluster15) and (Efficacy is in8cluster15) and (Manufacturing_issues is in9cluster15) and (Reimbursement is in10cluster15) then (Peak_Market_Penetration is out1cluster15) (1)
16. If (Usability is in1cluster16) and (Infrastructure is in2cluster16) and (Regulation is in3cluster16) and (Cost-effectiveness is in4cluster16) and (Safety is in5cluster16) and (Market_competition is in6cluster16) and (Product_indication is in7cluster16) and (Efficacy is in8cluster16) and (Manufacturing_issues is in9cluster16) and (Reimbursement is in10cluster16) then (Peak_Market_Penetration is out1cluster16) (1)
17. If (Usability is in1cluster17) and (Infrastructure is in2cluster17) and (Regulation is in3cluster17) and (Cost-effectiveness is in4cluster17) and (Safety is in5cluster17) and (Market_competition is in6cluster17) and (Product_indication is in7cluster17) and (Efficacy is in8cluster17) and (Manufacturing_issues is in9cluster17) and (Reimbursement is in10cluster17) then (Peak_Market_Penetration is out1cluster17) (1)
18. If (Usability is in1cluster18) and (Infrastructure is in2cluster18) and (Regulation is in3cluster18) and (Cost-effectiveness is in4cluster18) and (Safety is in5cluster18) and (Market_competition is in6cluster18) and (Product_indication is in7cluster18) and (Efficacy is in8cluster18) and (Manufacturing_issues is in9cluster18) and (Reimbursement is in10cluster18) then (Peak_Market_Penetration is out1cluster18) (1)
19. If (Usability is in1cluster19) and (Infrastructure is in2cluster19) and (Regulation is in3cluster19) and (Cost-effectiveness is in4cluster19) and (Safety is in5cluster19) and

(Market_competition is in6cluster19) and (Product_indication is in7cluster19) and (Efficacy is in8cluster19) and (Manufacturing_issues is in9cluster19) and (Reimbursement is in10cluster19) then (Peak_Market_Penetration is out1cluster19) (1)

20. If (Usability is in1cluster20) and (Infrastructure is in2cluster20) and (Regulation is in3cluster20) and (Cost-effectiveness is in4cluster20) and (Safety is in5cluster20) and (Market_competition is in6cluster20) and (Product_indication is in7cluster20) and (Efficacy is in8cluster20) and (Manufacturing_issues is in9cluster20) and (Reimbursement is in10cluster20) then (Peak_Market_Penetration is out1cluster20) (1)

21. If (Usability is in1cluster21) and (Infrastructure is in2cluster21) and (Regulation is in3cluster21) and (Cost-effectiveness is in4cluster21) and (Safety is in5cluster21) and (Market_competition is in6cluster21) and (Product_indication is in7cluster21) and (Efficacy is in8cluster21) and (Manufacturing_issues is in9cluster21) and (Reimbursement is in10cluster21) then (Peak_Market_Penetration is out1cluster21) (1)

22. If (Usability is in1cluster22) and (Infrastructure is in2cluster22) and (Regulation is in3cluster22) and (Cost-effectiveness is in4cluster22) and (Safety is in5cluster22) and (Market_competition is in6cluster22) and (Product_indication is in7cluster22) and (Efficacy is in8cluster22) and (Manufacturing_issues is in9cluster22) and (Reimbursement is in10cluster22) then (Peak_Market_Penetration is out1cluster22) (1)

23. If (Usability is in1cluster23) and (Infrastructure is in2cluster23) and (Regulation is in3cluster23) and (Cost-effectiveness is in4cluster23) and (Safety is in5cluster23) and (Market_competition is in6cluster23) and (Product_indication is in7cluster23) and (Efficacy is in8cluster23) and (Manufacturing_issues is in9cluster23) and (Reimbursement is in10cluster23) then (Peak_Market_Penetration is out1cluster23) (1)

24. If (Usability is in1cluster24) and (Infrastructure is in2cluster24) and (Regulation is in3cluster24) and (Cost-effectiveness is in4cluster24) and (Safety is in5cluster24) and (Market_competition is in6cluster24) and (Product_indication is in7cluster24) and (Efficacy is in8cluster24) and (Manufacturing_issues is in9cluster24) and (Reimbursement is in10cluster24) then (Peak_Market_Penetration is out1cluster24) (1)

25. If (Usability is in1cluster25) and (Infrastructure is in2cluster25) and (Regulation is in3cluster25) and (Cost-effectiveness is in4cluster25) and (Safety is in5cluster25) and (Market_competition is in6cluster25) and (Product_indication is in7cluster25) and (Efficacy

is in8cluster25) and (Manufacturing_issues is in9cluster25) and (Reimbursement is in10cluster25) then (Peak_Market_Penetration is out1cluster25) (1)

26. If (Usability is in1cluster26) and (Infrastructure is in2cluster26) and (Regulation is in3cluster26) and (Cost-effectiveness is in4cluster26) and (Safety is in5cluster26) and (Market_competition is in6cluster26) and (Product_indication is in7cluster26) and (Efficacy is in8cluster26) and (Manufacturing_issues is in9cluster26) and (Reimbursement is in10cluster26) then (Peak_Market_Penetration is out1cluster26) (1)

27. If (Usability is in1cluster27) and (Infrastructure is in2cluster27) and (Regulation is in3cluster27) and (Cost-effectiveness is in4cluster27) and (Safety is in5cluster27) and (Market_competition is in6cluster27) and (Product_indication is in7cluster27) and (Efficacy is in8cluster27) and (Manufacturing_issues is in9cluster27) and (Reimbursement is in10cluster27) then (Peak_Market_Penetration is out1cluster27) (1)

28. If (Usability is in1cluster28) and (Infrastructure is in2cluster28) and (Regulation is in3cluster28) and (Cost-effectiveness is in4cluster28) and (Safety is in5cluster28) and (Market_competition is in6cluster28) and (Product_indication is in7cluster28) and (Efficacy is in8cluster28) and (Manufacturing_issues is in9cluster28) and (Reimbursement is in10cluster28) then (Peak_Market_Penetration is out1cluster28) (1)

29. If (Usability is in1cluster29) and (Infrastructure is in2cluster29) and (Regulation is in3cluster29) and (Cost-effectiveness is in4cluster29) and (Safety is in5cluster29) and (Market_competition is in6cluster29) and (Product_indication is in7cluster29) and (Efficacy is in8cluster29) and (Manufacturing_issues is in9cluster29) and (Reimbursement is in10cluster29) then (Peak_Market_Penetration is out1cluster29) (1)

30. If (Usability is in1cluster30) and (Infrastructure is in2cluster30) and (Regulation is in3cluster30) and (Cost-effectiveness is in4cluster30) and (Safety is in5cluster30) and (Market_competition is in6cluster30) and (Product_indication is in7cluster30) and (Efficacy is in8cluster30) and (Manufacturing_issues is in9cluster30) and (Reimbursement is in10cluster30) then (Peak_Market_Penetration is out1cluster30) (1)

31. If (Usability is in1cluster31) and (Infrastructure is in2cluster31) and (Regulation is in3cluster31) and (Cost-effectiveness is in4cluster31) and (Safety is in5cluster31) and (Market_competition is in6cluster31) and (Product_indication is in7cluster31) and (Efficacy is in8cluster31) and (Manufacturing_issues is in9cluster31) and (Reimbursement is in10cluster31) then (Peak_Market_Penetration is out1cluster31) (1)

32. If (Usability is in1cluster32) and (Infrastructure is in2cluster32) and (Regulation is in3cluster32) and (Cost-effectiveness is in4cluster32) and (Safety is in5cluster32) and (Market_competition is in6cluster32) and (Product_indication is in7cluster32) and (Efficacy is in8cluster32) and (Manufacturing_issues is in9cluster32) and (Reimbursement is in10cluster32) then (Peak_Market_Penetration is out1cluster32) (1)
33. If (Usability is in1cluster33) and (Infrastructure is in2cluster33) and (Regulation is in3cluster33) and (Cost-effectiveness is in4cluster33) and (Safety is in5cluster33) and (Market_competition is in6cluster33) and (Product_indication is in7cluster33) and (Efficacy is in8cluster33) and (Manufacturing_issues is in9cluster33) and (Reimbursement is in10cluster33) then (Peak_Market_Penetration is out1cluster33) (1)
34. If (Usability is in1cluster34) and (Infrastructure is in2cluster34) and (Regulation is in3cluster34) and (Cost-effectiveness is in4cluster34) and (Safety is in5cluster34) and (Market_competition is in6cluster34) and (Product_indication is in7cluster34) and (Efficacy is in8cluster34) and (Manufacturing_issues is in9cluster34) and (Reimbursement is in10cluster34) then (Peak_Market_Penetration is out1cluster34) (1)
35. If (Usability is in1cluster35) and (Infrastructure is in2cluster35) and (Regulation is in3cluster35) and (Cost-effectiveness is in4cluster35) and (Safety is in5cluster35) and (Market_competition is in6cluster35) and (Product_indication is in7cluster35) and (Efficacy is in8cluster35) and (Manufacturing_issues is in9cluster35) and (Reimbursement is in10cluster35) then (Peak_Market_Penetration is out1cluster35) (1)
36. If (Usability is in1cluster36) and (Infrastructure is in2cluster36) and (Regulation is in3cluster36) and (Cost-effectiveness is in4cluster36) and (Safety is in5cluster36) and (Market_competition is in6cluster36) and (Product_indication is in7cluster36) and (Efficacy is in8cluster36) and (Manufacturing_issues is in9cluster36) and (Reimbursement is in10cluster36) then (Peak_Market_Penetration is out1cluster36) (1)
37. If (Usability is in1cluster37) and (Infrastructure is in2cluster37) and (Regulation is in3cluster37) and (Cost-effectiveness is in4cluster37) and (Safety is in5cluster37) and (Market_competition is in6cluster37) and (Product_indication is in7cluster37) and (Efficacy is in8cluster37) and (Manufacturing_issues is in9cluster37) and (Reimbursement is in10cluster37) then (Peak_Market_Penetration is out1cluster37) (1)
38. If (Usability is in1cluster38) and (Infrastructure is in2cluster38) and (Regulation is in3cluster38) and (Cost-effectiveness is in4cluster38) and (Safety is in5cluster38) and

(Market_competition is in6cluster38) and (Product_indication is in7cluster38) and (Efficacy is in8cluster38) and (Manufacturing_issues is in9cluster38) and (Reimbursement is in10cluster38) then (Peak_Market_Penetration is out1cluster38) (1)
39. If (Usability is in1cluster39) and (Infrastructure is in2cluster39) and (Regulation is in3cluster39) and (Cost-effectiveness is in4cluster39) and (Safety is in5cluster39) and (Market_competition is in6cluster39) and (Product_indication is in7cluster39) and (Efficacy is in8cluster39) and (Manufacturing_issues is in9cluster39) and (Reimbursement is in10cluster39) then (Peak_Market_Penetration is out1cluster39) (1)
40. If (Usability is in1cluster40) and (Infrastructure is in2cluster40) and (Regulation is in3cluster40) and (Cost-effectiveness is in4cluster40) and (Safety is in5cluster40) and (Market_competition is in6cluster40) and (Product_indication is in7cluster40) and (Efficacy is in8cluster40) and (Manufacturing_issues is in9cluster40) and (Reimbursement is in10cluster40) then (Peak_Market_Penetration is out1cluster40) (1)
41. If (Usability is in1cluster41) and (Infrastructure is in2cluster41) and (Regulation is in3cluster41) and (Cost-effectiveness is in4cluster41) and (Safety is in5cluster41) and (Market_competition is in6cluster41) and (Product_indication is in7cluster41) and (Efficacy is in8cluster41) and (Manufacturing_issues is in9cluster41) and (Reimbursement is in10cluster41) then (Peak_Market_Penetration is out1cluster41) (1)
42. If (Usability is in1cluster42) and (Infrastructure is in2cluster42) and (Regulation is in3cluster42) and (Cost-effectiveness is in4cluster42) and (Safety is in5cluster42) and (Market_competition is in6cluster42) and (Product_indication is in7cluster42) and (Efficacy is in8cluster42) and (Manufacturing_issues is in9cluster42) and (Reimbursement is in10cluster42) then (Peak_Market_Penetration is out1cluster42) (1)
43. If (Usability is in1cluster43) and (Infrastructure is in2cluster43) and (Regulation is in3cluster43) and (Cost-effectiveness is in4cluster43) and (Safety is in5cluster43) and (Market_competition is in6cluster43) and (Product_indication is in7cluster43) and (Efficacy is in8cluster43) and (Manufacturing_issues is in9cluster43) and (Reimbursement is in10cluster43) then (Peak_Market_Penetration is out1cluster43) (1)
44. If (Usability is in1cluster44) and (Infrastructure is in2cluster44) and (Regulation is in3cluster44) and (Cost-effectiveness is in4cluster44) and (Safety is in5cluster44) and (Market_competition is in6cluster44) and (Product_indication is in7cluster44) and (Efficacy

is in8cluster44) and (Manufacturing_issues is in9cluster44) and (Reimbursement is in10cluster44) then (Peak_Market_Penetration is out1cluster44) (1)

45. If (Usability is in1cluster45) and (Infrastructure is in2cluster45) and (Regulation is in3cluster45) and (Cost-effectiveness is in4cluster45) and (Safety is in5cluster45) and (Market_competition is in6cluster45) and (Product_indication is in7cluster45) and (Efficacy is in8cluster45) and (Manufacturing_issues is in9cluster45) and (Reimbursement is in10cluster45) then (Peak_Market_Penetration is out1cluster45) (1)

46. If (Usability is in1cluster46) and (Infrastructure is in2cluster46) and (Regulation is in3cluster46) and (Cost-effectiveness is in4cluster46) and (Safety is in5cluster46) and (Market_competition is in6cluster46) and (Product_indication is in7cluster46) and (Efficacy is in8cluster46) and (Manufacturing_issues is in9cluster46) and (Reimbursement is in10cluster46) then (Peak_Market_Penetration is out1cluster46) (1)

47. If (Usability is in1cluster47) and (Infrastructure is in2cluster47) and (Regulation is in3cluster47) and (Cost-effectiveness is in4cluster47) and (Safety is in5cluster47) and (Market_competition is in6cluster47) and (Product_indication is in7cluster47) and (Efficacy is in8cluster47) and (Manufacturing_issues is in9cluster47) and (Reimbursement is in10cluster47) then (Peak_Market_Penetration is out1cluster47) (1

48. If (Usability is in1cluster48) and (Infrastructure is in2cluster48) and (Regulation is in3cluster48) and (Cost-effectiveness is in4cluster48) and (Safety is in5cluster48) and (Market_competition is in6cluster48) and (Product_indication is in7cluster48) and (Efficacy is in8cluster48) and (Manufacturing_issues is in9cluster48) and (Reimbursement is in10cluster48) then (Peak_Market_Penetration is out1cluster48) (1)

49. If (Usability is in1cluster49) and (Infrastructure is in2cluster49) and (Regulation is in3cluster49) and (Cost-effectiveness is in4cluster49) and (Safety is in5cluster49) and (Market_competition is in6cluster49) and (Product_indication is in7cluster49) and (Efficacy is in8cluster49) and (Manufacturing_issues is in9cluster49) and (Reimbursement is in10cluster49) then (Peak_Market_Penetration is out1cluster49) (1)

Rule base for ramp-up duration

1. If (Usability is in1cluster1) and (Infrastructure is in2cluster1) and (Regulation is in3cluster1) and (Cost-effectiveness is in4cluster1) and (Safety is in5cluster1) and (Market_competition is in6cluster1) and (Product_indication is in7cluster1) and (Efficacy is in8cluster1) and (Manufacturing_issues is in9cluster1) and (Reimbursement is in10cluster1) then (Ramp-up_duration is out1cluster1) (1)
2. If (Usability is in1cluster2) and (Infrastructure is in2cluster2) and (Regulation is in3cluster2) and (Cost-effectiveness is in4cluster2) and (Safety is in5cluster2) and (Market_competition is in6cluster2) and (Product_indication is in7cluster2) and (Efficacy is in8cluster2) and (Manufacturing_issues is in9cluster2) and (Reimbursement is in10cluster2) then (Ramp-up_duration is out1cluster2) (1)
3. If (Usability is in1cluster3) and (Infrastructure is in2cluster3) and (Regulation is in3cluster3) and (Cost-effectiveness is in4cluster3) and (Safety is in5cluster3) and (Market_competition is in6cluster3) and (Product_indication is in7cluster3) and (Efficacy is in8cluster3) and (Manufacturing_issues is in9cluster3) and (Reimbursement is in10cluster3) then (Ramp-up_duration is out1cluster3) (1)
4. If (Usability is in1cluster4) and (Infrastructure is in2cluster4) and (Regulation is in3cluster4) and (Cost-effectiveness is in4cluster4) and (Safety is in5cluster4) and (Market_competition is in6cluster4) and (Product_indication is in7cluster4) and (Efficacy is in8cluster4) and (Manufacturing_issues is in9cluster4) and (Reimbursement is in10cluster4) then (Ramp-up_duration is out1cluster4) (1)
5. If (Usability is in1cluster5) and (Infrastructure is in2cluster5) and (Regulation is in3cluster5) and (Cost-effectiveness is in4cluster5) and (Safety is in5cluster5) and (Market_competition is in6cluster5) and (Product_indication is in7cluster5) and (Efficacy is in8cluster5) and (Manufacturing_issues is in9cluster5) and (Reimbursement is in10cluster5) then (Ramp-up_duration is out1cluster5) (1)
6. If (Usability is in1cluster6) and (Infrastructure is in2cluster6) and (Regulation is in3cluster6) and (Cost-effectiveness is in4cluster6) and (Safety is in5cluster6) and (Market_competition is in6cluster6) and (Product_indication is in7cluster6) and (Efficacy is in8cluster6) and (Manufacturing_issues is in9cluster6) and (Reimbursement is in10cluster6) then (Ramp-up_duration is out1cluster6) (1)

7. If (Usability is in1cluster7) and (Infrastructure is in2cluster7) and (Regulation is in3cluster7) and (Cost-effectiveness is in4cluster7) and (Safety is in5cluster7) and (Market_competition is in6cluster7) and (Product_indication is in7cluster7) and (Efficacy is in8cluster7) and (Manufacturing_issues is in9cluster7) and (Reimbursement is in10cluster7) then (Ramp-up_duration is out1cluster7) (1)
8. If (Usability is in1cluster8) and (Infrastructure is in2cluster8) and (Regulation is in3cluster8) and (Cost-effectiveness is in4cluster8) and (Safety is in5cluster8) and (Market_competition is in6cluster8) and (Product_indication is in7cluster8) and (Efficacy is in8cluster8) and (Manufacturing_issues is in9cluster8) and (Reimbursement is in10cluster8) then (Ramp-up_duration is out1cluster8) (1)
9. If (Usability is in1cluster9) and (Infrastructure is in2cluster9) and (Regulation is in3cluster9) and (Cost-effectiveness is in4cluster9) and (Safety is in5cluster9) and (Market_competition is in6cluster9) and (Product_indication is in7cluster9) and (Efficacy is in8cluster9) and (Manufacturing_issues is in9cluster9) and (Reimbursement is in10cluster9) then (Ramp-up_duration is out1cluster9) (1)
10. If (Usability is in1cluster10) and (Infrastructure is in2cluster10) and (Regulation is in3cluster10) and (Cost-effectiveness is in4cluster10) and (Safety is in5cluster10) and (Market_competition is in6cluster10) and (Product_indication is in7cluster10) and (Efficacy is in8cluster10) and (Manufacturing_issues is in9cluster10) and (Reimbursement is in10cluster10) then (Ramp-up_duration is out1cluster10) (1)
11. If (Usability is in1cluster11) and (Infrastructure is in2cluster11) and (Regulation is in3cluster11) and (Cost-effectiveness is in4cluster11) and (Safety is in5cluster11) and (Market_competition is in6cluster11) and (Product_indication is in7cluster11) and (Efficacy is in8cluster11) and (Manufacturing_issues is in9cluster11) and (Reimbursement is in10cluster11) then (Ramp-up_duration is out1cluster11) (1)
12. If (Usability is in1cluster12) and (Infrastructure is in2cluster12) and (Regulation is in3cluster12) and (Cost-effectiveness is in4cluster12) and (Safety is in5cluster12) and (Market_competition is in6cluster12) and (Product_indication is in7cluster12) and (Efficacy is in8cluster12) and (Manufacturing_issues is in9cluster12) and (Reimbursement is in10cluster12) then (Ramp-up_duration is out1cluster12) (1)
13. If (Usability is in1cluster13) and (Infrastructure is in2cluster13) and (Regulation is in3cluster13) and (Cost-effectiveness is in4cluster13) and (Safety is in5cluster13) and

(Market_competition is in6cluster13) and (Product_indication is in7cluster13) and (Efficacy is in8cluster13) and (Manufacturing_issues is in9cluster13) and (Reimbursement is in10cluster13) then (Ramp-up_duration is out1cluster13) (1)

14. If (Usability is in1cluster14) and (Infrastructure is in2cluster14) and (Regulation is in3cluster14) and (Cost-effectiveness is in4cluster14) and (Safety is in5cluster14) and (Market_competition is in6cluster14) and (Product_indication is in7cluster14) and (Efficacy is in8cluster14) and (Manufacturing_issues is in9cluster14) and (Reimbursement is in10cluster14) then (Ramp-up_duration is out1cluster14) (1)

15. If (Usability is in1cluster15) and (Infrastructure is in2cluster15) and (Regulation is in3cluster15) and (Cost-effectiveness is in4cluster15) and (Safety is in5cluster15) and (Market_competition is in6cluster15) and (Product_indication is in7cluster15) and (Efficacy is in8cluster15) and (Manufacturing_issues is in9cluster15) and (Reimbursement is in10cluster15) then (Ramp-up_duration is out1cluster15) (1)

16. If (Usability is in1cluster16) and (Infrastructure is in2cluster16) and (Regulation is in3cluster16) and (Cost-effectiveness is in4cluster16) and (Safety is in5cluster16) and (Market_competition is in6cluster16) and (Product_indication is in7cluster16) and (Efficacy is in8cluster16) and (Manufacturing_issues is in9cluster16) and (Reimbursement is in10cluster16) then (Ramp-up_duration is out1cluster16) (1)

17. If (Usability is in1cluster17) and (Infrastructure is in2cluster17) and (Regulation is in3cluster17) and (Cost-effectiveness is in4cluster17) and (Safety is in5cluster17) and (Market_competition is in6cluster17) and (Product_indication is in7cluster17) and (Efficacy is in8cluster17) and (Manufacturing_issues is in9cluster17) and (Reimbursement is in10cluster17) then (Ramp-up_duration is out1cluster17) (1)

18. If (Usability is in1cluster18) and (Infrastructure is in2cluster18) and (Regulation is in3cluster18) and (Cost-effectiveness is in4cluster18) and (Safety is in5cluster18) and (Market_competition is in6cluster18) and (Product_indication is in7cluster18) and (Efficacy is in8cluster18) and (Manufacturing_issues is in9cluster18) and (Reimbursement is in10cluster18) then (Ramp-up_duration is out1cluster18) (1)

19. If (Usability is in1cluster19) and (Infrastructure is in2cluster19) and (Regulation is in3cluster19) and (Cost-effectiveness is in4cluster19) and (Safety is in5cluster19) and (Market_competition is in6cluster19) and (Product_indication is in7cluster19) and (Efficacy

is in8cluster19) and (Manufacturing_issues is in9cluster19) and (Reimbursement is in10cluster19) then (Ramp-up_duration is out1cluster19) (1)

20. If (Usability is in1cluster20) and (Infrastructure is in2cluster20) and (Regulation is in3cluster20) and (Cost-effectiveness is in4cluster20) and (Safety is in5cluster20) and (Market_competition is in6cluster20) and (Product_indication is in7cluster20) and (Efficacy is in8cluster20) and (Manufacturing_issues is in9cluster20) and (Reimbursement is in10cluster20) then (Ramp-up_duration is out1cluster20) (1)

21. If (Usability is in1cluster21) and (Infrastructure is in2cluster21) and (Regulation is in3cluster21) and (Cost-effectiveness is in4cluster21) and (Safety is in5cluster21) and (Market_competition is in6cluster21) and (Product_indication is in7cluster21) and (Efficacy is in8cluster21) and (Manufacturing_issues is in9cluster21) and (Reimbursement is in10cluster21) then (Ramp-up_duration is out1cluster21) (1)

22. If (Usability is in1cluster22) and (Infrastructure is in2cluster22) and (Regulation is in3cluster22) and (Cost-effectiveness is in4cluster22) and (Safety is in5cluster22) and (Market_competition is in6cluster22) and (Product_indication is in7cluster22) and (Efficacy is in8cluster22) and (Manufacturing_issues is in9cluster22) and (Reimbursement is in10cluster22) then (Ramp-up_duration is out1cluster22) (1)

23. If (Usability is in1cluster23) and (Infrastructure is in2cluster23) and (Regulation is in3cluster23) and (Cost-effectiveness is in4cluster23) and (Safety is in5cluster23) and (Market_competition is in6cluster23) and (Product_indication is in7cluster23) and (Efficacy is in8cluster23) and (Manufacturing_issues is in9cluster23) and (Reimbursement is in10cluster23) then (Ramp-up_duration is out1cluster23) (1)

24. If (Usability is in1cluster24) and (Infrastructure is in2cluster24) and (Regulation is in3cluster24) and (Cost-effectiveness is in4cluster24) and (Safety is in5cluster24) and (Market_competition is in6cluster24) and (Product_indication is in7cluster24) and (Efficacy is in8cluster24) and (Manufacturing_issues is in9cluster24) and (Reimbursement is in10cluster24) then (Ramp-up_duration is out1cluster24) (1)

25. If (Usability is in1cluster25) and (Infrastructure is in2cluster25) and (Regulation is in3cluster25) and (Cost-effectiveness is in4cluster25) and (Safety is in5cluster25) and (Market_competition is in6cluster25) and (Product_indication is in7cluster25) and (Efficacy is in8cluster25) and (Manufacturing_issues is in9cluster25) and (Reimbursement is in10cluster25) then (Ramp-up_duration is out1cluster25) (1)

26. If (Usability is in1cluster26) and (Infrastructure is in2cluster26) and (Regulation is in3cluster26) and (Cost-effectiveness is in4cluster26) and (Safety is in5cluster26) and (Market_competition is in6cluster26) and (Product_indication is in7cluster26) and (Efficacy is in8cluster26) and (Manufacturing_issues is in9cluster26) and (Reimbursement is in10cluster26) then (Ramp-up_duration is out1cluster26) (1)
27. If (Usability is in1cluster27) and (Infrastructure is in2cluster27) and (Regulation is in3cluster27) and (Cost-effectiveness is in4cluster27) and (Safety is in5cluster27) and (Market_competition is in6cluster27) and (Product_indication is in7cluster27) and (Efficacy is in8cluster27) and (Manufacturing_issues is in9cluster27) and (Reimbursement is in10cluster27) then (Ramp-up_duration is out1cluster27) (1)
28. If (Usability is in1cluster28) and (Infrastructure is in2cluster28) and (Regulation is in3cluster28) and (Cost-effectiveness is in4cluster28) and (Safety is in5cluster28) and (Market_competition is in6cluster28) and (Product_indication is in7cluster28) and (Efficacy is in8cluster28) and (Manufacturing_issues is in9cluster28) and (Reimbursement is in10cluster28) then (Ramp-up_duration is out1cluster28) (1)
29. If (Usability is in1cluster29) and (Infrastructure is in2cluster29) and (Regulation is in3cluster29) and (Cost-effectiveness is in4cluster29) and (Safety is in5cluster29) and (Market_competition is in6cluster29) and (Product_indication is in7cluster29) and (Efficacy is in8cluster29) and (Manufacturing_issues is in9cluster29) and (Reimbursement is in10cluster29) then (Ramp-up_duration is out1cluster29) (1)
30. If (Usability is in1cluster30) and (Infrastructure is in2cluster30) and (Regulation is in3cluster30) and (Cost-effectiveness is in4cluster30) and (Safety is in5cluster30) and (Market_competition is in6cluster30) and (Product_indication is in7cluster30) and (Efficacy is in8cluster30) and (Manufacturing_issues is in9cluster30) and (Reimbursement is in10cluster30) then (Ramp-up_duration is out1cluster30) (1)
31. If (Usability is in1cluster31) and (Infrastructure is in2cluster31) and (Regulation is in3cluster31) and (Cost-effectiveness is in4cluster31) and (Safety is in5cluster31) and (Market_competition is in6cluster31) and (Product_indication is in7cluster31) and (Efficacy is in8cluster31) and (Manufacturing_issues is in9cluster31) and (Reimbursement is in10cluster31) then (Ramp-up_duration is out1cluster31) (1)
32. If (Usability is in1cluster32) and (Infrastructure is in2cluster32) and (Regulation is in3cluster32) and (Cost-effectiveness is in4cluster32) and (Safety is in5cluster32) and

(Market_competition is in6cluster32) and (Product_indication is in7cluster32) and (Efficacy is in8cluster32) and (Manufacturing_issues is in9cluster32) and (Reimbursement is in10cluster32) then (Ramp-up_duration is out1cluster32) (1)

33. If (Usability is in1cluster33) and (Infrastructure is in2cluster33) and (Regulation is in3cluster33) and (Cost-effectiveness is in4cluster33) and (Safety is in5cluster33) and (Market_competition is in6cluster33) and (Product_indication is in7cluster33) and (Efficacy is in8cluster33) and (Manufacturing_issues is in9cluster33) and (Reimbursement is in10cluster33) then (Ramp-up_duration is out1cluster33) (1)

Appendix 5.4 ATMP commercialisation market data and rNPV model assumptions

Duration of phases (Years)		Reference
Phase 1	1	Pharmaceutical Manufacturing and Research Association
Phase 2	2	
Phase 3	3	
Regulatory authority (US)	2	
Number of Clinical trial subjects (non-orphan)		
Phase 1 US	50	20-80; Pharmaceutical Manufacturing and Research Association
Phase 2 US	200	100-300; Pharmaceutical Manufacturing and Research Association
Phase 3 US	2000	1,000-5,000; Pharmaceutical Manufacturing and Research Association
Additional clinical trial subjects EU	0	if required by the specific market
Additional clinical trial subjects China	0	if required by the specific market
Additional clinical trial subjects Australia	0	if required by the specific market
Number of Clinical trial subjects (orphan)		
Phase 1 US	20	Approximation
Phase 2 US	17	Approximation
Phase 3 US	0	
Additional clinical trial subjects EU	0	if required by the specific market
Additional clinical trial subjects China	37	if required by the specific market
Additional clinical trial subjects Australia	0	if required by the specific market

Costs	
Per patient Phase 1	100,000.00
Per patient phase 2	75,000.00
Per patient phase 3	62,500.00
Approval costs (US)	310,764.00
Approval costs (EU)	454,890.00
Approval costs (China)	23,040.00
Approval costs (Australia)	16,933.50
Annual regulatory costs (US)	-

Annual regulatory costs (EU)	125,434.00
Annual regulatory costs (China)	7,704.00
Annual regulatory costs (Australia)	136,667.90
Annual patent costs US	5,980.00
Annual patent costs EU	5,000.00
Annual patent costs China	3,580.00
Annual patent costs Australia	1,200.00
Facility set-up cost US	50,000,000.00
Facility set-up cost EU	50,000,000.00
Facility set-up cost China	50,000,000.00
Facility set-up cost Australia	50,000,000.00
Product economies of scale (Patients < 500)	-
Product economies of scale (500 < Patients < 1000)	0.15
Product economies of scale (Patients >1000)	0.20
Product economies of scale (Patients >5000)	0.25
Marketing cost (US)	0.15
Marketing cost (EU)	0.15
Marketing cost (China)	0.15
Marketing cost (Australia)	0.15
Discount rate m1 (early)	0.20
Discount rate m1 (mid stage)	0.17
Discount rate m1 (late stage)	0.14
Discount rate EU (early)	0.18
Discount rate EU (mid stage)	0.16
Discount rate EU (late stage)	0.14
Discount rate China (early)	0.15
Discount rate China (mid stage)	0.14
Discount rate China (late stage)	0.13
Discount rate Australia (early)	0.15
Discount rate Australia (mid stage)	0.14
Discount rate Australia (late stage)	0.13

Chapter 6 Conclusions and Future Work

6.1 Conclusions

The research objective of this thesis was to model the challenges associated with the commercialisation of autologous cell therapies and to identify better ways of addressing these challenges. The main body of work consists of three levels of decisions as summarised in Figure 6.1: operational (supply chain), tactical (portfolio and capacity planning), and strategic (project valuation in multiple countries).

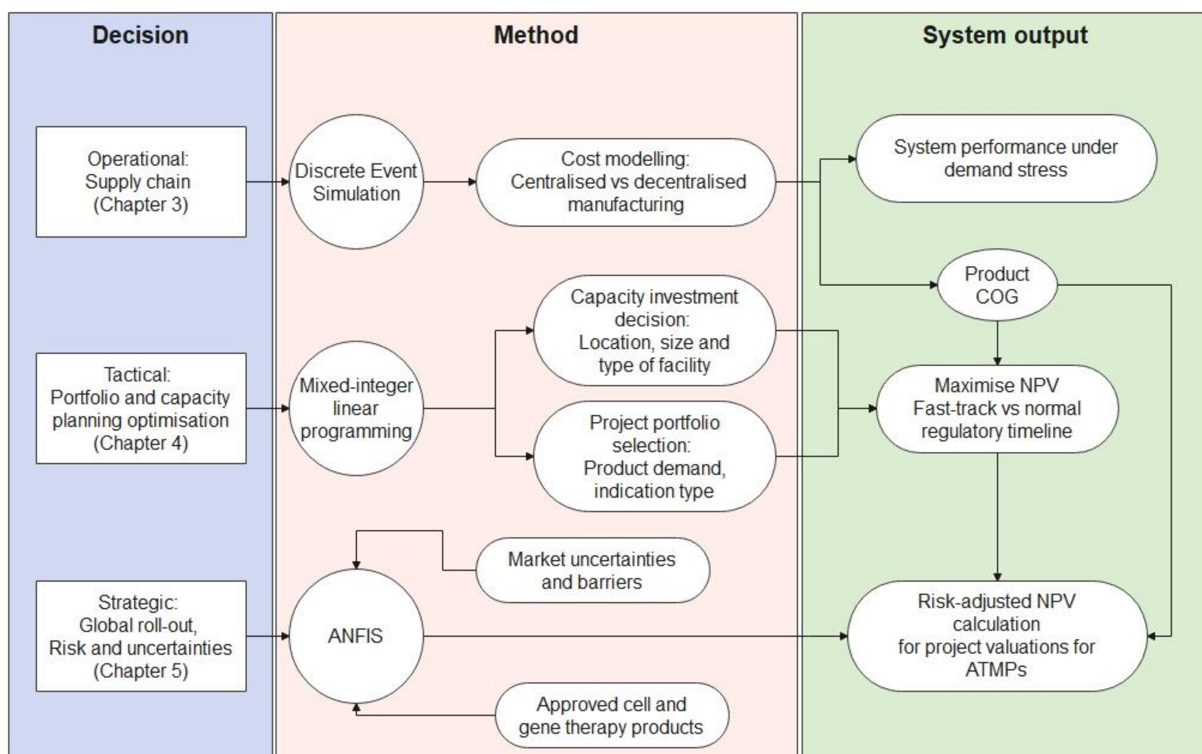


Figure 6.1 Chapter outcomes schematic

Based on the studies represented in this thesis, the following conclusions can be derived in connection with the levels of decisions mentioned above:

1. Centralised manufacturing offers comparatively better economies of scale, process uniformity, reduced capital expenses and regulatory costs. It is the favoured manufacturing scheme at lower demand levels and for geographically smaller regions. However, the manufacturing scheme is less resilient to demand fluctuations.
2. Decentralised manufacturing offers a shorter turnaround time due to reduced time for transportation, product packaging and freeze-thaw and better resilience to demand changes. It can be the favourable option where the demand levels are high and for bigger regions/ cross-borders where transportation time has a significant impact on the turnaround time.
3. The main cost driver for decentralised manufacturing is quality control and GMP requirements. Sterility testing lays on the critical path of the needle-to-needle supply chain.
4. Accelerated regulatory mechanisms constitute powerful levers to usher products into the market, offering earlier breakeven and higher overall NPV. To take advantage of fast-track regulatory policies to maximise overall returns, facility capital investments should occur earlier and therefore, the associated risks of commercialisation are also greater.
5. The key barriers of commercialisation are usability, nicheness of product indication, cost-effectiveness, reimbursement and manufacturing issues. Especially where profit margins are lower, it is critical to mitigate these uncertainties through better planning and risk-sharing entry models.

Furthermore, the following learnings have been generated with respect to the modelling approaches for supporting decisions:

1. Discrete-event simulation (DES) was demonstrated to be an effective tool for comparing cost of operations at a granular level to identify cost drivers. To maximise the reliability of the results of DES in this context, it is important to ensure that process and cost assumptions are close to reality. To validate the model, the results can be benchmarked against literature or industry expert opinion.
2. The mixed-integer linear programming (MILP) model built in this study was shown to be capable of supporting capacity planning and investment strategies for autologous cell therapies in a regional context, including the capture of the impact of regulatory schemes. However, the current model handles a single objective and is of a deterministic nature and therefore requires extensions for more complex decisions involving uncertainties and multiple objectives.
3. The adaptive neuro-fuzzy inference system (ANFIS), an approach that has long been considered to be a ‘universal estimator’, was shown to be a reasonably accurate approach for predicting market penetration and ramp-up duration for cell therapy products given fuzzy linguistic expert opinion over a range of factors identified in this work as of important influence. The approach was shown to be able to handle complexities around variable interdependencies and ambiguous qualitative reasoning. To maximise the predictive power of ANFIS, information of more commercialised products needs to be incorporated into the database.

6.2 Future Work

This thesis presents a first attempt of holistically evaluating the operational, tactical and strategic decisions in the commercialisation of autologous cell therapies. The following aspects can be improved:

1. The current approach makes it difficult to consider multi-level decisions at the same time due to the differences in system boundaries and modelling platforms. A more flexible modelling platform which can integrate these different modelling approaches can be considered. Further, model validation through case studies partnered with industry can improve the validity of the model.
2. The complexity of ATMP pricing and reimbursement was considered out of scope for the thesis given the highly heterogenous decision-making pathways for drug pricing and reimbursement. Further work into analysing ATMP pricing will be important for improving reliability of the model.
3. The current model does not look into the complexities surrounding global supply chains due to general geographical restrictions of autologous cell therapies. Complexities surrounding international tax implications and raw material supply restrictions are also important for the global roll-out problem. Further studies looking into the area can be beneficial for the industry at large.
4. Another commercialisation hurdle not considered in this thesis is the patent landscape and intellectual property rights. The validity of these patents may be a potential challenge that, when not tackled properly, can lead to significant losses in sales and profit, causing further uncertainties in the commercialisation landscape.

To further speed up the commercialisation of autologous cell therapies, the following areas deserve effort for research and development:

1. Supply chain digitalisation enabled by better sensor technologies, real-time digital capabilities and blockchain-based technologies allow more consistent process data collection and analysis. The feasibility for a more interconnected supply chain and the regulatory impact especially around product release and decentralised manufacturing are important areas to investigate.
2. Further research into market entry and entry mode decisions of ATMPs can be an interesting research direction. Optimisation of international product entry decisions such as product launch window, price and local regulations can allow further maximisation of global rNPV and inform partnership and joint venture decisions.
3. Local pricing, reimbursement and payment models are also important topics to consider as NPV is highly sensitive to selling price and the profit margin is important for the decision for market entry.

This work set out to better understand the commercialisation challenges for autologous cell therapies and provide researchers and industry decision-makers in the field with methodological insights at different decision-levels. From supply chains to capital investment decisions, this thesis analysed the impact of two main trends in the field: decentralisation and opportunities in regulatory incentives using various modelling approaches. From tissue repair to unmet medical needs such as cancer and Parkinson's disease, we hope the modality will soon realise its potential as an important pillar of medicine.

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