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A New Business Model for Cell-Based Therapeutics

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Dedication

This research would not have been possible without the love, commitment and support of my wife, Beryl, and my children, Robert and Ruth. I dedicate the work to them.

Abstract

Cell-based therapeutics have attracted large amounts of investment as they may offer effective treatments for a wide variety of health problems. In spite of extensive research relatively few examples of successful businesses exist. The products have several features that are challenging to manage when manufacturing at full scale. This feature is an obstacle to commercialisation that is often overlooked during research.

For some cell-based therapeutics this may not be a problem. Traditional, centralised business models can be used with confidence for low volume production to treat high value indications, such as life-threatening disorders: the margins justify the expense. By contrast, when the products are required in large numbers and applied at high cell doses for less dramatic conditions the traditional model of business will be difficult to manage and to fund at full scale. An example is the cell-based repair of osteoarthritic damage to joints such as the knee. Overall business value for this target is high because the market is large and is growing. Effective therapy requires large cell doses and commands a modest value per dose. When using a traditional business model (requiring centralised manufacture and a long-distance, low temperature supply chain) very large sums of money must be put at risk during development in order to build adequate capacity.

New ways of manufacturing and supplying such products are needed. A new model of business is developed in this thesis. The model requires lower initial capital investment and the business can be grown incrementally in line with demand rather than putting all the investment at risk at once.

Data from published work and from laboratory experiments are used to derive the direct costs of manufacture. Structured Analysis and Design Technique and Activity Based Cost analysis are used to build a quantitative model of a centralised business. The model is compared with suitable alternatives based upon the extended enterprise model. The points of sensitivity in the cost model for the extended enterprise are identified and the model is refined to provide a less capital-intensive route for business development. The results and methods are of general applicability to similar products.

Acknowledgements

The ideas in this thesis have many roots.

My thanks go to Professor Frank Barry of REMEDI at NUIG and to Dr James Huckle of Smith & Nephew for the initiative to start the project known as ‘Cellular Arthroplasty for Regeneration in Arthritis’. CARA was a four year project initiated in October 2007 between Smith & Nephew and REMEDI at NUIG. The Project provided some of the data for this thesis.

During the initial phases of this thesis Dr. Jim Browne had the best reason for delegating the role of principal tutor to a colleague but did not let his promotion to President get in the way of his supervisory activities.

Dr. David O’Sullivan and Professor Hari Jagdev supported the mechanics of the model-building with their experience in industrial consultancy.

Dr John Posnett, VP of Health Economics at Smith & Nephew, may recognise some of his own suggestions hiding behind the quantitative models of this study. I gratefully acknowledge his contribution in inspiring me to treat innovation in manufacture and supply as seriously as the cell-based inventions themselves.

Professor David Williams, Director of the Research School of Health and Life Sciences at the University of Loughborough, kindly offered his advice and support in the latter stages of the work when it became necessary to test the realism of the analyses.

The author sincerely hopes that this thesis will go some way to providing new modes of operation that will, in time, provide direct patient benefits.

List of Abbreviations

BPM	Business Process Modelling
CBT	Cell-Based Therapeutic
CoGs	Cost of Goods
DFD	Data Flow Diagramming
DPM	Downstream Production Module
FTE	Full-Time Equivalent
ICAM	Integrated Computer-Aided Manufacturing
IDEF	ICAM Definition language
IDEF0	Integrated DEFinition method 0
QALY	Quality-Adjusted Life Year (see Glossary)
QMS	Quality Management System
SADT	Structured (or Structural) Analysis and Design Technique

Glossary

Allogeneic cell therapy	Therapy that uses cells derived from one donor to effect treatment in a population of other patients
Autologous cell therapy	Therapy in which cells are isolated from an individual patient and, following manipulation, are returned to the same patient only
Phenotype	The pattern of properties and behavioural traits which, taken together, comprise the identity of a cell in a given metastable state
QALY	Quality Adjusted Life Year i.e. a means of comparing the outcome of different therapeutic choices in terms of impact on the patient. One year of perfect health = 1.0 QALY while death = 0.0

Chapter 1

Business Process Reengineering in Regenerative Medicine

1.1 Introduction

Regenerative medicine is capable of repairing the human body using living cells or tissue that has been cultured *in vitro* [NIOH 2006; Mason 2007 (1); Mason 2007 (2)]. ‘In vitro’ in this context means ‘outside the body in laboratory conditions’. Business in this sector has received large-scale investment since the early 1990s with relatively few cases of commercial success [Mason 2005]. Often the narrow margin between the cost of goods and the reimbursement or selling price for the product has been a surprise to the business investors [Hellman, Johnson et al. 2010]. Return on investment in new technology is often expected in a short time and most start-up companies are managed by innovators rather than those who are familiar with design for manufacture. This means that attention is rarely given to operations at full scale when developing medicinal products from advanced technology.

This Chapter introduces the general reader to the causes of these problems and their impact on regenerative medicine. It concludes with the objectives of this thesis, a brief description of the methods that are used and a description of the layout of the thesis.

1.2 The Nature of the Product

Cell-based therapeutics are one embodiment of regenerative medicine (the other main category is engineered tissue). Cell-based therapeutics have the potential to be widely applicable [Caplan 2008; Sorensen 2008]. Some resolve disorders by regenerating tissue and restoring the patient to a condition similar to the one that preceded the disease. Others influence metabolism or immune response in the patient. Cell-based therapeutics are thus of wide potential applicability. Conventional drug therapy is becoming limited

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by a growing awareness of unwanted side-effects in long-term use in some cases, by expense in manufacture and generally by the observation that, while symptoms may be managed, long-term resolution of the underlying disorder is seldom attained. Cell-based therapeutics offer the attraction of an elegant, targeted and biologically-enduring solution. The products attract enormous interest and the business is estimated to be worth between \$100M and \$200M *per annum* [Mason and Manzotti 2010].

Some cell-based therapeutics have the potential to resolve health problems that would otherwise be manageable only with palliative care, if at all. In many cases the products may be administered by a simple parenteral route, encouraging their use in out-patient clinics. Each year billions of dollars are spent worldwide on research in this subject. There are more than one hundred and fifty active companies [Mason 2007 (1); Mason 2007 (2)] and a much larger number of research groups. Researchers are investigating treatments for conditions as diverse as heart disease, diabetes and Duchenne muscular dystrophy [IDI 2008]. However, relatively few treatments are commercially successful. New companies have begun to encounter serious difficulties in attracting investment [Giebel 2005; Parson 2006]. Products that generate satisfactory levels of revenue are few.

Cell-based therapeutics may be directed towards a wide spectrum of disorders but this does not mean that all are likely to be business successes. When the product indication is life threatening, the cell dose small and the global market is modest in size then relatively few units need to be made and shipped. A large margin is justified by the business value in such cases and business success can be straightforward. When the product indication is not life-threatening, the cell dose large and the global market large in size then business success is more challenging. This is due to the demands of manufacturing to capacity and supplying delicate materials in large numbers over long distances. The apparent value of the latter case can be deceptive if it is derived simply by multiplying the global sales by the expected price and assuming that cost of goods is the direct cost of production only.

A cell-based therapeutic product is typically a suspension of cells delivered with suitable adjuvants. The product is often delivered by injection. This is the form of product examined in this thesis. It is the role of the development team to ensure that the product is supplied at prices within the reach of health care providers.

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Cell-based therapeutics fall broadly into two classes. ‘Allogeneic’ therapies contain cells derived from a donor other than the recipient. ‘Autologous’ therapies are made from the patient’s own cells. Unless the cells are modified, or the patient is immunosuppressed, or the site of treatment is immunoprivileged in some way an allogeneic therapy is likely to cause an immune reaction. While this limits its applicability to some indications, two of the most popular sites for structural repair, dermis and white zone, or ‘hyaline’, articular cartilage are, for different reasons, immunoprivileged sites and thus amenable to allogeneic therapy.

Although these products have unique characteristics that present big challenges to development these challenges may receive scant attention when the business is set up because of other, seemingly more urgent, commercial pressures. The management team of a small regenerative medicine company is likely to comprise entrepreneurial members of the research team who have not been exposed to the obstacles that are likely to be encountered during development. In the experience of the author most business plans for cell-based therapeutics include a section on ‘scalability’ that focuses on two things only. The first point of focus is on whether the cells can be propagated (or ‘expanded’) to commercially meaningful numbers without losing their therapeutic phenotype. The second point of focus is how well the conditions for expansion have been characterised and appraised for cost. Usually this means conducting experiments at bench scale in disposable laboratory plastic ware [Bonab, Alimoghaddam et al. 2006]. This assessment is a necessary but insufficient condition for commercial success. The item that is usually missing is an examination of operability at full scale and what that means for economical production. It is quite possible to construct a business plan that appears to show potential value and yet to miss this essential point. If the plan for full-scale operation is inadequate the problem will become apparent late in development when the business has committed itself to the expected method of production and discovers too late that the capital investment required is huge. Automation is sometimes cited as a solution to the problem [Kempner and Felder 2002; Aldridge 2007; Dennis, Esterly et al. 2007] but automation may not help. Without a study of operability automation may be applied at the wrong point in the value chain. If so it will merely increase the rate of throughput without

resolving the issues of plant size and management of materials movement. Alternative models of operation are needed in order to address these other issues.

1.3 Enterprise in Cell-Based Therapeutics, the Fundamental Problems

There are several obstacles to business development in regenerative medicine.

- a) Reluctance of investors to support the sector [Giebel 2005]
- b) Reluctance of big pharmaceutical companies to buy up new technologies
- c) Poor recent business performance in the sector [Mason 2005]
- d) Low reimbursement
- e) High cost of goods
- f) Over-optimistic business models
- g) Lack of investment in manufacturing design

These problems arise from the newness of the industry, from the lack of helpful precedents for successful business structure and from the lack of tried and tested methods for converting research findings into manufacturing methods.

Start-up companies in cell based therapeutics find it hard to raise capital. Investor confidence has been eroded over time because of the poor returns made by the businesses that have reached the market and because of the high rate of attrition of new start-ups [Giebel 2005]. An example is Carticel® [Economist 2008; Genzyme 2008] which was introduced to the market by Genzyme in 1995. Over the ten years following launch this ‘autologous’ product was applied to approximately 10,000 patients although the market projection was much larger. This has been said to be due to the unfamiliarity of the product, the fact that it is not available off-the-shelf when needed and its high price. Similar issues led to the insolvency of the tissue engineering company Advanced Tissue Sciences, Inc. in 2002 [Bagley 2006; Jones 2006]. The features common to many of these products are: the need for a clinic to apply the products, the unfamiliar product format

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and the high price [Leventon 2002]. The result is poor market penetration. This will lead to poor utilisation of plant and facilities (the biggest front-end cost) and thus to a delayed return on investment. There are few service facilities in which a new company may develop or manufacture its product [Buckelew 2006; Smith 2007] and so new companies look to venture capitalists for the money to buy custom production equipment. Investors dislike such projects because in the event of business failure the resale value of the expensive new plant will be negligible.

A popular exit strategy [Langer 2007] is to sell the new business to a large pharmaceutical company as soon as clinical efficacy has been proved [Prescott 2006]. In regenerative medicine this is not easy to do. The unusual manufacturing methods do not fit easily into existing plant space. Most pharmaceutical companies are already committed to specific layouts of production floor which are unsuited to regenerative medicinal products. The application of the product must often take place in a clinical setting but the product is difficult to store in clinic; coordination of supply is required. This is very different from the familiar distribution channels used for high volumes of stable drugs that are used for self-administration at home by the patient.

There are few compelling success stories that will motivate investors [Mason 2005; Mason and Manzotti 2010]. Consider, for example, the acquisition by Novartis of SyStemix, Inc. Novartis later spun the company back out after deciding that it could not make a business out of it. Dr Irving Weissman of Stanford Medical School (who set up SyStemix) made the comment “I don't think a great business model with high profits has come out yet.” [Pollack 2001] He has since developed an effective cell expansion method and combined this with SyStemix to make the company Cellerant. Novartis had a similar experience with Organogenesis' tissue product Apligraf® [Connolly 2002]. Like Dermagraft® from Advanced Tissue Sciences, this product cost almost as much to make as it returned in sales price [Leventon 2002]. The product was supported by revenue from other products [Connolly 2002] until Novartis sold the rights back to Organogenesis.

Many researchers are chasing the same therapeutic targets. Few begin with commercial experience and many falsely assume that manufacturing can be ‘bolted on’ at the end of their work. In reality regulations require [ICH 2006] that design for manufacture must

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begin *during* research. Cells and tissues are formally referred to as ‘complex products’. In the view of the regulators their safety and efficacy relies as much upon compliance with a validated method of production as it does upon satisfactory Quality Control measures for product release. Regulators require proof that any changes to the process will not adversely affect safety or efficacy. This means that if a significant process change is made late in development then a company may be obliged to repeat earlier clinical trials in order to gain regulatory approval by showing that the important product features remain unchanged. This extra work can be very expensive and is likely to delay product launch.

The temptation to neglect issues of reimbursement during business start-up can store up problems that will only become apparent later. A company may be tempted to manage costs by committing only limited funds to clinical trials, restricting claims for the product efficacy. Such cost-control can result in a disproportionate loss of reimbursement when the time comes to sell the product, reducing the margins on sale.

The cost of manufacture of cell- and tissue-based therapies is usually dominated by the overheads. Quality Assurance and Quality Control costs are unusually high; sometimes as high as 30% of the indirect costs of the operation [Jones 2006]. Many such goods must be transported in a frozen state and the distribution costs alone can be around 50% of the cost of goods ex factory [Jones 2006]. While it may be true that there is little that can be done about this within a traditional business model it does suggest that a radically different approach to manufacture is needed.

The assumption is usually made that there is only one way of doing business in this sector. Nineteenth century models of production are usually assumed to be the only way of making these twenty-first century products. Robert Nelson, co-founder and Managing Director of ARCH Venture Partners says that venture capitalists “roll their eyes” at traditional stem cell business models [Morrison 2007]. Nevertheless there are examples of innovative business models; for example Cytori Therapeutics, Inc. offers cell processing at the patient bedside using a machine for cell separation during an operation [Mason 2006].

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The manufacturing method needs to be economical, robust and safe to operate [Hoffman 2008]. Economical, robust production requires an understanding of how the process features are likely to vary and the influence that this will have upon product quality. The ‘Quality by Design’ approach, in which a business determines the control strategy early in development, is encouraged by the regulators [ICH 2009]. However, the pressure to generate revenue means that real-life cell-based therapeutic processes are seldom treated in this way. The research phase usually lasts longer than planned and consumes money and time leaving little option for development other than to use the scaled-out version of the research procedure [Laird 1990]. Such processes usually have a high failure rate in production and are costly to operate. Once the process is registered with the regulator it will usually cost too much time and money to replace it with a more attractive one. The company will then be locked into high production costs without being able to accumulate enough profit to allow it to register a better process. As noted above automation alone is not necessarily the answer; if there is no accurate forecasting of the overall impact of automation on costs then the capital outlay may go straight to the bottom line without improving efficiency [Aldridge 2007].

1.4 The Consequence

The consequence of these obstacles is that the cell therapeutics industry is relying mainly on the excitement generated by the research effort to generate investment. While this may work in the short term, over time credibility in the industry will erode. For sustainable growth to be achieved satisfactory models of production and business must be generated.

For example, the supply chain, so long a neglected subject in regenerative medicine, contributes significantly to the bottom line. Business structure and business processes must be re-examined. Descriptions are not enough, quantitative models are needed.

The opportunity exists for a radical re-think of the format of production and supply for cell-based therapeutics. Business models are needed that are designed to take advantage of the product characteristics instead of trying to force the products to fit current paradigms.

1.5 Objectives and Approach

This thesis proposes that the reason for the poor business success for cell based therapeutics is the unexamined adoption of an unsuitable traditional centralised model of manufacture and supply. New models of production and supply are needed. This will enable entrepreneurs to make fresh business offerings with confidence and will restore the business credibility of the sector, allowing researchers to innovate within a practical framework for commercialisation.

This thesis therefore has three main objectives. They are:

To generate alternative business models

The primary reason for undertaking the work is to identify suitable alternative business models for cell-based therapeutics that are of moderate value and aimed at high-volume markets (i.e. those examples in which the cost of production and supply cannot be ignored relative to the reimbursement value and for which operation at full scale poses practical challenges). In the course of this work especial emphasis was placed on finding solutions that will be attractive to ‘early adopters’ in the health care market because such individuals are instrumental in assuring rapid market entry.

To provide a method for technology appraisal

There is a trend for larger pharmaceutical or medical device companies to populate their new product pipelines with innovations sourced from outside the company. A risk associated with appraisal of such technologies is that obstacles to production at full scale will remain unidentified while attention is diverted to the questions of efficacy. Over-reliance on cost of goods projections based only upon small-scale production can be misleading. Efficacy is a necessary but insufficient condition for commercial success. A methodology is needed that will ensure that all the features of the development pathway are addressed systematically. This thesis aims to provide such a methodology. In the course of the work a case study is provided that will illustrate a generic method that can be applied to new regenerative medicine technology offerings.

To initiate a library of partial models

Thirdly the thesis addresses an aspiration that has been mentioned in the modelling literature: the assembly of useful ‘reference models’ or ‘partial models’ of operations that can be adapted and re-used [Cheng-Leong, Pheng et al. 1999]. Such models can greatly reduce the amount of time and effort required to build models of enterprises if they contain pre-assembled data and can be re-used with the minimum of editing.

A formal statement of the research questions that are addressed by this thesis follows.

1. “Is it possible to construct a model of business for regenerative medicine that avoids both the technical challenge of bulk cell manufacture and the high capital investment that is needed for a conventional supply chain?”

A subsidiary question is:

2. “Does a business model exist that can be used as a platform for the delivery of more than one cell-based or tissue-based therapeutic by terminal customisation of the product?”

Cell-based therapeutics can take a number of forms but the one that has been considered for this thesis is an injectable therapeutic agent for treatment of osteoarthritic damage to the knee based upon mesenchymal stem cells extracted from bone marrow aspirate. The manufacturing process flow can be regarded as a sequence of six discrete processes. The flow of the processes involved in the manufacture is outlined in Figure 1.1. The first process is the aspiration of bone marrow to provide the initial tissue. The method then requires the separation of the cell fraction of interest followed by the culture of the cells to industrially-useful levels.

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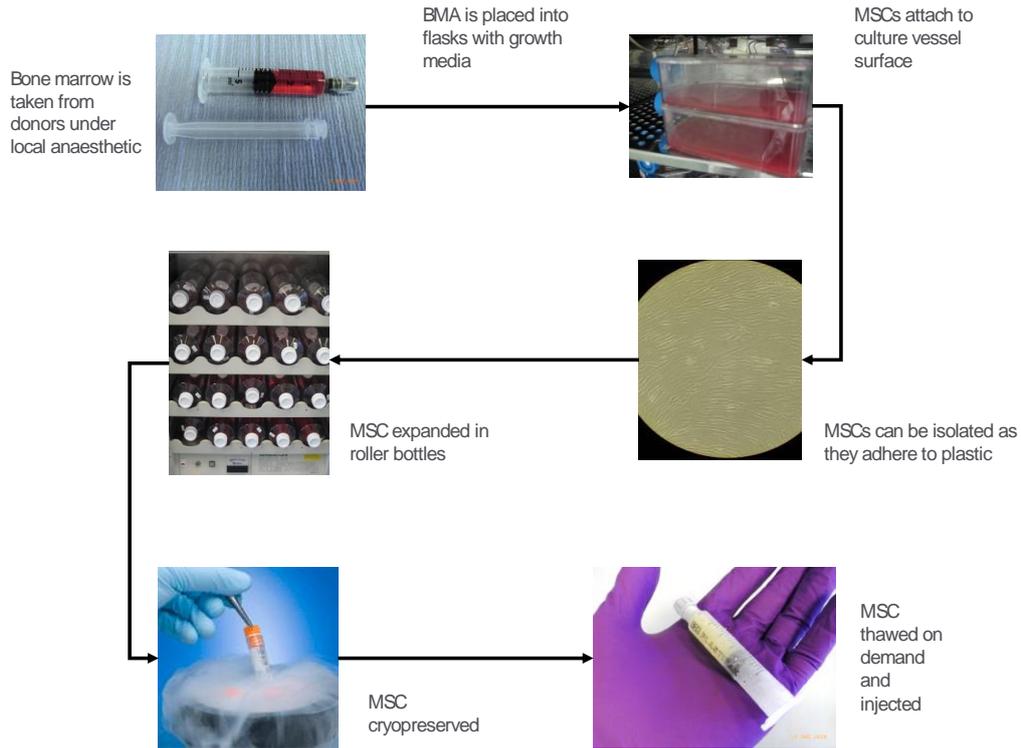


Figure 1.1: Outline of method of production

The product requires a high cell dose and is a good example of a simple-to-apply therapy for a non life-threatening condition with a large market; it is a good case study for the challenging situation for such products. The typical patient lifetime trajectory for severe osteoarthritic knee damage is shown in Figure 1.2.

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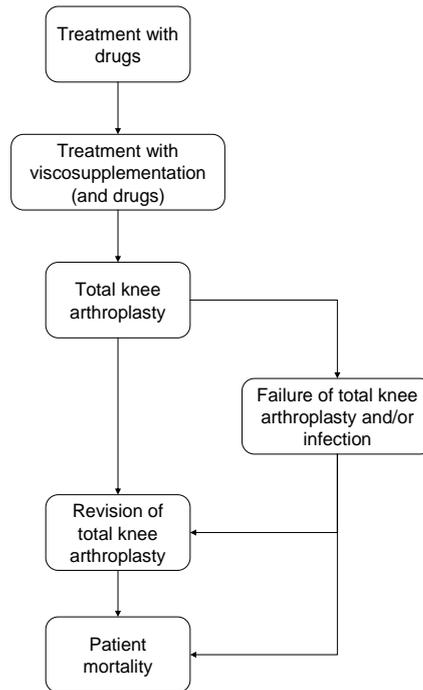


Figure 1.2: Typical patient trajectory for osteoarthritic knee damage with conventional therapies

Treatment with mesenchymal stem cells is aimed at relief of pain and restoration of function to an extent greater than that which is possible using viscosupplementation alone. The injection is to be local, not systemic, and is to be a single step procedure (intra-articular injection on an outpatient basis). The value proposition can be calculated in terms firstly of the delay in, or avoidance of, radical surgery (typically a total knee replacement) and secondly as the improvement in patient mobility that results from pain management. The value proposition in turn relates to the market price that can be achieved.

Joint replacement is a high-value business and the products are designed to provide a durable solution to joint immobility. However, if a total knee replacement can be avoided altogether there is considerable value gained. This arises from:

- Avoidance of the risk of infection following a total knee replacement operation
- Higher-quality restoration of mobility by the regenerative route
- Avoidance of expensive knee surgery

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- Removal of the risk to the (possibly elderly) patient following on an operation that requires general anaesthesia
- Avoidance of, or delay to, revision surgery if the first total knee replacement should eventually require renewal

A production sequence is considered in which the desired cells are extracted from bone marrow aspirate by means of their adhesion to tissue culture plastic. Such plastic is used to make T-flasks and roller bottles (the workhorses of the tissue culture suite). Unwanted cells (mainly blood and haematopoietic cells) are washed away. Cell isolation is followed by cell culture (or 'expansion') to make the maximum practical number of therapeutic cells per bone marrow aspirate [Bellett 2010]. The harvested cells will be formulated with a carrier gel (hyaluronic acid, an adjuvant facilitating cryopreservation and helping to prevent premature elimination of the cells from the injection site). The formulation is then dispensed into individual dosage forms (a custom form of cryo-vial) before being frozen ready for shipping. At the point of use in clinic the dosage form will be thawed and the contents will be injected directly into the synovial capsule of the knee.

The cells will be presented at the point of use as a frozen vial at a temperature of -70°C that will be thawed at a controlled rate and warmed to body temperature (37°C) before injection.

1.6 The Approach

The work was conducted in eleven steps. (In practice there was some recursion during the work and so the steps were not carried out strictly in series.) The relationship between the steps is shown in Figure 1.3. The steps were as follows.

1. A search was conducted to establish whether any business process reengineering work had been carried out in the regenerative medicine sector and, if so, how. Examples of comparable business were collected if they possessed features that were shared by regenerative medicine.

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2. The recent history of the methods and tools used for business process reengineering was examined; suitable methods, software and techniques were identified that were applicable to this thesis.
3. Current methods for the manufacture of cell-based therapeutics were reviewed in the literature and from the author's experience. Systematic choices of methods were made for use in this thesis.
4. Data were collected from published experiments in which mesenchymal stem cells were expanded and harvested. Published market figures for the indication were collected. These data were compared with data from laboratory culture experience at the Smith & Nephew Research Centre. The most appropriate figures were used to construct models of production.
5. Directly attributable costs of manufacture for the cells were calculated for roller bottle based manufacture. (The reason for choice of roller bottle culture is explained later.)
6. A model of a hypothetical centralised business (the 'as is' case) was constructed and cost roll-ups of the operation were made.
7. An operability assessment was made for the projected volumes based upon conventional technology and the projected market size.
8. Deficiencies in the 'as is' model were identified and remedies were proposed.
9. The preferred alternative structure (the 'to be' case) was modelled. Cost roll-ups were prepared and compared with the 'as is' case. Shortcomings in the 'to be' model were addressed to give a more attractive business format; the 'refined' model.
10. A sensitivity analysis was conducted on the refined 'to be' model and points were identified that needed further elaboration. The model was validated. Validation was done by means of three methods: a sensitivity analysis demonstrated how likely it was that the results were correct, opinions from experts were sought to

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confirm the conclusions and the trends within the sector were examined for evidence that the time is right for such a business model.

11. The results were summarised and topics for further work were identified.

The approach to the research is shown in Figure 1.3.

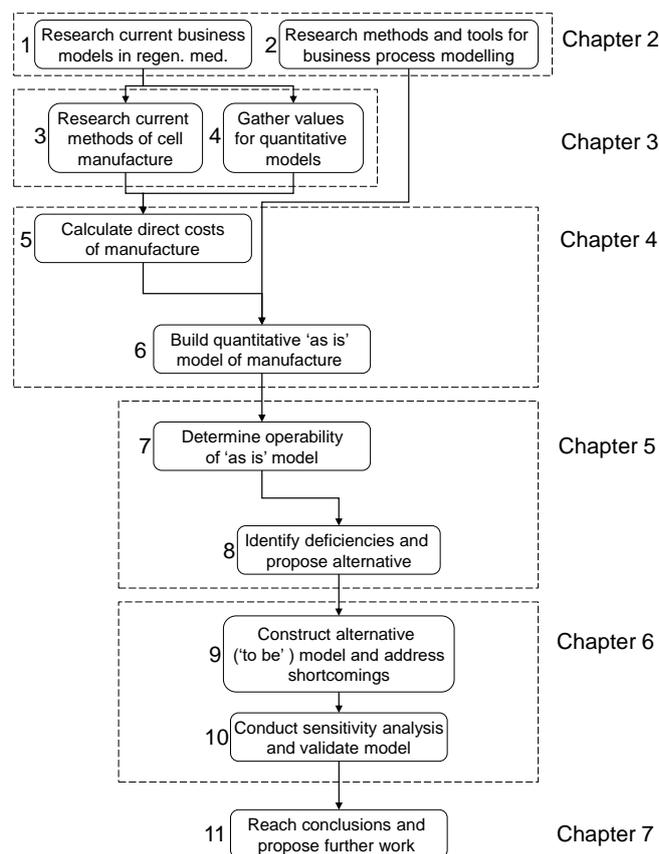


Figure 1.3: Approach to the research and relationship to the thesis layout

The steps in the analysis are shown in the diagram along with the chapters in this thesis at which each point is addressed. In each chapter of this thesis the steps are identified as they are described in the diagram.

1.7 Structure of the Thesis

Chapter 1 introduces the thesis and describes how various impediments to commercial success have limited the use of cell-based therapeutics to date.

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Chapter 2 reviews the background information to the thesis. Regenerative medicinal products are described along with the ways in which they differ from other health care products. Chapter 2 also reviews the current form of the industry. Examples of modelling studies are given that are of relevance to this thesis alongside a review of tools for enterprise modelling. The strengths and weaknesses of each tool are presented in the context of their usefulness in this thesis and the selection of the tool is justified.

Chapter 3 is about methods. It concentrates upon the case study from which this thesis is developed. It explains the choices of technology that are available for manufacture of cells and the strengths and limitations of each choice. Chapter 3 also describes the method of analysis used in the thesis and lists the values used in the models together with their sources.

Chapter 4 contains the first part of the analysis. Production and operating costs are projected using Activity Based Cost analysis based upon laboratory production data. The directly attributable costs of manufacture are calculated and the scale of the operation is defined in relation to the projected market. At this stage no overhead components are examined; just the costs of the manufacturing operations.

Chapter 5 examines the operability of the 'as is' model. Conclusions are drawn about the risks for high volume manufacture that will result from implementing the 'as is' model.

In Chapter 6 an alternative model is proposed. The costs of implementation and the capital requirements are estimated. The model is subjected to a sensitivity analysis. The validity of the findings is also considered based upon evidence from established experts. Shortcomings in the model are identified and described.

Chapter 7 summarises the results and expands upon the areas where further research will prove fruitful.

1.8 Summary

The commercial success of cell-based therapeutics has often been hampered by the inexperience in manufacturing of those managing the R&D effort. The shortcomings of an uncritical adoption of a traditional centralised manufacturing and distribution model of

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operation have not become apparent until too late a stage in commercialisation. The poor success rate of the industry has shaken investor confidence. Nevertheless the rewards for the patient and for the business of constructing effective means of production and supply remain very large. New models of business are needed that are designed to take advantage of the unusual features of the production methods that are used in regenerative medicine. This thesis sets out a method for modelling such businesses and proposes a new business model for cell-based therapeutics that will reduce risk and restore confidence. Chapter 2 examines the history and techniques of enterprise modelling in a search for any studies that might act as a suitable precedent in this thesis and also to identify tools and techniques that are applicable to this thesis.

Chapter 2

Review of Industry Models and Modelling Methods

2.1 Introduction

In this Chapter the literature for the two main subjects of relevance to the thesis is reviewed in order to provide material for use in the main argument. The aims of these two reviews are as follows.

The first review (Step 1 in Chapter 1, Figure 1.3) shows the enterprise modelling approaches that have been used in medical business engineering and identifies businesses that contain features in common with regenerative medicine. (The results are developed in this Chapter to compile a shortlist of applicable generic models of regenerative medicine business.)

The second review (Step 2 in Chapter 1, Figure 1.3) identifies suitable tools for use in this thesis based upon the history of enterprise modelling and the experience of past researchers concerning the strengths and weaknesses of each method.

2.2 Review Methods

The reviews are based upon interviews with experts, examination of the history of organisations in this sector and searches of relevant literature. In the first search (Section 2.3) the focus is on finding good examples of enterprise models of medicinal product manufacture or health care industry that have been constructed using business process modelling (BPM) techniques. The aim is to confirm that the regenerative medicine industry has not previously been analysed by business process engineers and to collect helpful precedents for use in the main thesis. In the second part (Section 2.9) the tools and techniques for enterprise modelling are examined in terms of their applicability to the regenerative medicine industry. As a result of the second search appropriate software tools for the thesis are identified.

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Regenerative medicine is subject to stringent regulation. This restricts the choice of business models. To inform the choice the financial, regulatory and operational requirements were collected from real-life sources, chiefly within Smith & Nephew Group.

The details of the history of selected organisations and the Good Manufacturing Practice (GMP) of the industry are derived from personal communications and from trade and technology publications, both electronic and hard copy, including:

- a) Cell Therapy News (<http://www.celltherapynews.com/>)
- b) GMP Review (Euromed Publications)
- c) ISPE European Informer
- d) Stem Cells eNewsletter

The searches were conducted according to the following parameters.

Dates covered: 1990 – 2011 following relevant ‘leads’ back into earlier publications.

Tool used:

- a) Google Scholar®
- b) e-Knowledge, Engineering Village and direct browsing of e-resources at NUIG
- c) Science Direct
- d) RSS alerts from the following journals:
 - a. International Journal of Production Economics
 - b. International Journal of Production Research
 - c. International Journal of Production Planning and Control

Science Direct was set up to deliver alerts on tissue engineering and cell based therapeutics.

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Online searches used employing the following parameters singly or in combination:

‘regenerative medicine’, ‘activity based cost*’, ‘business process reengineering’, ‘cell based therap*’, ‘cell therap*’, ‘enterprise model*’, ‘healthcare’, ‘health care’, ‘medicin*’, ‘tissue (engineer*)’, BPM, BPR, ERP

Citation searches are used as appropriate. References are collected using EndNote®.

Much of the material derives from interviews. These were conducted using manual recording techniques only. In some cases reference is made to earlier work conducted by the author.

In addition specific material is derived from manual searches of publications relevant to the issues in regenerative medicine. Titles are selected from the business literature, engineering literature and a range of scientific journals usually associated with cell biology:

- a) Biotechnology and Bioengineering
- b) International Journal of Production Economics
- c) International Journal of Production Research
- d) International Journal of Production Planning and Control
- e) Journal of Tissue Engineering and Regenerative Medicine
- f) Regenerative Medicine

2.3 Business Models Relevant to Regenerative Medicine

In order to understand the relevant work in this area it is first necessary to understand the nature and requirements of the products. Regenerative medicine has been defined as “the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects.” [DoHHS 2006] This definition includes cell-based therapeutics (CBTs) and tissue engineering.

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The following definition of a ‘cell-based therapeutic’ is used in this thesis.

“A cell-based therapeutic is a medical product that relies for its efficacy upon a mode of action that can only occur during prolonged and intimate contact between cells that have been manipulated outside the body and the tissue of the patient into whom they are implanted.”

This definition excludes the use of cells merely as a tool for manufacture (as in a biopharmaceutical). The definition is not restricted to cells that achieve their effect mainly by structural repair of the body (as is the case for tissue engineering). The cells may achieve their therapeutic goal by growth, catalysis, metabolism, immune stimulation and expression of matrix or any combination of these roles.

The first impression is that such cells may be generally applicable across a wide range of disorders. On closer inspection it can be seen that some conditions are more amenable to treatment than others. For example, repair of dermal tissue and repair of white-zone articular, or hyaline, cartilage has been the target of a large amount of research activity [Mason 2007; Epsicom 2008]. This is partly due to the large potential markets. It is also due to the fact that both of these tissues, for different reasons, are suitable for ‘allogeneic’ therapy. This makes for a less demanding route to market.

2.4 The Special Requirements of Regenerative Medicine Business

When manufacturing an allogeneic product it is usual to construct a small number of cell banks from which cells can be expanded to make large numbers of products that can be applied to many patients without risk of rejection. This simplifies the process design because the number of cell banks, each of which is expensive to qualify, is kept small and no patient-based line segregation is needed [Mason 2005].

By contrast in cases where immuno-rejection can occur the cell banks must be raised a) from the patient themselves (autologous therapy), b) from cell banks that have been rendered immuno-transparent or c) from a limited number of different cell banks that broadly match the immunological sub-groups of the patient population. This last approach is uncommon but is similar to blood typing for transfusion.

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Option (b) will probably require genetic manipulation of the cells. The risks, especially from cell transformation, do not outweigh the benefits except in treatment of life-threatening disorders. The objection to (c), the ‘stratified medicine’ approach, is that to manage such ‘typing’ requires a large amount of work and the margin of error in applying the product may be narrow. Nevertheless, examples do exist [Bobic 2007; Genzyme 2008; Sensebé 2008].

Option (a) is the most accessible for a business embarking on regenerative medicine. Although there are several examples of a successful autologous therapy business it is generally expensive to operate [Mishra, Andresen et al. 2005; Frey-Vasconcelis 2010]. It requires flawless line segregation and rigorous line clearance procedures. This leads to poor utilisation of plant space and operator time. There are few opportunities for economies of scale. The cells vary a lot in behaviour and this must be accommodated in extremely robust processes. Harvest times may be difficult to predict.

In this thesis an allogeneic product is assumed. The findings will be applicable to autologous products only with enhancement of the models.

For a new therapy to succeed it must accomplish four things [Posnett 2011].

- a) It must be must be at least as effective as the current standard treatment in improving patient quality of life.
- b) It should be available at a total cost which is lower than the cost of standard treatment. (Cost parity will not provide sufficient incentive for clinicians to abandon more familiar, conservative treatments.)
- c) It must be available in a manner that is consistent with current clinical practice; preferably off-the-shelf with the minimum of forward planning.
- d) It must be easy to use with minimal additional training.

If a new therapy does not satisfy these four criteria then it may still attain a good market share provided that the perceptible improvement in the condition relative to overall cost

is high enough. This will provide the incentive for use even if the treatment is difficult to apply or needs careful scheduling.

The value provided by a new medical product may be thought of in terms of the incremental value addition (i.e. Value added = Improvement in efficacy/Difference in cost). In practice this is expressed using the 'ICER' (incremental cost-effectiveness ratio) which equals the difference in cost divided by the Quality Adjusted Life Years (QALYs) gained [Posnett 2011]. This topic will be addressed further in Section 6.6.

Regenerative medicine products have special requirements. Typically they are based on cell or tissue components that must be viable at the point of use and so they are very sensitive to variations in temperature, to the nature and quantity of adjuvants and to infection. They are very perishable, similar in this respect to transplantable organs or blood. Their important properties, or 'Critical Quality Attributes' [ICH 2009], depend upon the history of the unit up to the point of use. Adequate controls for these features add to the cost of supply.

Medicinal products are amongst the most highly regulated goods in the world [DoHHS 2006]. In this thesis discussion of the regulations will be restricted to those with most impact upon the business model.

The products must be manufactured to current Good Manufacturing Practice, or cGMP, standard [Aldridge 2007; Shadle 2008]. The facilities used for manufacture must be approved by the regional 'Competent Authority' (usually, but not always, the national regulatory agency). Training and procurement must be conducted diligently and evidence must be retained to prove that suitable selection methods were used [EMA 2008]. Environmental control and monitoring must be maintained in production and storage areas in compliance with applicable standards [DoHHS 2006; Thomas, Hourd et al. 2008]. A Quality Management System must be created and maintained that will address all important aspects of manufacturing, control, distribution and corrective action [EMA 2008]. Procedures must be created and observed for prompt, effective action in the event of process deviations, batch failures or environmental failings [FDA 2006]. Notification procedures must be set up that will ensure public safety in the event of an unexpected pattern of harmful effects from a product released onto the market. This must

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include capacity for rapid, effective recall [DoHHS 2006]. The ability to maintain compliance is the defining feature of any facility that is intended for production or distribution and limits the choice of manufacturing centres in the business model to those that can maintain the standard. This is likely to mean either the business placing the goods on the market or those facilities that have been set up by some hospitals to handle cells, tissues and organs for treatments that are permitted on a named-patient basis.

Clinical coordination further constrains the potential models of business. Regenerative medicinal products are usually supplied either ‘fresh preserved’, i.e. maintained with oxygenation and nutrition at 37°C, or deep frozen to allow warehousing and supply using a cold-chain system [Aldridge 2007; MacGabhann 2010 (1)]. The conditions used for food cold-chain supply (usually -20°C) are insufficient because at such temperatures modest fluctuations in temperature may change ice crystal structure within the product and thus degrade it [Franks 2003]. Temperatures of -70 to -80°C are more normal. This temperature control imposes a double burden. Firstly expensive low temperature freezers or liquid nitrogen Dewar flasks must be installed and maintained. Secondly records must be made of the thermal history of the product [MHRA 2006]. Such low temperature freight is considerably more expensive than chilled freight. All that is required to spoil a consignment can be, say, 24 hours’ hold-up at an air terminal while way-bills are checked.

Milder conditions for transit may now be possible. Special storage media have extended tissue storage times under conditions of chilling (+2 to +8°C) for some products, extending the potential supply window from approximately 36 hours up to 21 days [Rice 2009].

Once a consignment has reached its destination Quality Control checks will be necessary prior to use.

- a) Check packing integrity
- b) Confirm identity of product, expiry date and match to order details
- c) Confirm thermal history since dispatch

- d) Transfer to clinic, OR
- e) Transfer to low temperature storage

There is a minimal infrastructure needed to apply the product. In the clinical setting [Prior 2010] coordination of supply with application is critical. Out-patient procedures for intra-articular injection vary widely over different centres but the typical arrangement is shown in the flow chart of Figure 2.1.

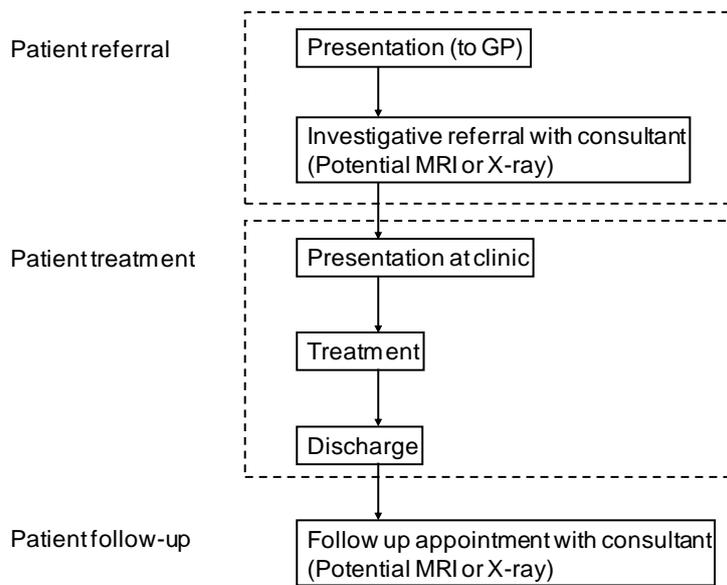


Figure 2.1: Typical arrangements for out-patient treatment

For the purposes of this thesis the significant stage is the ‘Patient treatment’ block. On the day of treatment the clinical team that is required is typically: Admissions Clerk, Pharmacy Officer, Senior Orthopaedic Nurse, Orthopaedic Surgery Nurse, Orthopaedic Recovery Ward Nurse, Physician, Houseman, Ward Manager and Registrar. Thus the administration of even a simple intra-arthrodial injection cannot readily be carried out at locations such as a manufacturing centre or a clinician’s office. The destination for the product must remain the specialist clinic. The end point of the supply chain is thus defined by the clinical environment and the legal framework for patient care and cannot readily be changed without increasing patient risk.

2.5 Previous Models of the Regenerative Medicine Business

There are a number of industries which illustrate the principles that must be observed in regenerative medicine business. None, however, contains all the components.

There has been research on supply of high-value medical goods. A recent publication [Stefansson, Jensson et al. 2009] proposes a dynamic model as a way to ensure responsiveness in make-to-order supply of such items. However, the treatments are insufficiently close to relate to regenerative medicine.

Organ transplantation has several features in common with the supply of CBTs:

- a) The goods need rapid cold-chain supply (where harvest and implant sites differ)
- b) There must be close coordination of harvest with the schedule for implantation
- c) Quality testing or pre-qualification of donor and recipient is needed

There are key differences. Usually the donated organ becomes available due to a death and therefore the system must be responsive to less predictable delivery than for CBTs. Supply of organs will most often be as individual units on wet ice by dedicated courier. (This can be justified by the high value of the organ.) Organ implantation will be carried out as a single, tightly supervised operation whereas cell injection will probably be conducted by a clinician as a short campaign for several patients. Existing publications concentrate on decision-making tools in organ transplant management. The subject of coordinating larger volumes with clinical scheduling has not been addressed. Some features can be used in models for the CBT case.

Plant meristem culture, like regenerative medicine, requires aseptic handling of tissue explants followed by controlled growth of large volumes of multiple units. Unlike regenerative medicine the industry is typically operated at low margins with extremely high volumes per consignment. Each business must make a minimum of around three million units *per annum* at around a maximum of £1-2 per item merely to remain viable [Medcalf 2009].

The supply of frozen medical goods to military field hospitals has been studied. The goods are resistant to some fluctuations in temperature control because they do not contain viable cells. They are normally supplied at -20 to -10°C so the comparison is of limited value.

Tissue engineering has much in common with cell-based therapy. Nordstrom *et al* [Nordstrom, Narhi et al. 2009] have considered the special demands made upon business structures by these products. The authors present a case for research into the supply chain for such advanced products. Skin, cartilage and kidney tissues are examined in detail. In this work the tissue engineering products are categorised in terms of three positions in the product life cycle: 'experimental', 'therapy' and 'standard'. 'Standard' is the stage at which the product is established in the market and is undergoing regular manufacture. In the case of cartilage the authors consider only autologous supply. The authors use engineered dermal replacements to illustrate how to take the decision whether to make-to-order or make-to-stock. The authors do not regard any of the therapies as being at the 'standard' stage of development. Nevertheless they assert that new models of supply are needed and they describe the characteristics that the supply chain must have. The authors stop short of building business models and no examples of such models are cited in the bibliography.

No truly analogous publication could be found that addresses the same research target as this thesis.

2.6 A Comparison of Alternative Models of Business for Cell-Based Therapeutics

Having considered the constraints and special features of regenerative medicine it is possible to turn attention to the ways that value can be derived from it. By examining this aspect first it is then possible to construct detailed models that can be used to build a successful new enterprise.

This section considers the generic business models that may be used by a company wishing to generate a revenue stream from a mesenchymal stem cell therapy for topical

treatment of osteoarthritis. The models are presented here with general descriptions. Each model may be realised in various ways.

Model 1 'Allogeneic Product Sale'

In this model stem cells are isolated from the bone marrow of one or more donors and then expanded to form a corresponding number of cell banks sufficient to provide treatment for many patients. The keys to low production cost are centralisation and economy of scale. Each cell bank incurs its own Quality Control cost. The cells are expanded in a robust, large-scale, low-cost process and then dispensed into their final containers (the 'dosage forms'). It is a make-to-stock model based upon market projections. There is a centralised distribution network, comprising a low temperature cold supply chain from frozen, warehoused stock. The goods will be delivered either 'just in time' for immediate use or stored temporarily in the few clinics that happen to possess suitable low temperature freezers. Clinicians administer the product in an outpatient centre in campaigns of a dozen or more patients per session.

The typical production flow is illustrated in Figure 2.2 and Figure 2.3. Cells from only one bank will be processed at any one time to minimise the risk of line mix-ups. Patient safety is assured using sterility checks and the relatively simple plant layout minimises the chance of introducing pathogens.

The allogeneic model of sale will work only if the mesenchymal stem cells are capable of expansion to commercially useful levels without losing their phenotype. Inadequate levels of expansion will result in the need for fresh cell banks to be raised and qualified frequently. This will quickly increase costs because donors may be hard to recruit and the costs of qualifying each cell bank will be loaded onto small numbers of product units. Variation will occur in the behaviour of the cell banks and the process design must take account of this natural variability.

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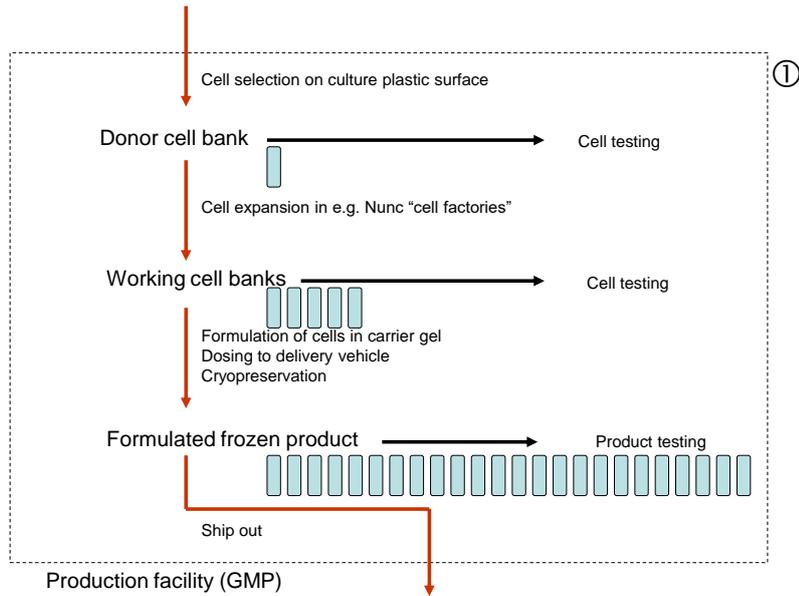


Figure 2.2: Process flow, allogeneic product (comprises the 'Production facility' block in Figure 2.3)

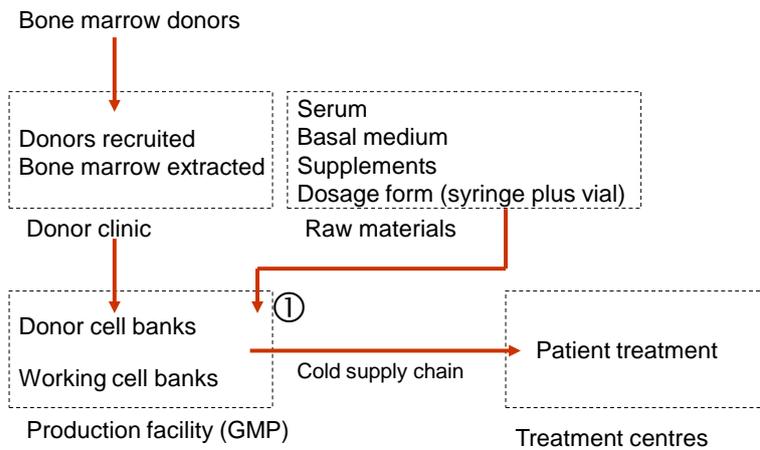


Figure 2.3: Supply chain, allogeneic product (see Figure 2.2 for the contents of the block marked ①)

Model 2 'Autologous Product Sale'

This model takes cells from each patient and returns the product to the same patient only. The manufacturing protocols will have been tested to ensure that product of predictable quality is made in spite of the variability in patient age, health and genetic makeup. The main challenge is to receive, test, expand and ship the cells in relatively low volume without cross-contaminating any product intended for a different patient. Excellent line segregation and clearance procedures are needed. The process flow for this model is shown in Figure 2.4 and Figure 2.5. There is a good case for miniature 'closed' automated manufacturing stations (i.e. with no ingress or egress of materials during processing) similar to the microfactories that have been proposed for the electronics or machine-tool industry [Kussul, Baidyk et al. 2002; Honegger, Langstaff et al. 2006].

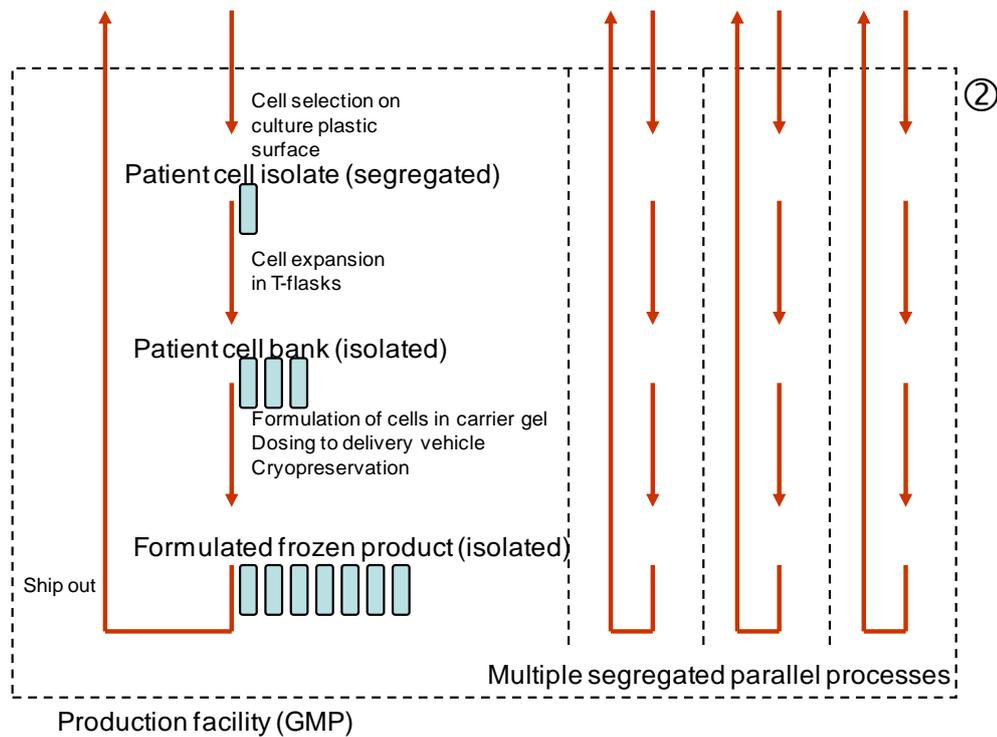


Figure 2.4: Process flow, autologous product (each line operates as shown at left, diagram comprises the 'Production facility' block in Figure 2.5)

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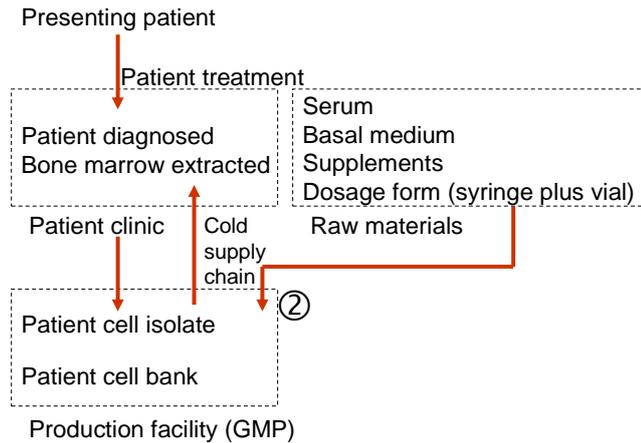


Figure 2.5: Supply chain, autologous products (see Figure 2.4 for the contents of the block marked ②)

Such a microfactory [Kussul, Baidyk et al. 2002; Okazaki, Mishima et al. 2004; Verettas 2006] with its own self-contained medium make-up, in-line or at-line monitoring and incubator arrangements would be set up at the start of production, charged with the cells and growth medium, connected to utilities and left to incubate until the monitors report that the goods are ready for harvest. There is a precedent for this in devices like those manufactured by Aastrom for blood cell expansion [Palsson, Emerson et al. 1998] and by Millenium Biologix Corporation for neo-tissue made using the ACTES system [Wendt, Jakob et al. 2005]. A cell expansion device as a microfactory is currently in development by Beckman [Marks 2010]. This arrangement would allow three additional possibilities.

- a) Rather than relying on a single recipe-driven protocol the controls might be varied automatically on the basis of feedback to accommodate the unique characteristics of each patient's cells.
- b) The process could be validated using data to create algorithms that can predict the preferred harvest date during production. This would allow the production team to coordinate with confidence the delivery of the cells in the fresh-preserved state to the clinical centre.
- c) Product quality would be predicted from results gathered at or before the time of harvest based upon in-process monitoring. The data would be calibrated against

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results from process validation. This would permit immediate release of goods 'at risk' rather than having to wait pending the results of post-production laboratory release testing; testing that might compromise the product by delaying dispatch.

However, a large area will be taken up for preparing each treatment. It will be important to ensure that the revenue stream will justify the front-end investment. It seems likely that treatments aimed at life-threatening conditions, e.g. cardiac muscle damage, will pay their way but this may not be true for less critical disorders like osteoarthritis.

Model 3 'Equipment Sale'

Here the inefficiencies of line-segregation are avoided by decentralising production and selling the capability to make the product instead. This approach lends itself most clearly to autologous therapy where production would be moved out of the plant and into the clinic. The kit for production is sold instead of the cells. The equipment must allow for the natural variation of raw materials and the level of skill of the production staff. Careful validation of the operating range is essential. Automatic operation and tamper-proof settings will be best so as to avoid attempts to override the validated control settings.

The equipment must be suitable for use in general purpose clean space adjacent to the clinic itself. (If it relies upon a cleanroom environment there will be limited market penetration.) The production of cells will be carried out by specially trained clinical staff only. The manufacturing company will provide training and supplies.

A risk arises because it is difficult to control the sterility of the product when it is made outside of the direct supervision of the central business. It is important carefully to specify and to manage responsibility for quality and especially for risk of infection at each stage in the supply chain. Any failure in asepsis or failure to adhere to the production protocol, no matter where this might occur in the product journey, could be blamed upon the company that has manufactured the equipment even if this is quite unjustified. For example, if a patient were to become seriously ill or die due to poor hygiene during production or administration of the cells there will be no reliable data trail for an investigator to follow; the product will have been used up. Litigation could tie the company resources down for years. Contrast this situation with that arising in Model 1

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where a single large allogeneic batch of product has been made and from which the required number of samples has been withdrawn for sterility testing prior to batch release. Under such circumstances the sterility is assured by process validation and by testing of the final batch. Any legal challenge can be met by offering archival samples for independent analysis. This constitutes a serious business risk in this model. This risk will become important later in this thesis and so it is important to elaborate it here.

Management of this special risk is a prerequisite for success with this business model but the burden is lighter for autologous products because the source of any problem is likely to be the patient themselves.

An example of an approach to this type of business is provided by the instrument manufacturer Cytori Therapeutics, Inc. [Mason 2006]. Cytori manages the risk of poor product performance by:

- Applying their ‘Celution®’ system at bedside, isolating stem cells from the adipose tissue of the patient.
- Keeping turnaround times to a minimum (about 1 hour before re-administration)
- Using closed automatic systems with a very low risk of operator error
- Supporting this approach with rigorous customer training and re-training schedules

Model 4 ‘Cell Manipulation In Vivo’

In cases where the localisation or stimulation of autologous cells is effective without increase in their overall number then it may not be necessary to remove them at all. In this context ‘*in vivo*’ means ‘within the living organism’. This is in contrast to the ‘*in vitro*’ situation as discussed earlier (Chapter 1). This model works by:

- Directing therapeutic cells found within the patient’s own body to the injury site without removing them first e.g. localisation of stem cells from within the general haematopoietic system

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- Relying upon the introduction of chemotactic agents or materials that concentrate, bind and retain cells in therapeutic locations.
- Showing advantages in efficacy or ease of use when compared with a systemic pharmaceutical approach.

Given that the systemic approach would be more predictable in outcome this model seems an unattractive option.

Model 5 'Diagnostic Sale'

Sale of diagnostics will be an enhancement to any of the other business models rather than being a business model in its own right. CBTs tend to be costly and clinicians need confidence that the CBT will work for the patient under their care. There will always be a portion of the population for whom the CBT will be ineffective. The diagnostic device will enable the clinician, or the patient, to determine whether the cell-based therapy will benefit a particular patient. The diagnostic adds value by preventing the expense and discomfort of applying the therapy unnecessarily.

An attractively priced, or freely donated, diagnostic will empower a clinician or a patient to justify cell-based therapy. This will encourage use in regions such as the United States where part- or full-payment by the patient allows them to exert more influence over the choices available to the physician. Rapid market penetration (which is essential for full utilisation of plant capacity and therefore for business viability) will occur as confidence in the outcome increases. The diagnostic will need to be trustworthy. It will also have to be cheap (possibly sold below cost or supplied free to physicians) and simple to use. The impact of this parameter upon the value chain is shown in Figure 2.6 which is referenced in the next section.

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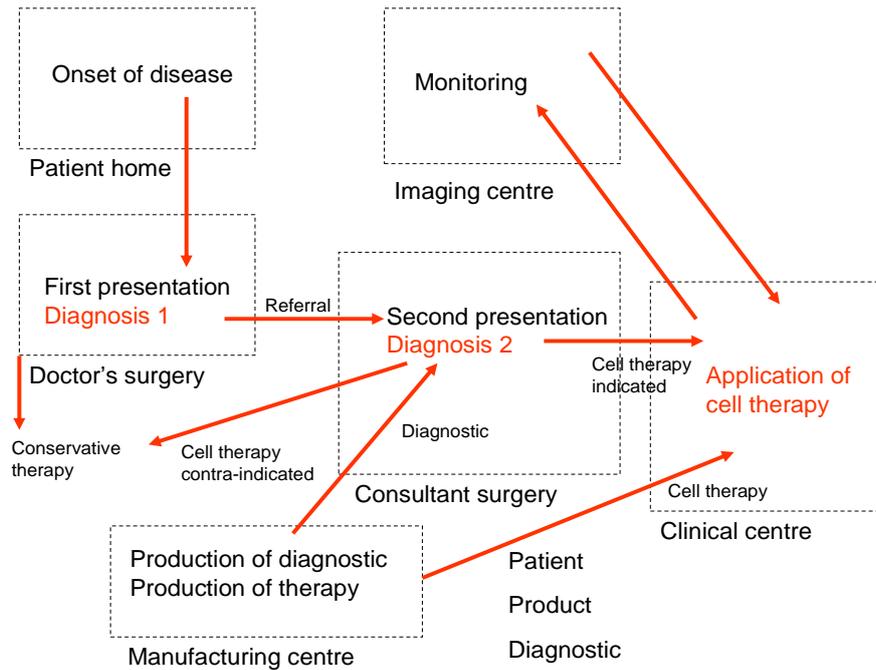


Figure 2.6: Points of addition of value by a diagnostic in the supply chain

2.7 Discussion of the Business Models

The viability of any one of the models presented here will be determined by the balance of several related factors.

- Selling price of goods or service
- Variable and fixed costs of production
- Costs of distribution
- Commercial and business risk

As noted earlier the supply of a stem cell-based therapy to clinic will almost certainly need a low-temperature supply chain. From marketing information the estimated selling price will be no more than around \$2,000 per unit (for one injection only per course of treatment). For commercial viability the preferred manufacturing price will be of the order of \$300 to \$500 per unit (in an allogeneic model of production). The viability of the allogeneic model can therefore be assessed directly from experimentation and cost modelling.

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The autologous model, by contrast, requires more innovation in manufacturing technology as well as assessment of the science. There are more ‘unknowns’ to this approach at present.

Sale of the equipment (Model 3) has some features in common with the microfactory version of Model 2. Both would rely upon good understanding of cell behaviour in relation to the disease state and both would require processes that tolerate patient-to-patient variation in cell behaviour. Both would require closed small-scale production systems that are tamper-proof.

For the purposes of the current study Model 4 may be discounted because it is too speculative.

Model 5 may be used to add value to any of models 1-3. To understand the value addition, refer to Figure 2.6 and bear in mind that the desired outcome for the clinician is overall minimisation of cost while resolving the condition. The advantage over any established therapy will arise from:

- a) Increased quality of resolution of osteoarthritis
- b) Increased longevity of resolution of osteoarthritis
- c) Lower overall outlay

Therefore any treatment that is no more complex than injection into the joint and that will result in delay until any invasive intervention is needed will increase the number of QALYs purchased by the therapy.

On this basis increased confidence in diagnosis 1 (Figure 2.6) may not be relevant: consultant opinion will be needed first. However, increased confidence in diagnosis 2 impacts directly on value and the amount of additional value is directly related to accuracy in prediction.

The clinician will be more confident and therefore more motivated to use the CBT as a first line of treatment if he or she is confident that it will resolve the patient condition straightaway. Any false negative diagnosis must, of course, be kept to a minimum but a false negative diagnosis does not directly impact the clinician’s budget because the value

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is lost only to the manufacturer of the diagnostic and therapy. In such circumstances there is no change to the patient's status relative to their status before the CBT became available and so they are no worse off than before.

By contrast false positives directly impact the clinician's budget because they result in wasted purchase and treatment. However, the value released by the true positive diagnoses may outweigh all of this as will now be shown.

Consider a population of 1,000 patients and a new therapeutic with price \$2,000 per dose.

Let us suppose that 60% of the patients will benefit and the value of the benefit is \$3,000 per patient.

Without the diagnostic the total cost of treatment will be \$2M ($1,000 \times \$2,000$) while the total benefit will be \$1.8M ($60\% \times 1,000 \times \$3,000$). The net value is \$200k ($\$2M - \$1.8M$).

If the diagnostic can identify responders with 90% accuracy (i.e. the value of A in Figure 2.7 is 600 while the value of B is $600 \times (1/0.9 - 1)$ or 67 and the value of C is zero). Then the therapy need only be given to 667 patients instead of 1,000 and 600 will benefit.

Then the total cost becomes \$1.334M ($667 \times \$2,000$) and the total benefit remains \$1.8M ($600 \times \$3,000$). The net value increases to \$466k ($\$1.8M - \$1.334M$).

Thus the value of the diagnostic is \$266k per 1,000 patients ($\$466k - \$200k$) or \$266 per test ($\$266k/1,000$ patients).

The demonstration of such a value addition can be based upon evidence gathered during Phase III clinical trial and the data then published prior to product launch in order to boost initial sales and decrease time to peak sales.

		Responder
True positive A	False negative C	
False positive B	True negative D	Non-responder
Positive	Negative	
Test result		

Figure 2.7: Relationship of test results to patient knowledge for a diagnostic

2.8 Summary: Business Models

It is helpful at this point to review the main findings. The sections above describe the special features of CBTs and how value may, in principle, be created from them. It has been found that CBTs have not been studied in any depth with quantitative modelling techniques and that peer-reviewed publications focus on the management of health care rather than the operation to provide advanced therapeutics.

The recent publication by Nordstrom et al has highlighted the need for quantitative analysis, especially of the supply chain, for one type of regenerative medicine: engineered tissue.

These findings underline the importance of undertaking a BPM-based case study of commercial regenerative medicine. Attention is now turned in the next section to the tools that are suitable for this study.

2.9 Research Methods and Tools for Enterprise Modelling

Any useful comparison of business models must address the two dominant issues of cost and operability. For this thesis any modelling methods that can manage a database containing both quantitative and qualitative data in the form of a process model are therefore of interest.

In Table 2-1 the available software packages are compared on the basis of criteria that are important for the thesis. The ‘Weighting’ represents a priority for that feature. In the rest of this Chapter the reasons for this selection and the justification for these rankings are given. The Table is shown at this point in the thesis to give context to the narrative that follows.

Table 2-1: Comparison of the available tools for Enterprise Modelling using the structured approach of IDEF0 (see Section 2.10; Scoring: 1=Poor, 2=Acceptable, 3=Good)

	Score for each available tool (brackets show value with weighting)						
	Weighting	AIOWin	iGrafx	MetaDesign	Design/IDEF (Meta Software Corp.)	VC++	Visio
a) Ease of use	3	3 (9)	3 (9)	3 (9)	2 (6)	1 (3)	2 (6)
b) Graphic presentation	3	3 (9)	3 (9)	3 (9)	3 (9)	1 (3)	3 (9)
c) Data management	9	3 (27)	2 (18)	1 (9)	3 (27)	1 (9)	1 (9)
d) Auto-updating	3	3 (9)	3 (9)	1 (3)	3 (9)	1 (3)	1 (3)
e) Cost analyses	9	3 (27)	1 (9)	1 (9)	2 (18)	1 (9)	1 (9)
f) Integration with other packages	1	2 (2)	3 (3)	2 (2)	3 (3)	1 (1)	3 (3)
Total with weighting		83	57	41	72	28	39

There are a variety of terms used to describe methods of business modelling. It is helpful at the outset to distinguish ‘enterprise modelling’ from BPM. Enterprise modelling [Doumeingts, Ducq et al. 2000] concerns the abstract representation of an organisation while BPM [Prescott 2006; Atkin and Bjork 2007] is concerned with the representation of one or more of the processes which constitute that organisation. BPM is thus a

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subdivision of enterprise modelling. In this thesis BPM is regarded as a tool to build enterprise models i.e. the models that will be used to reengineer the business processes.

For clarity: the focus throughout this thesis is on the group of business processes comprising manufacturing and distribution. These comprise a portion only of the larger operation to produce the CBT. The general features of the larger operation will not be considered except when they provide necessary context.

Enterprise modelling is a valuable tool in business process reengineering (BPR). The main reason for conducting BPR in this sector is to remain competitive. Regenerative medicine addresses a global marketplace where much of the manufacture of health care products has moved to regions with lower labour costs and educated workforces; principally India and China. American and European operations must understand and manage the overhead contribution to their costs of production in order to improve efficiency in their operations and remain competitive on costs. The market for software for enterprise modelling and BPM is therefore increasing in spite of the current global recession [Lamont 2009].

The pressure to undertake BPR is not new [Hammer 1990; Mahoney 1997]. Twenty years ago one of the founding researchers in this field, Davenport [Davenport and Short 1990], gave a list of possible reasons for undertaking BPR. The first of these is cost reduction but Davenport makes it clear that this not a sufficient reason in itself; cost reduction is best achieved through optimisation based upon other criteria. If the operations are optimised, he maintains, the desired cost reduction will take care of itself. Davenport also asserts [Davenport and Stoddard 1994] that total business transformation is not usually a sensible business aim for a reengineering project. This is because the business environment will change significantly during such a project and managers simply do not have enough attention to give to all the events that will eventually need to be controlled. As a practical measure Davenport advocates beginning the redesign at the top but ensuring that implementation takes place at the detailed level in order to recruit expert local knowledge.

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There are five fundamental ideas [Davenport and Stoddard 1994] that distinguish business reengineering from the piecemeal optimisation more familiar from the 'kaizen' approach of the Japanese. These are:

- a) Adopting a 'clean slate' approach with no areas that are to be protected from change
- b) Adopting a cross-functional outlook
- c) Setting stretching, rather than gradual, targets and having the confidence to achieve them
- d) Using information technology to enable change
- e) Making all the required changes in behaviour and in processes that are needed to enable the reengineering

Davenport and Stoddard use the phrase, "Design using a clean slate but implement using the existing slate." While the piecemeal approach is better than no change at all the problem with it is that the business may become trapped in a local, rather than a global, optimum. There is a balance to be struck: if massive change is undertaken rashly or too frequently then business continuity is threatened and value is squandered in excessive internal management of change. However, occasionally taking a clean slate approach will ensure that the necessary change takes place at a pace that does not threaten business viability. In this thesis the alternative model of business for CBTs is a radical change and yet subsequent development of the model is likely to be incremental only.

In the health care industry the processing needs of novel therapeutics have already created the need for new information systems. The performance of the resulting structures can be highly unpredictable [Lenz and Kuhn 2004]. Enterprise modelling and BPM offer a way of testing the systems before committing to them in practice. Porter and Teisberg [Porter and Teisberg 2006] consider the shortcomings of health care systems in the US and in Europe and conclude that value-based competition is the only viable way to reform the efficiency of health care provision. Value-based competition (which will increase the need for creative change on an ongoing basis) must be achieved over the whole cycle of patient care in order to have meaning; it cannot achieve its results piecemeal. Porter points out that if a hospital tries to deliver a large diversity of

treatments from a local centre the result is that rare, difficult or specialised treatments are not delivered to as high a standard as that which can be reached by specialist units. He also points out that business processes vary from hospital to hospital. It would be preferable to have common business processes for ease of communication, continuity of practice and training and for easy data transfer.

Other reasons than costs have been given for undertaking BPR. It is said [Damij, Damij et al. 2008] that there are three main reasons: to learn, to make decisions or to re-engineer the operation. Whatever the motive might be it is very important to concentrate on the low-level business processes when reengineering an enterprise. Failure to address the low-level processes will lead to lack of joined-up processes at higher levels in the operation. Modelling can help in three main ways:

- a) Increasing operational efficiency
- b) Enabling better management accounting
- c) De-risking business planning

Effective change management is based upon sound understanding. Modelling an existing operation will impart knowledge about the business that is deeper than the knowledge obtained simply by recording current assumptions. Quantitative modelling can identify bottlenecks and points of sensitivity in the existing system. Changes to these features can then be prioritised in the reengineering project.

Over time there is a trend in manufacturing for the ratio of fixed to variable costs of production to increase (see Figure 2.8). For simple products in early factories the costs of production such as direct labour and especially raw materials could easily be traced in the form of value added to a given product; administration costs were light and therefore did not contribute significantly to the general operational costs. With the arrival of high technology industries more complex supporting services were needed. For example the high costs of quality assurance for these more complex products and the costs of machine maintenance dramatically increased the overheads. This trend continues. The extra expense is normally borne in the form of staff or systems that serve more than one product. In a mixed portfolio it can thus be difficult to ascertain what the true ratio of

value to cost will be for each product. Under these circumstances there is a risk that any efficiency measures will be taken without reliable insight. Such measures will be at best ineffective and at worst deleterious to business success. Only accurate cost models can inform these actions by making it possible to identify the marginal costs incurred for the additional business revenue.

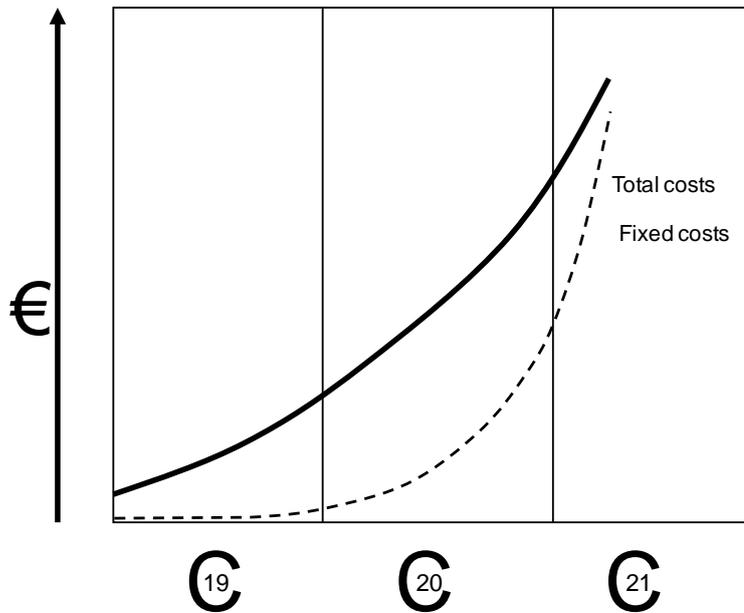


Figure 2.8: The trend towards higher overheads in high technology manufacturing

Throughout the history of business modelling there has been an overlap between tools for BPM and tools for business accounting. What distinguishes the two activities is their primary aims. Business accounting seeks primarily to optimise the use of resources. Business reengineering (and therefore business modelling) has the main aim of increasing the efficiency of the operation as a whole (and thereby to increase profitability).

A solid grounding in data is needed for both approaches but this has not always been adopted. During the 1980s and 1990s the drive to increase competitiveness using BPR led to many over-optimistic applications. Aggressive project management and a lack of any empirical basis for many recommendations led to a loss of credibility for the techniques. At the time there was a tendency to exclude the very people who knew the systems best and this reinforced the idea that the projects were only about staff cuts. It is

now recognised that there must be adequate validation of the results of BPM and unless the people doing the reengineering are the people who know the systems the result is likely to be poor [Lenz and Kuhn 2004]. Most systematic approaches to BPR in recent publications emphasise the need for a progressive approach in which user involvement and accurate analysis of the 'as is' situation is as important to success as the creation of new models of operation.

The need for cross-functional working has increased and operators with quite different backgrounds and practices must act together to improve overall operational efficiency. However, BPR projects with Health Management Organisations often fail due to a lack of engagement from the end users and lack of management support. Encouragingly, the information handling capability of Health Management Organisations is now being improved. This leads to a situation in which just-in-time scheduling with manufacturers may become easier. The work of Porter et al [Porter 1985; Porter and Teisberg 2004 (1); Porter and Teisberg 2004 (2); Porter and Teisberg 2006; Porter 2008; Porter 2009; Porter 2010] reinforces the need for what Porter calls 'integrated practice units' i.e. specialist multidisciplinary units that have the talent and the facilities to deliver excellent care over the whole patient cycle for a limited range of indications or techniques. Such units will deliver high quality care to patients from a large catchment area. At present most providers divide their units along the opposite principle which is to organise along the lines of technical discipline in large hospitals intended to serve smaller catchments and attempting to be good at a wide range of treatments.

In order to satisfy a global market for advanced health care products it is not enough merely to produce a better solution to an existing problem. The solution must be low enough in cost to compete both against conservative methods of managing the patient and against production based upon low labour rates in developing countries. Since the advanced therapies are likely to cost more to produce and to apply it follows that the value across the whole patient care cycle must be optimised for a new therapy to be adopted. Such a situation demands new models of business. These may be radically different from existing models and, if so, gradual change will not take an organisation to the new structure.

BPR is thus a complement to continuous improvement. The latter is incremental and seeks to optimise the system 'as is'. BPR takes a fresh look at the whole structure and seeks a new form built around the needs of the system [Damij, Damij et al. 2008]. We see in the evolution of natural systems that continuous improvement can result in very effective procedures but it can also lock systems into outmoded behaviour that is unsuited to environmental changes. When this happens a step-change is needed for the system to survive. Such step-changes are risky and rash replacement with untried new formulae at the enterprise level should be avoided [Colter 1984]. The advent of regenerative medicine may be such a step-change in the environment. Quantitative modelling allows the proposals to be tried out *in silico* rather than making unpleasant discoveries during implementation.

BPM is thus a rigorous version of problem solving. It makes issues that were previously understood only by those involved with them easier for outsiders to understand; this creates better teamwork. BPM aids mutual understanding through better definition of roles and relationships. Through integration of data (Computer-Aided Design, internet-based communication, document management systems etc.) communications may be dramatically improved. This is especially important for industries with geographically separate sites.

Since the 1970s there has been increasing use of organisational models to improve operational efficiency. The body of literature is large and comprises examples of several different approaches for representing operations. The next section describes these changes and introduces the methods from which the tools for this thesis were selected.

2.10 The Evolution of Enterprise Modelling

There are said to have been five stages in the evolution of methods for analysing systems [Colter 1984; Damij, Damij et al. 2008]. These comprise one pre-computer age and four ages of computer-aided tools.

In the first, pre-computer, age techniques such as probability maps and decision trees, manual value chain mapping [Porter 2011], process flow diagrams and card-based inventory- or decision-mapping tools were used, often accompanied by longhand

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calculations. In chemical engineering, for example, it was usual to analyse processes by constructing mass balance tables to account for the disposition of raw materials and products during manufacture and to link the results of these tables back to accounting tables for the business as a whole. In 1939 the concept of Petri Nets was created. Their application quickly adapted to the computer age [Bradley, Browne et al. 1995; Karhu 2001]. They were created to represent chemical reactions but their general format made them suitable for the depiction of organisations because they are concerned with decision points, can allow for a degree of iteration and are capable of representing concurrent events. The formal language of Petri Nets made them amenable to computerised treatment.

The advent of the first generation of computers accelerated the growth of modelling methods but also resulted in difficulties in communication between technical and non-technical staff [Colter 1984]. At first this reduced the usefulness of the techniques. There was a tendency to build computer methods based rigorously upon the previous manual methods, thus missing the chance to create more efficient architecture. There was also a tendency to regard human data flow as somehow ‘external’ to the model even though its presence must be accommodated in real life. Data Flow Diagramming or DFD [Cho and Lee 1999; Karhu 2001; Finne 2006] was introduced at this stage and has since been applied in the construction industry and, more extensively, in digital programming. In common with some other methods, such as Integrated DEFinition method 0 (IDEF0, which is dealt with in more detail below), DFD is capable of hierarchical decomposition and represents the flow of data, even during iterations. In common with IDEF0 the method is time-independent; unlike other methods it concentrates on data alone. However, DFD does not deal with the performer of a process. (In IDEF0 this would be represented by ‘Mechanisms’ and such data can be used for cost analysis.)

With the second generation of computers the methods began to accommodate the architecture of the computing process rather than merely reproducing the previous manual methods in a digital form. This led to greater efficiency in operation.

The so-called ‘third computer generation’ of modelling was characterised by the inclusion of the requirements of automation in the modelling architecture. This allowed

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for command sequences suitable for conversion to automation software with minimal change. Since this time the connection between BPM/enterprise modelling and automation has been clear to see and many published projects concentrate on automation and data exchange rather than on other features of the operation such as human or mechanical aspects.

The 'fourth computer generation' stage was characterised by the so-called 'structured revolution' which started in the mid 1970s and extended until the mid 1980s [Colter 1984]. An emphasis was placed upon method and the ability to exchange results between tools. The 'structures' referred to are those which derive meaning by progressive decomposition of the model to the required level of detail. In spite of this advance no single technique could be regarded as a complete solution to systems analysis. An early review described these techniques in terms of passage through three distinct stages in development associated with, respectively, the realisation of the importance of entity coding followed by the faithful definition of solutions and finally the accurate depiction of the real-world problem.

The creation of 'System Analysis and Design Technique', sometimes referred to as 'Structured Analysis and Design Technique' (SADT), made available a method that is arguably the most comprehensive or complete of the structural tools. SADT™ was created by Douglas T Ross and SofTech, Inc. [NIST 1993]. The technique is a graphical one and was developed originally to facilitate communication between teams working on projects involving very large business systems. A method was needed that is systematic, easily understood by inspection and can be used as a graphical front-end for a database containing information about the system under analysis. SADT can be applied in a number of ways depending upon which features of a system are important to the study. In the 1970s the US Air Force applied SADT when it introduced the Integrated Computer-Aided Manufacturing (ICAM) program. Formal standardised modelling methods became a requirement for effective operation of the program and these were generated as the series of tools known as the IDEF methods. IDEF0 was created by Knowledge Based Systems, Inc. (KBSI) in response to a request for the principles of operation analysis to be captured as a US standard. IDEF0 is described as a 'function modelling method' and is intended to allow modelling and communication of the processes to facilitate corporate

inception, start-up, contract work and business management. IDEF0 may be used to model both automated and non-automated Systems. The Computer Systems Laboratory of the National Institute of Standards and Technology put IDEF0 forward in 1993 as the standard for Function Modelling [NIST 1993]. The Standard remains an excellent source of information about the techniques, methods and applications for the tool.

The elements of a System that are described by IDEF0 are the System Functions, functional relationships and 'data'. 'Data' in this context means both objects and information. The technique is independent of, and stands above, any specific software package that is created to allow its implementation; it remains primarily a method of modelling and not a computer programme, although it has been incorporated in computer tools as will be seen (Section 2.13).

The main characteristics of IDEF0 are that it is generic, conceptual and flexible. This last characteristic is important: although it is normally used at project inception the technique remains viable for different stages of project development. Nevertheless, the method is described as "rigorous and precise", in spite of its conceptual character it must include all relevant functions.

The ICAM program gave rise to the following IDEF versions.

- a) IDEF0 A 'function' model
- b) IDEF1 An 'information' model i.e. covering the semantics and structure of information within the System
- c) IDEF2 A 'dynamics' model i.e. representing the features of the System that change over time
- d) IDEF3 'Process flow and object state description capture method'
- e) IDEF4 'Object oriented design method'
- f) IDEF5 'Ontology description capture method'

Structured analysis techniques built upon or incorporated earlier techniques [Colter 1984]. For example the GRAI method that is used to analyse decision nodes within systems [Doumeingts, Vallespir et al. 1995; Dowless 1997; Doumeingts, Ducq et al. 2000; Dossou 2003; Girard and Doumeingts 2004] is complementary to the earlier IDEF

methods but is more holistic. Its origins lie in the same US military projects but the developments by Doumeings and his team have spawned a host of spin-off techniques and products. GRAI has been placed in prescriptions for project methods that end in IDEF techniques in an attempt to make it easier for non specialists to execute projects. Another example, ARIS from IDS Scheer AG, is a comprehensive business architecture tool that now incorporates decision record systems that enable users to trace the evolution of whole projects [Martinez-Olvera 2009].

2.11 An Alternative Classification

In contrast to the description of the previous section some authors have divided all BPM tools into 'First generation' or 'Second generation' categories. The difference between the two lies in their scope. First generation tools attempted to model the entire system. Later there was a growing realisation that one tool would never be wide ranging enough to include all relevant features and so the concept of 'analysis packages' arose with the second generation [Colter 1984; Vosniakos and Barla 2006]. By the mid 1980s there were a series of techniques that were competitive rather than mutually compatible. None of these techniques addressed the complete path from problem definition to project conclusion; each represented a part of that journey. (Note that SADT comes closest to being a global modelling method for those questions that can be answered by representing a business at steady state i.e. not during periods of development or perturbation.)

Meanwhile special types of business sometimes require special solutions. For example 'value stream mapping' has been proposed for several industries where economy of scope is as important as economy of scale [Agyapong-Kodua, Ajaefobi et al. 2009]. This approach has its origins in the motor industry and was championed by Toyota. There are, however, no satisfactory examples of value stream mapping for regenerative medicinal products.

2.12 Less Formal Methods

Alongside the history of development given above (Sections 2.10 and 2.11) less formal methods are still relevant in some contexts.

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At the simplest level there is the concept of ‘checklists’ (e.g. those published by trade associations) [Atkin and Bjork 2007]. Checklists are applied as a generic aid to systems mapping especially within the realm of quality assurance for the software engineering industry. However, their application for mapping systems is very limited.

Data Flow Diagrams [Cho and Lee 1999] (referred to in Section 2.10) are a graphical representation of the interdependence of data in terms of origin, destination and control of flow. In common with IDEF0 there is no time-based component to the representation and they can be derived from a context-level diagram supplemented with decomposition to the required level of detail in lower, process level diagrams. DFDs are an important tool in the computer control industry.

Grenzplankostenrechnung (also known as GPK or ‘flexible margin costing’) is a method dating from the 1950s. As the name suggests GPK is pertinent to cost analysis and has been used in list pricing [Beaulieu and Mikulecky 2008]. GPK has been put forward as an alternative to Activity Based Cost analysis in the context of hospital resource planning and control [Sharman and Mackie 2005]. Like IDEF0 it can be converted into cost analyses and is based on the concept of optimisation of resource. GPK also takes into account the value of non-utilised resources i.e. it accounts for lost opportunity. It is thus an example of resource consumption accounting. Although GPK was introduced as a long-hand technique over 50 years ago it has since been absorbed into computerised methods and is employed as the costs analysis method of choice by some German companies such as Mercedes, Porsche and Stihl.

These less formal techniques are still powerful methods of analysis. A robust analysis is likely to use traditional techniques combined with a structured approach [Colter 1984]. There is no universal panacea that can be applied to any problem without consideration of the nature of the question. The choice of methods must reflect the purpose of the project if a successful outcome is to be achieved. In this thesis traditional methods like flow sheets have been applied alongside computer-based BPM.

2.13 Software Tools

(Note: it is not the purpose of this review to describe automation architecture or data management software. However, reference will be made to some features of these for examination of automation in Section 6.8.)

There are software solutions to complement or support BPR. These ancillary methods help with building new structures, effective communication of proposals or insight during problem solving. The main ones are described below.

As noted above (Section 2.10) KBSI introduced the IDEF methods and has since adapted them into software tools. IDEF0 is embedded in the application now known as AIO WIN®, the application used to conduct the analyses in this paper.

iGrafx software comprises a related family of tools for analysing and representing the features needed for business reengineering and problem-solving. The tools derive from a number of separate techniques and are available as nested packages.

FlowMark from IBM [Stegmaier, Ebbers et al. 1998; Lin, Ettl et al. 2000] is a tool that was created to manage the flow of work from person to person. It is oriented around the operator and is an example of a ‘push’ workflow control system.

SAP NetWeaver® [Li, Fan et al. 2005] is arguably one of the most comprehensive business management platforms around today. It is presented as an integrated system for financial management but it lacks the structural interrogation characteristics of IDEF0 as SAP is concerned primarily with tracking the system ‘as is’ [SAP America Inc.; SAP(1); SAP(2)].

The Process Definition Interchange Specification (WFMC-TC-1025) has been proposed for communicating vendor specific models of work flow [Li, Fan et al. 2005]. Again, it is complementary to, but not a replacement for, the structural interrogation of IDEF methods.

2.14 Recommended Methods of Modelling

It is more helpful to conduct modelling and to identify problems before a system is implemented than it is to attempt BPR once a mistake has been made [Lamont 2009]. All good BPR studies use the current business functions and processes to form the basis of the analysis [Jang 2003]. In this thesis the ‘as is’ case is a composite view derived from industry history, interviews with those working in the regenerative medicine business and data from cell expansion in the laboratory. The work was undertaken to inform choices, not *post hoc* to repair an existing business.

At the level of interest for this thesis it is the structure, operational form and economical viability of the business that are important. To this end the alternative approach to modelling, that of stochastic simulation of the enterprise, was rejected in favour of steady-state deterministic modelling. This is because the level of detail, the dynamics and the stochastic information that could be generated are not directly relevant to the key questions. Simulation will provide much more information about process performance, such as task scheduling, queuing, in-process losses etc., but the important issue in this thesis is business structure, cost and the management of materials movement at full production scale. Simulation is therefore not within the scope of the current work but will form a part of any future work on this subject.

It is possible to visualise an enterprise modelling and BPR project by analogy with the treatment of a patient in hospital [Damij, Damij et al. 2008]. There is a condition or ‘illness’ to cure and this requires admission (project set-up), diagnosis (investigation or analysis phase), treatment (derivation of preferred model) and cure (implementation). Clarity of purpose is essential at the start of any study in order to avoid loss of control during what may become a lengthy project [Colter 1984].

BPR differs from hospital treatment because there is usually an elected reason for undertaking the work and this will be predicated upon a particular viewpoint. A minimum of four different viewpoints is possible for any system, based upon function, information, resource and organisation [Cheng-Leong, Pheng et al. 1999; Prescott 2006]. Frequently one modelling tool is not flexible enough to deal with all the features of

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interest; it may become necessary to re-enter data into several different systems. Changes that are implemented in one model may need to be separately invoked in others if no automated update is possible.

In 2001 Vernadat [Vernadat 2001] gave a list of eight principles to apply in all good process models. These have been widely cited since and they have been applied in this thesis. They are:

Principle of separation of concerns: Break down the overall view into discrete blocks, each of which comprises the processes to achieve some of the goals of the enterprise.

Principle of functional decomposition: In other words the major functions are self contained but may be analysed at the desired level by progressively decomposing them.

Principle of modularity: Related to the decomposition, this requires the researcher to group activities in such a way that they may be managed in logical blocks. A list of conventions has been given to manage this aspect.

Principle of model genericity: Processes fall into different classes. These often have generic characteristics and if these characteristics are subjected to a degree of standardisation in the model they can be re-used in a variety of settings with minimal manipulation.

Principle of reusability: For maximising the benefit the model must be assembled and filed in such a way that it can be updated or used as a template for other cases.

Principle of process and resource decoupling: Elementary processing steps are designated 'functional operations'. Resources are then assigned to them. The separation allows alterations to be made to the mode of execution of an activity.

Principle of separation of behaviour and functionality: Similar in intent to the previous principle this ensures that different styles of execution can be tried without affecting the desired outcome.

Principle of conformity: The model must be accurate in a way that is consistent with current modelling practice. This ensures that it can be understood by those skilled in the art.

The successful modelling procedure requires an initial statement of the problem, a project planning stage and then ‘domain exploration’ in the form of gathering information about the ‘as is’ case through interviews, observation and inspection of records. This is then followed by the building of work packages, conceptual design, implementation and testing [Lenz and Kuhn 2004].

Just as the start of a hospital treatment must be an accurate diagnosis so good modelling must be informed by the first step: an accurate problem statement.

Data gathering is the next step. BPR requires rigorous analysis and simulation with the right amount of detail [Damij, Damij et al. 2008]. This detail is normally acquired through a combination of interviews and direct observation but ultimately must be a subjective decision and good judgement is called for. The art to building successful models lies in balancing the need for detail with pragmatic simplification; for example, integrated models of an entire company are difficult to prepare, time-consuming and may not address the important issues [Kiefer 2000]. Reduction in data entry is likewise an important consideration [Klischewski and Wetzel 2003; Lamont 2009]. Reduction of complex sets of information to a few items can be done qualitatively [Lamont 2009]. Alternatively, simplification to important points can be achieved by judicious use of data reduction techniques such as ANOVA [Lin 2009]. In this thesis a model of a real business in regenerative medicine was first built (Advanced Tissue Sciences, Inc. and its interaction with the distribution network of the Advanced Wound Management business of Smith & Nephew plc). The model was based upon direct observation and interviews with holders of various posts in the organisation. Features that were regarded as essential for this thesis were then drawn out. The detailed model of the ATS/S&N joint venture is too extensive to be included in this thesis but the information gained was invaluable in giving context to the thesis itself. Examples of the insights gained during this exercise are:

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- The dynamics of the ordering process
- The logistics and the packaging required for the cold supply chain
- The individual roles of the staff members
- The dynamics of the management of the quality system

Looking at the detailed level of the model Cho recommends the decomposition of a shop floor into three hierarchical levels [Cho and Lee 1999]: shop, workstation and equipment. Analysis can then be conducted with the appropriate level of scrutiny without the need to create a global plant model. This principle can be applied to a wide variety of models and not just to shop floors. It is a technique that is adopted in this thesis at the levels of cost centre, workstation and micro factory unit as will be seen in Sections 4.2 and 4.3.

The next step in systems analysis is the identification and characterisation of all relevant relationships [Colter 1984]. It is possible to create exhaustive lists of all relationships but this may add little value if the high-level system behaviour is dominated by only a subset of those relationships. The impact of the others need only be represented as outliers beyond the scope of the range of interest. The high level view required for this can usefully be obtained using GRAI-grids and this was the approach taken in this thesis (see Section 4.4 and 5.4).

If the source of a problem can immediately be localised to one feature of the organisation then hybrid models may be used in which a simple framework model of the whole operation hosts detailed models of specific parts that are of interest. This approach combines the benefits of an holistic view with the problem-solving potential of detailed local studies [Kiefer 2000]. For a regenerative medicine business the modeller may restrict the view to manufacturing, inventory control, product release, distribution and treatment scheduling. It is less useful to model payroll, training, recruitment, procurement, facility management etc. except insofar as they impact upon the other features. This approach has been applied in this thesis: the infrastructure of the central operation and of the clinic in which the goods are applied has been ignored in order to

focus on the areas of relevance. Whichever way the project is conducted it is certain that process analysis is a pivotal part of the BPR [Lin 2009].

A model cannot be considered adequate until it has been validated. Validation can be qualitative (e.g. by peer review) or quantitative (e.g. by re-calculation using dummy sets of data of known outcome). This thesis was validated via the scrutiny of a health economist and experts in the manufacture of CBTs. Quantitative validation was done in two ways. The values and output from the cell expansion operations were examined by two technical consultants. The overall model was subjected to a sensitivity study to determine which parameters exerted the most influence over the model results and therefore which parameters needed to be the most realistic.

The detail and effort required to build a model can demand a lot of resource; thus the concept of 'Reference Models' can be very appealing. Reference Models are generic models, often modular in form, which can be archived ready for customisation to apply to fresh projects, thus reducing the effort in model-building. A generally applicable Reference Model is probably unattainable [Martinez-Olvera 2009]. However, a Reference Model for a specific sector seems a reasonable aim. Reference Models are a means to accelerate BPR. They show the organisational structures and the operational practices that characterise a particular business sector. The Reference Models are usually partial models that can be reused and circulated. In this sense they resemble the blocks of code that are employed by software developers [Baines and Colquhorn 1991; Vernadat 2001]. In conducting the study in this thesis the author's intention is to build a Reference Model that can be adopted and enlarged for new technology evaluation projects.

2.15 Modelling using IDEF0

It has been pointed out [Bertoni, Bordegoni et al. 2009] that the real strength of IDEF0 is at the concept design stage and it is thus appropriate that IDEF0 is used in this thesis. It is usual to build an 'as is' model before advancing to speculative models of change (the 'to be' model) [Cheng-Leong 1999; Cheng-Leong, Pheng et al. 1999; Li, Fan et al. 2005]. IDEF0 allows modelling of different viewpoints of the same system to answer different questions. This is an advantage because models may otherwise only be built from

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different viewpoints using methods that are not necessarily mutually compatible [Prescott 2006].

SIMA reference architecture [Martinez-Olvera 2009] forms the basis for IDEF0. Thus IDEF0 can be used to define information inputs and outputs i.e. the logical structure. IDEF3 can be used to represent the dynamics if required [Cho and Lee 1999].

IDEF0 models are constructed as a hierarchy of levels each of which represents a different level of complexity. There are two key components to the diagrams of these levels: functions and data. The functions are represented by boxes and the data (or 'concepts': information or materials) by arrows connecting the boxes.

It is not the intention of this report to reproduce detailed instructions about the application and use of IDEF0. The interested reader is directed to the Standard or to suitable texts describing its use [NIST 1993].

IDEF0 defines the meaning of a series of activities in terms of what is achieved through the flow of information, materials or value [Atkin and Bjork 2007]. Interactions between activities are defined in terms of Inputs, Controls, Outputs and Mechanisms (referred to as ICOM). It is hierarchical and can be decomposed progressively to the required level of detail.

IDEF0 can be enhanced to provide cost information. For this to happen there must be effective data exchange accompanied by good monitoring of process status [Klischewski and Wetzel 2003]. Four hierarchical levels of attention are needed [Beaulieu and Mikulecky 2008] as shown in Table 2-2. The incorporation of this approach in this thesis is described in Sections 4.2 and 4.3.

Table 2-2: Levels of attention in IDEF0-based cost analysis

Costs	Type of cost	Behaviour of cost
Unit level costs	Variable and direct	Proportional to output
Batch level costs	Strictly not variable but often treated as such. Direct.	Usually treated as proportional to output.
Product sustaining costs	Direct and fixed	Invariant with output volume over wide ranges
Facility level costs	Indirect and fixed	Majority of components are invariant with output

There are several advantages to using IDEF0: mainly its realism [Atkin and Bjork 2007], its use as an aid to communication, its thoroughness and its conciseness [Jang 2003]. However, IDEF0 also has limitations. The hierarchical nature must be used with care: IDEF0 can be restricted by its top-down approach [Atkin and Bjork 2007]. A more objective bottom-up method is sometimes used in combination [Cantamessa and Paolucci 1998]. IDEF0 gives an image of ‘steady state’ and lacks dynamic information. For this reason IDEF0 is difficult to apply to production stock control [Lin 2009]. It is labour intensive and considerable time must be spent in interviewing and detailed analysis in order accurately to derive costs and drivers if Activity Based Cost analysis is to be added on [Beaulieu and Mikulecky 2008]. Most importantly, IDEF0 is not time-based: timing is better represented by tools such as ProVision [Lamont 2009]. IDEF0 fails to capture issues such as lead time, quality and manufacturing order [Jang 2003]. No information is provided about the dynamic behaviour e.g. the time-dependency of control events or instabilities in work flow. The image is static and logical; IDEF0 handles dependencies but not flows. Likewise it cannot give information about process performance in terms of lead times [Cho and Lee 1999]. IDEF0 does not generate stochastic information about the subject of the model or about the results of multiple decisions in the process flow but rather it gives information about the overall structure and is thus more deterministic. If IDEF0 is used to generate models from which Activity-Based Cost analysis is to be conducted then this can be done by applying fractions of contribution at those points in the model where alternative work flow can occur e.g. decision points.

Inevitably some subjective decisions must be made about the way that some costs are allocated [Beaulieu and Mikulecky 2008] even if subjectivity is kept to a minimum through careful analysis of overheads. Robert Kaplan of Harvard popularised Activity Based Cost analysis (often derived from IDEF0) and even he asserts that facility level costs should be excluded from models for this reason. IDEF0 is therefore very qualitative and has been accused of lack of mathematical rigour [Chin, Zu et al. 2006]. Decision points are difficult to represent and flexibility in pathways may not be captured [Klischewski and Wetzel 2003]. IDEF0 can become unwieldy when faced with modelling operations that are intrinsically complex [Chin, Zu et al. 2006].

The fact that IDEF0 can be applied so broadly and so systematically has encouraged some researchers to try and bridge the shortcomings while retaining the advantages [Cheng-Leong 1999]. A systematic approach that extends IDEF0 has been published [Jang 2003]. Attempts have been made to produce ‘dynamic’ versions of IDEF0 models that may be simulated using other applications. In order for this to happen two additional classes of information have to be installed in the IDEF0 model:

- a) Information about the IT support systems
- b) Information about how the system behaves under perturbation

Such an enhanced system is capable of aiding real time decision making. Cheng-Leong [Cheng-Leong, Pheng et al. 1999] derives simulations via the mediation of an ASCII text file and there have been other attempts to do similar things, notably Meta Software’s application for converting IDEF0 models into Petri Nets for enhanced simulation. Similarly the use of SLAM II [O’Reilly 1991] has been proposed [Kim, Yim et al. 2001] for simulation based upon directly-parameterised versions of the IDEF0 model.

‘IDEF*’ represents a further step. The new tool differs from the previous tools because it is able to integrate different viewpoints within the same model and can look at both the overarching and the detailed levels.

For operations at the very detailed level where the work is value-adding, costly and highly iterative (e.g. mould making for the plastics industry) the IDEF0 method becomes unwieldy. Under these circumstances a fusion of IDEF0 with Coloured Petri Nets may

offer a solution. For the regenerative medicine industry such an approach may work when analysing the responsive, iterative and complex operations involved in cell expansion through passage rather than cell expansion using batch or semi-batch vessels [Chin, Zu et al. 2006]. However, for this thesis it is an over-refinement because the focus of the work is on a viable format of the business rather than on task scheduling or queuing or on work throughput. The inclusion of Petri Nets would constitute a useful next step in the dynamic simulation of the business.

Whatever form of IDEF0 is used quantitative methods are necessary in order to overcome the qualitative limitations. Without this enhancement process performance analysis cannot be achieved. Three alternative approaches were identified and compared by Chin et al [Chin, Zu et al. 2006] to enhance IDEF0.

- a) Use IDEF0 for specification of the process and then a different modelling application for the simulation (time-consuming and clumsy)
- b) Extend IDEF0 methods to include additional functionality (not what IDEF0 was intended to achieve)
- c) Transfer results from IDEF0 in an integrated way into a modelling method that can add the additional functions (e.g. incorporation of Activity Based Cost results via text file transfer, the approach used in this thesis)

Cho [Cho and Lee 1999] described another enhancement which is designated 'IDEF1X data modelling'. IDEF1X was developed to model the relationships of data within sets of relationships involving other information [Mayer, Painter et al. 1992].

For the purposes of this thesis the key questions all relate to the costs, risk and performance of the business at steady state. The dynamic element that is lacking in IDEF0 is overcome by relating year-on-year production costs through a Profit and Loss projection. Each year of the P&L chart is regarded as a stand-alone steady state output from the model. Quantitative output of costs is desirable and so the text output of Activity Based cost calculations is essential. The next section describes how this can be achieved.

2.16 Activity Based Cost Models and Enhancements to IDEF0

Cost modelling tools are essential for this thesis because the origin and scale of operating costs must be identified in order to compare the viability of alternative business models. The points in the process at which costs are incurred must be accurately represented before the cost benefits of alternative business practices can be perceived. Enhancements to IDEF0 for addressing decision points and responsibility are helpful because of the importance of showing exactly where responsibility lies for product release, product recall and reacting to deviations and exceptions in production cycles and this is achieved using GRAI-grids.

Accurate, user-friendly cost modelling software has existed in the chemical and biochemical engineering sector for some time. Specific sectors make use of expert systems and data look-up tables maintained by the software supplier. Examples of such products are BioSolve® from Biopharm Services Ltd [BPS 2010] and aspenONE® [Aspen 2010]. Such software shows business systems only at the detailed level of operator shifts in the shop floor and alterations in flow during batch manufacture. In order to understand the impact of changes in business structure it is necessary to analyse the system at a higher level.

Activity-Based Cost (ABC) models that are run alongside IDEF0 simulations can provide an answer [Giebel 2005]. ABC analysis provides objective cost attribution by associating each cost with the point in the process where it is incurred [Bartholomew 2004]. This is the basis of the inclusion of 'Easy ABC®' in some offerings of software to enable cost modelling in Microsoft Excel®. Easy ABC® has been included with IDEF0 in the AI0Win® package from KBSI, Inc.

In this thesis it would have been helpful to apply work from precedents but the reviews in this Chapter showed that work on cost-related BPM for health care focuses on the point of care only (e.g. use of resources, scheduling of operations, and optimisation of theatre space). For example IDEF0 has been applied to facilities management [Atkin and Bjork 2007]. BPM has been used from the viewpoint of a specialist in a hospital setting but this is from the customer perspective only, not necessarily the supply of goods

[Hoffman 1997; Ho, Chan et al. 1999; Klischewski and Wetzel 2003]. Even examples of the customer value viewpoint [Finne 2006; Kumar, Ozdamar et al. 2008] do not address the unique features of the supply chain in regenerative medicine. Case studies of the application of SADT/IDEF0 in different sectors related to regenerative medicine or extended enterprises include:

- a) Orthopaedic procedures [Klischewski and Wetzel 2003]
- b) Generic manufacturing model [Martinez-Olvera 2009]
- c) Surgical treatment with Tabular Application Development [Damij, Damij et al. 2008]
- d) Data management through web based interface [Klischewski and Wetzel 2003]
- e) Patient data management [Lenz and Kuhn 2004]
- f) China-Europe collaborative network 'DRAGON' [Li, Fan et al. 2005]
- g) Formation of collaborations with IDEF0 [Li, Fan et al. 2005]
- h) Two tier flexible manufacturing systems under Enterprise Resource Planning [Choi and Kim 2002]

It is therefore necessary to begin from basics in the models for this thesis. The features that are incorporated are:

- a) Ease in use without specialist programming capability (for additional work later by non-specialists)
- b) Easy-to-understand graphical output format (for presentation to a variety of senior management)
- c) Ability to model activity, cost data and logic with flexibility and breadth
- d) Transferability of model data into cost models
- e) Ability to update databases without excessive data entry e.g. when unit cost values are adjusted.
- f) Ability to integrate data output with other models

These requirements are included in the decision regarding the choice of tools (Section 2.17).

2.17 Summary and Choice of Modelling Tools

The way in which the BPM tools have developed reinforces the importance of choosing tools that are designed for computers, which can easily be understood by non-specialists and are controlled by a recognised standard.

The idea of Reference Models lends itself very well to the current study. Such models can be tailored to represent the features of the supply chain that are common to regenerative medicine. Costs for cold transport, release assays, cell expansion etc. can be linked to look-up tables that can then be updated periodically. The thesis can be regarded as the first step to creating a series of Reference Models that can be used as an aid to future case studies.

No matching precedents were found for models of the regenerative medicine industry. It is appropriate to begin with an SADT method. The recommended approaches to BPR made IDEF0 a suitable choice. There are several different ways of constructing IDEF0 models using commercial software packages. These were compared before commencing the modelling project.

The available tools were compared on the basis of the degree to which they satisfied the requirements of this thesis and the results are shown above in Section 2.9, Table 2-1. Some of the tools only address a few of the modelling requirements (e.g. Visio will provide graphical output but will not link to a database, C++ will allow full functionality but will start from too basic a level in the modelling cycle). None is as complete a solution for this thesis as AIOWin®.

Overall VC++ has the potential to outperform the others but it is not a tool for non-programmers and is unsuitable for this thesis.

Visio is capable of creating and manipulating the graphical data but is unsuitable for management of information about the activities and cannot be used for cost roll-ups.

MetaDesign's offering appears to be a flowcharting method only and its current status on the market is unclear.

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Design/IDEF and iGrafx are used by some consultants but their relationship to Activity Based Cost analysis is not as clear as the KBSI offering.

The modelling tool AI0Win® (version 8) from Knowledge Based Systems, Inc. (KBSI) is therefore the application of choice to conduct both the IDEF0 modelling and the Activity Based Cost analysis within a single package. Cost roll-ups can be exported as text files to Microsoft Excel® where they may be manipulated to represent the chosen intervals of operation and to conduct sensitivity analyses.

There is an additional requirement. As described in Section 2.6 it is important to analyse the business processes in terms of the locus of decision-making and control. Without this provision the risk remains that the ownership of vital steps in the supply chain will be assumed and not clearly assigned. The result could be errors of omission that would compromise patient safety. Combinations of GRAI-grid and IDEF0 analysis can address this subject and this approach is the one selected for the thesis. An enhancement with ABC analysis is included. The precise method is detailed in Chapter 3.

In summary, as manufacturing has increased in sophistication it has become ever more important to be able to discern where costs arise in order to increase efficiency and to remain competitive. IDEF0 combined with Activity Based Cost analysis provides the tools to do this with confidence. The graphical output enables a convincing case to be made to non-specialists. Methods involving GRAI-grids allow the contents of decision nodes in the business processes to be specified.

The overall approach in the thesis is based upon flow sheets, GRAI-grids, IDEF0 and Activity Based Cost analysis rolling up to spreadsheet-based treatment of cost centres.

The next chapter, Chapter 3, introduces the case study in this thesis for the general reader, with a description of the process flow for manufacture of a typical CBT. This gives the context for the values that are chosen for the important independent and dependent variables. The variables are given together with their sources.

Chapter 3

Basis of the Model: Description of Manufacturing

Process

3.1 Introduction

This Chapter provides a description of the series of operations that comprise the process for making the CBT. It goes on to identify the independent variables in the analysis and the models and provides realistic values for them based upon precedent in the literature or upon current business practice. The contents of this Chapter correspond to steps 3 and 4 in the thesis as illustrated by the flow diagram (see Chapter 1, Figure 1.3).

3.2 Constraints on the Business Model due to the Nature of the Cell

In step 3 it is necessary to review the features of human cells that may be influenced by the method of manufacture. An understanding of these features is essential for designing a robust manufacturing process. These features must also be taken into account in the design of the business systems within which manufacture must take place. Some of these features are shared with other products. For example the clean environment required during culture is in some ways similar to that used in microchip manufacture; the cold supply chain and 'just in time' delivery of goods is reminiscent of the supply constraints for transfusion of blood or for organ transplants. However, no single other product type has all of these challenges.

In normal aseptic production the cleanliness of the environment is verified by means of regular microbiological testing. Where it is believed that the environmental controls cannot easily be compromised, e.g. within an isolator, the burden of Quality Control is much lower. When considering the possible changes that may be made to a centralised business model the issue of environmental cleanliness during manufacture is dominant.

Isolator technology has a part to play in making choices about this as will be shown (Section 5.4).

In law the ultimate responsibility for the quality, safety and efficacy of a medicinal product will remain with the organisation that has been granted a Marketing Authorisation for that product, even if the site of the final stages of manufacture differs from the central facility where the product is registered. Each site must possess a Manufacturing Authorisation referring to the types of product that it is authorised to make. One of the reasons that centralised manufacture has been so important to regenerative medicine is that it is difficult to ensure that the product is made to the right standard when it is being finished on a remote site. With the advent of web-based tools for monitoring and control this operational restriction can be reappraised. Foremost amongst these is use of XML-based systems for remote process control.

Cells for therapeutic use must be free from pathogens and their residues, such as pyrogens. The cells must be viable at the point of use and so the products cannot be terminally sterilised by heat, radiation or chemical treatment. Unlike parenteral drug solutions they cannot be sterilised by filtration. Consequently the entire process must be conducted aseptically. The process must be validated to show that ingress of pathogens is extremely unlikely and each batch of product must be tested for freedom from adventitious micro-organisms.

Mesenchymal stem cells are anchorage dependent. They must be presented with a biocompatible surface upon which to grow or they will cease to proliferate and will soon die. Mesenchymal stem cells as a class contain a number of sub-populations. Recent work that suggests that for some of these sub-populations the requirement for anchorage can be circumvented, allowing the cells to be grown in suspension [Kallos and Behie 1999; Behie, Kallos et al. 2003; Baksh and Davies 2008]. At present it is reasonable to assume that the cells must be grown either on a planar surface, typically the tissue culture plastic of a T-flask, roller bottle or 'cell factory' unit, or on a suspended particle such as a microcarrier bead [Frauenschu, Reichmann et al. 2006; Andrade, dos Santos et al. 2007].

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Fermenter culture, in stirred tanks of single cells or microcarrier beads, allows intensive expansion with concentrations up to hundreds of millions of cells per millilitre of medium in very good cases [Baghbaderani, Behie et al. 2008]. If microcarrier beads are used then clean separation of cells from the beads at harvest is vital. Mixing in such systems can be a problem. While prokaryotic organisms such as bacteria have relatively robust cell walls, and are able to resist the shear force required for good batch mixing, mammalian cells such as mesenchymal stem cells are not so robust [Chisti 2001; Matthew S. Croughan 2006]. This places a limit upon how much energy can be dissipated through stirring before the cells start to die. Even at sub-lethal rates of energy dissipation the cell phenotype may be adversely affected. This is important because in practice the mixing efficiency is often the feature of mammalian cell culture that limits the batch size; good mixing is needed to provide the oxygen transfer necessary for growth [Doran 1995]. It cannot be assumed that a suitable mixing regime even exists; for any given cell type there may be no suitable energy range between these two opposing needs.

This leads to an important technological risk during development. This risk is one of the main reasons why new models of business are needed. The implications of this risk hold true for any cell-based therapeutic that must be used at high cell dose for a large global market. As the product is developed, a point is reached at which the business must make a choice whether to invest time and money in attempting some form of bulk production based on suspension culture ('scaling up') or to proceed on the basis of the tried and tested flask-based methods that were used in the laboratory ('scaling out'). This difference is said to be one of the biggest challenges in regenerative medicine [King and Miller 2007; Kirouac and Zandstra 2008]. The dilemma can only be avoided if it is possible to make the bench process into the basis of full scale manufacture [FDA 1995]. As will be shown in Chapter 5 the sheer number of cells required for many indications makes the scale-out option impractical for most businesses.

It is the impact of this dilemma that makes this thesis relevant for all cell-based therapeutics that address non-life-threatening conditions in large numbers; treatment of damage due to osteoarthritis is used here merely as an illustration of the principle.

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The goal of cell expansion is to prepare the maximal number of usable cells from each bone marrow aspirate. There are many possible variations in the cultural conditions; the pathway down which the cell will be driven depends on the degree of conformity of the conditions with the requirements of the desired phenotype [Bradley T. Estes 2008]. The growth of the cells is ‘contact inhibited’: the cells cease to proliferate once they come into long-term physical contact. If this is permitted during expansion the cells will adopt an unwanted phenotype. This imposes a natural limit upon the time in culture in any one cycle of expansion (or ‘Passage’) and upon the number of cells that can be harvested from a given surface area of flask.

It is very important to avoid contamination and this is especially important at the end of culture when the system must be manipulated to remove the cells from their support. A ‘closed system’, i.e. one that allows no ingress of micro-organisms or dust from the surroundings, is preferred. Contamination also inhibits the use of the more intensive microcarrier-based methods of expansion. If microcarrier beads are used then fine particles are created as beads fracture during mixing. If these fine particles are carried over into product it can result in batch failure. Scale-up of mesenchymal stem cell culture in agitated systems remains a big technical challenge; one that is not easily addressed by a company avoiding unnecessary investment risk. Scale-out remains the normal route.

There are features of the supply chain that must be managed in order to provide cells in a form suitable for clinical use. ‘Fresh preserved’ cells (i.e. shipped at room temperature or body temperature) must be only a few hours in transit if they are to remain viable. Such transit is routinely carried out in some centres. For example the Etablissement Français du Sang at Tours [Rae and Duffy 2008] sends cell batches to clinical centres throughout the rest of France. By contrast the dispatch of cells or tissue in a frozen state (on dry ice, wet ice or liquid- or vapour-phase liquid nitrogen) is best conducted in custom-made carriers and completed within about thirty-six hours. An example of this is the supply of Dermagraft® formerly made by Advanced Tissue Sciences, Inc. and now made by Advanced BioHealing, Inc. at La Jolla, California.

A validated shipping procedure is therefore needed. Increasingly, the regulators require verification of the transit conditions. Self-monitoring shipper units have been developed

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containing tamper-proof real-time logging devices from which data can be downloaded at point of delivery [Ward 2006; MacGabhain 2010 (1)].

Coordination with clinical use is essential. The right cells must be provided at the right time for successful clinical use. Few clinics have freezers capable of maintaining goods at temperatures lower than -20°C , so a just-in-time delivery arrangement is usually needed. This is challenging for a centralised distribution hub. If regional distribution hubs are set up then final delivery distances can be shortened but this involves additional operational expense. This issue of successful transfer of large numbers of low temperature goods has been the cause of slow market penetration with several existing products [Bagley 2006; MacGabhain 2010 (2)].

3.3 Information Sources

As this thesis does not start with an existing business many of the costs have to be approximated. This approximation does not lead to a lack of realism because the estimates are based as far as possible on published literature results for similar cell-based processes and on experimental results obtained in-house. The features that are estimated are shared by both the ‘as is’ model and the ‘to be’ model and so to a large extent they cancel out in the final analysis.

Global operating costs can only be obtained by modelling the whole enterprise. As noted above (Section 2.14) such an undertaking is too large in scope for this thesis and is unnecessary for addressing the questions of interest. Focus is maintained on the portion of the business that manages production and distribution.

The sources used for this thesis were:

- a) Primary data: Cell culture results from studies at Smith & Nephew and NUIG and cost information gained through operational experience managing a cleanroom at the Smith & Nephew Research Centre, York
- b) Literature: NUIG James Hardiman Library physical collections and e-Resources, online search engines, Science Direct, PubMed

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- c) Interview, industry: Employees or ex-employees of the companies Advanced Tissue Sciences, Biospherix, Biostór, Smith & Nephew, The Automation Partnership
- d) Interview, academia: Staff and associates at NUI Galway, University College London, University of Loughborough
- e) Interview, clinical: UK NHS Blood and Transplant service

3.4 The Process Flow

A campaign to produce a batch of an allogeneic cell product will typically contain the following steps in this order.

1. Facility preparation and procurement of raw materials
2. Preparation of the cell inoculum (drawn from the cell bank)
3. Bioreactor set up
4. Cell expansion
5. Cell harvest
6. Line clearance following cell expansion
7. Formulation of cells
8. Filling of dosage forms
9. Packaging of dosage forms
10. Cryogenic preservation of the dosage forms
11. Line clearance following product manufacture
12. Dispatch

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The SADT analyses are prepared from the viewpoint of the Production Manager. For comparison two issues are kept at the forefront of the analysis: overall operability and the cost of goods (CoGs) per product unit.

Viable regenerative medicinal products are supplied either fresh preserved on a make-to-order basis or they are frozen to allow warehousing and supply using a cold chain system on a make-to-stock basis (see Figure 3.1).

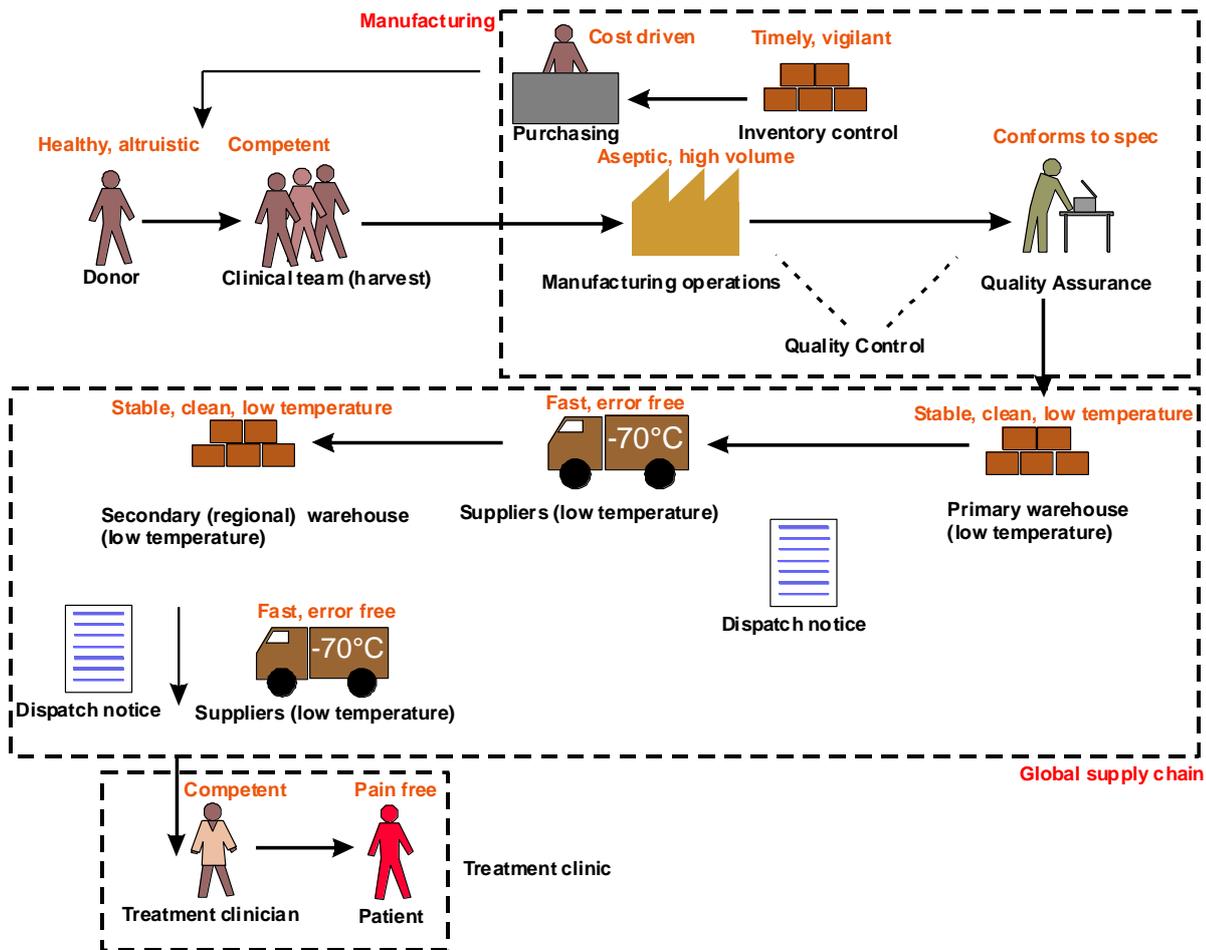


Figure 3.1: Process flow for typical stem CBT agent

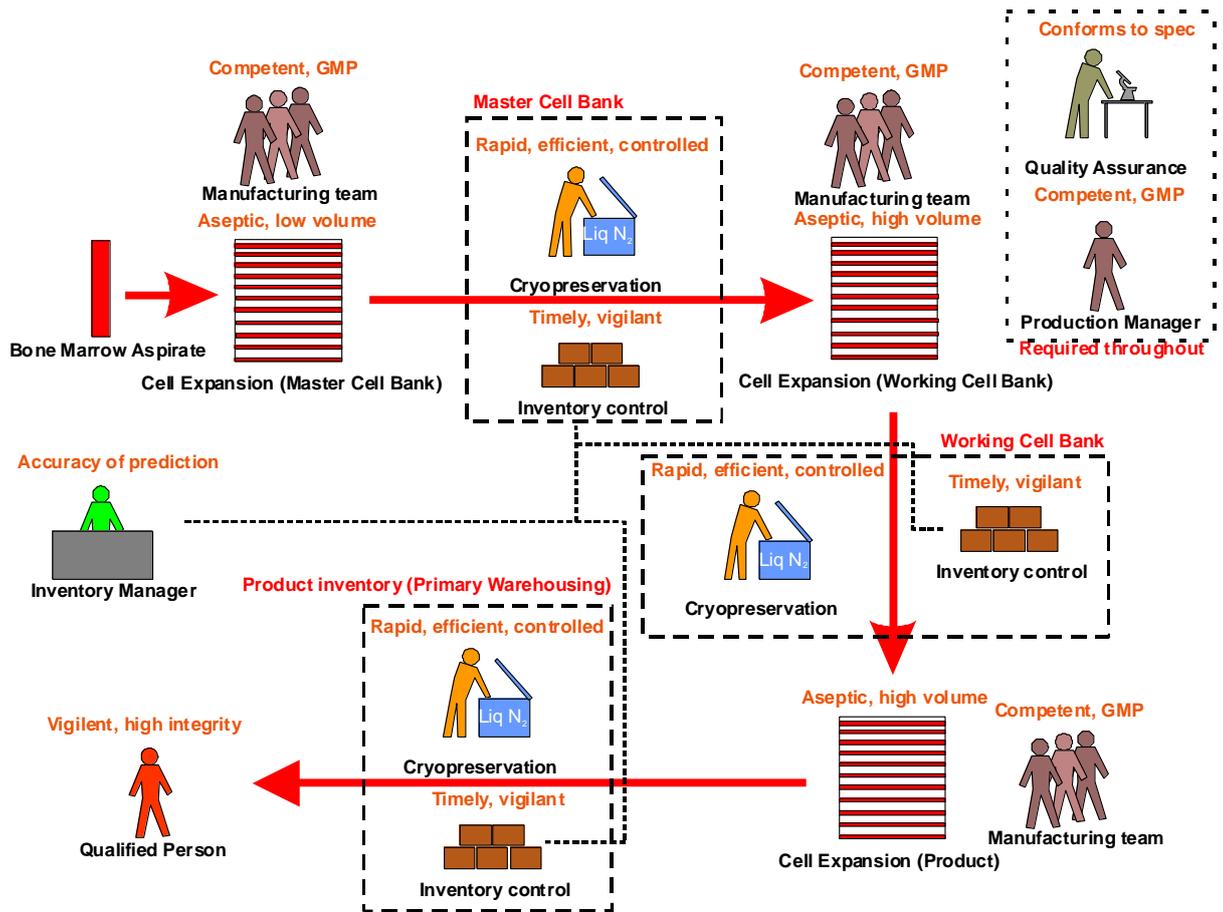


Figure 3.2: Process flow within manufacturing

Bone marrow aspirate is obtained from informed, healthy, adult volunteers. The cells are separated using adhesion to the plastic surface of culture flasks (blood cells do not adhere). During culture the cells are fully immersed in growth medium at a constant temperature of 37°C. The medium is replaced at suitable intervals and this requires emptying or part-emptying of the flasks. (This manipulation has consequences for the management of materials movement at large scale.) The cells are expanded, typically in culture flasks. At the end of each Passage the cells are removed from the growth surface using an enzyme and then counted, subdivided and re-seeded at lower density into a larger number of growth vessels to repeat the cycle. The productivity and cost effectiveness of the operation is influenced by several factors. As the number of Passages increases so the cell yield will increase geometrically and the longer the cells remain in culture the less significant will be the fixed costs, especially the costs of Quality Control and the cell bank qualification, in relation to the variable costs. Direct cost of production

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will converge on the cost of consumables per Passage and concomitant labour as the number of Passages increases. Ultimately the number of Passages will be limited only by cell senescence. The number of individual vessels in culture also follows a geometric progression and so materials movement and operability of the process become challenging at high Passage. A cell strain that is capable of very high levels of expansion without loss of its phenotype may be limited in batch size solely by materials movement problems.

The overall process flow is shown in Chapter 2, Figure 2.2 and Figure 2.3.

The following operational assumptions are made.

- a) Normal operational costs of the organisations within which the central operation and satellite operation would be managed are regarded as ‘sunk costs’ and are not estimated.
- b) A working year for one labour full-time equivalent (FTE) is regarded as 47 weeks at 37 hours per week.
- c) At the clinic it is assumed that there will be a cleanroom facility, perhaps of basic grade. (This is reasonable given that many transfusion services and in-house device preparation areas now exist within hospital networks. In practice only some clinics are so equipped but most clinics have access to such a facility.)
- d) Only one break-point in production is envisaged. This is the point at which vials of the Master Cell Bank are frozen down for later resurrection and onward expansion to make a product batch. (A more elaborate arrangement is developed for the ‘to be’ model.)
- e) The scope of the work is restricted to an examination of the relationship between manufacturer and clinic, clinical coordination and management of responsibilities.

Unless otherwise stated US dollars are used as the basis of cost analysis throughout.

3.5 Treatment of Directly Attributable Costs of Production

This section in the analysis comprises step 4 in the thesis (see Chapter 1, Figure 1.3). The aim is to gather together the costs of the raw materials.

The directly attributable costs of production are derived from studies of expansion. The expansion ratio per Passage is dependent upon the seeding density at the start of the Passage. This density must be adequate for healthy cell growth but not so large that the limitation on space imposes a poor expansion ratio. A seeding density of 1,000 cells.cm⁻² has been recommended [Sensebé 2008] and this value is adopted in the model for Passages P1 and higher (i.e. once the initial cell isolation has been made). The absolute limit on expansion is imposed by the footprint of the cells at about 40,000 cm⁻² [Bonab, Alimoghaddam et al. 2006] although the normal harvest aims to recover the cells before they become so tightly packed (see below). The values used are shown in Appendix 1, Table A1- 1.

Manufacture using any of the cell culture plastic methods can be analysed to a first approximation by using the fact that the cells are grown in a two-dimensional layer to a point at which they are just sub-confluent. The mesenchymal stem cells have a characteristic footprint area where they attach to the surface. This imposes a limit on the number that can be grown on the available area (about 31,000 cm⁻² for human mesenchymal stem cells).

The maximum expansion ratio per Passage is thus defined by the seeding density at the start of the Passage and the limit to area imposed by contact inhibition. This density must be adequate for healthy cell growth but not so large that limitation on space imposes a poor expansion ratio.

The cost of consumables is estimated by working out the amount of medium, the number, type and cost of plastic disposables and the consumption of other reagents and vials in order to handle culture in T-flasks and roller bottles. The value of this aggregate cost per cycle is then applied using a scaling factor based upon culture area within the chosen vessel (flasks, roller bottles or cell factories). This preliminary assessment of cost allows calculation of the direct cost without assumptions concerning plant type or layout. Once

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this is done using spreadsheet analysis the implications for the type and size of facility, for materials movement and for operations can be considered using SADT.

The values that are used for the costs of the raw materials are shown in Appendix 1, Table A1- 2.

Operability using cell attachment to plastic ware is determined by working out the capacity needed from the market projection. The prevalence of osteoarthritic damage to the knee is very large as shown in Table 3-1 [Hootman and Helmick 2006].

Table 3-1: Projected market volumes applied to the model

	2020	2021	2022	2023	2024
Prevalence of debilitating osteoarthritis (US)	22,052,000	22,355,000	22,657,000	22,960,000	23,262,000
Prevalence of debilitating osteoarthritis (global)	44,104,000	44,710,000	45,314,000	45,920,000	46,524,000
Assumed market share	1.0%	1.5%	1.5%	1.5%	1.5%
Demand/units	441,040	670,650	679,710	688,800	697,860

The values for market size that are shown in Table 3-1 are derived by interpolating from the published figures for the US alone. Applying a modest market penetration estimate of 1.5% at maximum gives the cumulative numbers of vessels to be processed annually (shown in Appendix 1, Table A1- 3). (This market penetration is loosely adopted from market information within Smith & Nephew. The assumed market share is modest but realistic given that there is a difference between the stages of osteoarthritic damage and the extent to which it may be treatable by remedial therapy. The prevalence in Table 3-1 is large but the prevalence of early-stage damage is more similar to the annual incidence. If it is assumed that incidence is approximately 10% of prevalence and that the available market comprises 15-20% of that population then the rule of thumb of 80% market share

for first-to-market products gives a range of 1.2 to 1.6% of the prevalent population of sufferers; hence the ramp up from 1.0 to 1.5% in the Table.)

3.6 Summary

The development of a novel cell-based therapeutic product poses a considerable risk for a business if the annual production volume of anchorage-dependent cells is large. The risk arises from the fact that the cells upon which the business proposal is based have typically been grown in static culture and in order to obtain economies of scale a bulk method is preferred. However, the conditions of bulk production are likely to impose a stress on the cells that will either kill them in unacceptable numbers or will modify the phenotype sufficiently to oblige the business to repeat the early work using the new cell batches. The alternative to scaling up is to scale out using many units of the same characteristic as those used in the early laboratory work. However, this may impose an insupportable burden from the point of view of materials movement. This issue will be examined in the next chapter.

It is possible to identify suitable cost, technical and market data from sources in the public domain for application in a spreadsheet-based model of directly attributable costs of goods. These costs and volumes can then be used to determine whether a realistic and operable manufacturing business could be constructed.

The next steps in this analysis are to derive the direct cost of goods and to place this in the context of a centralised 'as is' model. Chapter 4 addresses both of these steps.

Chapter 4

Direct Costs of Manufacture and the ‘As Is’ Business Model

4.1 Introduction

This Chapter describes the calculation of the direct costs of manufacture for the cells. It also presents the model of the business ‘as is’, in other words as it would be were it to be based upon a centralised operation model. The work presented in this Chapter is equivalent to steps 5 and 6 in the development of the thesis (see Chapter 1, Figure 1.3).

The reason why these two steps are grouped together in this Chapter is that the model of centralised manufacture is constructed starting with a spreadsheet for the directly attributable costs of goods ex-factory. In the centralised model the facility in which the cells are isolated and banked is the same as that in which the cells are expanded, formulated and packaged into both dosage forms (primary packaging) and outer boxing and labelling (secondary packaging). The product will degrade at ambient temperature and so the centralised model also assumes low temperature cold chain supply to a global market.

The business is regarded as an operating division of a larger enterprise. Some services will be available in-house and some are outsourced. In a real business the capability of the wider business will affect the decision to outsource a service. For the sake of establishing a reference model it is assumed in this thesis that the business possesses the capability to carry out certain functions. These functions are shown in Figure 4.1 which also shows the relationship of the Company to its parent organisation.

Chapter 4

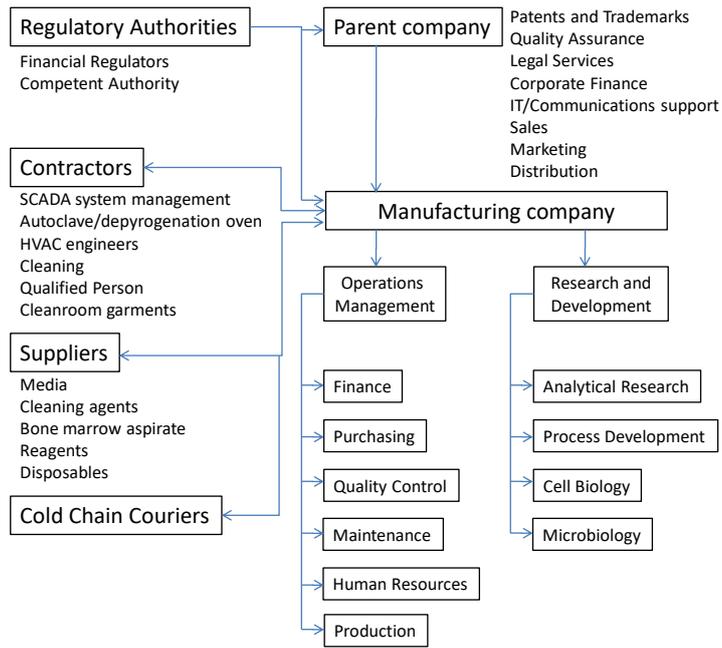


Figure 4.1: Hierarchy chart for centralised manufacturing facility

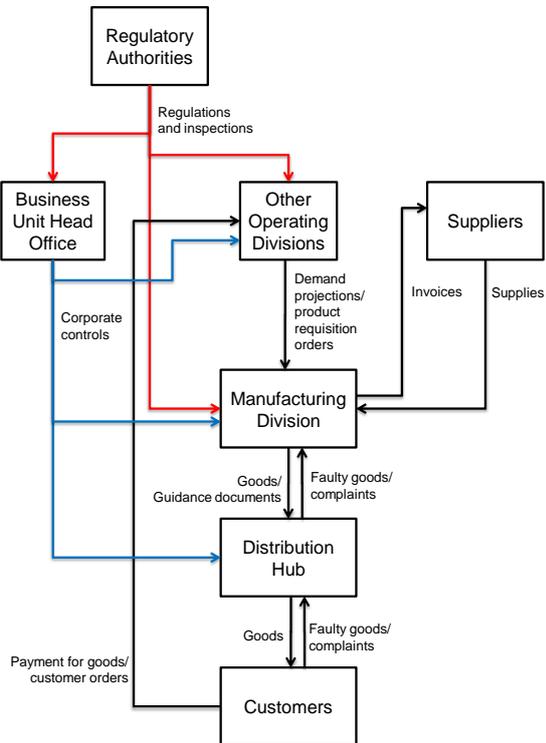


Figure 4.2: Relationship of the manufacturing operation to other organisations

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4.2 Cost of Goods Analysis

Step 5 (see Chapter 1, Figure 1.3) is to calculate the direct cost of processing, beginning with the cost of processing one roller bottle.

As noted above (Section 3.5) the raw data for this step are given in Appendix 1. The values recorded in Table 4-1 are based upon in-house laboratory results. The initial costs of recovering cells from the bone marrow aspirate are not included. These are dealt with as part of the profit and loss projections in Chapter 6.

Table 4-1: Cost of processing one roller bottle

Item	Units	Cost per unit	
Culture medium without FGF	mL	\$0.04	
Culture medium with FGF	mL	\$0.09	
Cost per bottle of culture medium			
500ml MEM	500	\$15.62	
50ml HIFCS	50	\$5.03	
5ml L-glutamine	5	\$0.32	
5ml NEAA	5	\$0.21	
FGF	0.1	\$29.13	of diluted soln (see below)
Total without FGF	560	\$21.18	
Total with FGF	560	\$50.30	
Cost per mL without FGF		\$0.04	'Handling medium'
Cost per mL with FGF		\$0.09	'Culture medium'
FGF solution			
Solution volume on delivery	1	mL	
Dilution applied	1	units	
PBS			
Dilution to	100	mL	
Cost to passage one Roller Bottle			
Medium without FGF	50	mL	\$1.89
Medium with FGF	900	mL	\$80.84
Trypsin-EDTA (SIGMA)	2.5	mL	\$0.45
PBS	50	mL	\$0.06
50ml pipettes X1	10	units	\$1.84
Roller bottle X1	1	units	\$9.17
Falcon tubes	5	units	\$1.16
Total			\$95.40

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The cumulative consumables cost for processing is, to a first approximation, constant per product unit. The average of \$742.43 from P4-P7 is used for this analysis (i.e. the average of P4 to P7 in the ‘Variable cost per unit’ column of Table 4-2).

Table 4-2: Cost of cell expansion using roller bottles

Passage	Cells at end of passage	Cost to passage (cumulative)	Variable cost/unit
Aspirate	8.18E+03	Not applicable	Not applicable
P0	1.70E+06	\$1	Not applicable
P1	5.27E+07	\$192	Not applicable
P2	1.63E+09	\$6,109	Not applicable
P3	5.07E+10	\$189,936	\$189.94 per vial of bank
	Broken down into vials each containing 50 million cells ↓		
	5.00E+07		
P4	1.55E+09	\$5,615	\$724.52
P5	4.81E+10	\$179,678	\$747.88
P6	1.49E+12	\$5,575,807	\$748.64
P7	4.62E+13	\$172,849,838	\$748.66

4.3 Cost of Operation: ‘As Is’ Model

Resuming the analysis steps from Section 4.2 and assuming that the conservative choice (see Section 3.2) of scale-out using roller bottles is taken then the next step is to derive the operational costs for a centralised business. (The implications of this choice for operability are examined later in Section 5.2.)

For the ‘as is’ or centralised case the cost of consumables for one cycle of production comprises the average cost of expanding the cells from P4 to P7 (a batch cycle) plus the cost of generating the vial of cells from the Master Cell Bank that was used for that cycle. This is the basis of the average cost per unit in Section 4.2.

The cost of the vial of cells is derived by working out the expansion costs from P0 (the bone marrow aspirate) to P3 (the cell banking stage) then dividing by 1,013 (the number of vials of cells made, see Section 4.1). When the consumables cost of expanding one vial of the resultant cell bank from P4 to P7 is added the result is \$172.85M for the whole batch. This is too much money to put at risk as a single batch during production. In practice a change would need to be made to spread the risk across smaller batches.

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To address Step 6 in the thesis (see Chapter 1, Figure 1.3) a model of the 'as is' case, is built using AIOWin® based upon the interviews with experts and upon the author's operational experience. The IDEF0 diagrams are shown in Appendix 2.

The directly attributable costs of one cycle of production are incorporated as an input to activity A22 in the Activity Based Cost analysis of the centralised campaign. Estimates of labour required for each contributing activity are built into the model. The model is used as the basis for a cost roll-up to Microsoft Excel®. This allows the full costs for each cycle to be estimated (see Table 4-3). To this basic cost the full Quality Control costs, the amortised costs of capital (including a Batch Process Control System and Supervisory Control And Data Acquisition system) and cold chain distribution must be added. It is known that the latter can be as high as 50% of ex-factory CoGs [Bagley 2006; Jones 2006]. As stated earlier (Section 2.15) items such as access to cold warehousing and plant maintenance are not separately estimated but are regarded as sunk costs incurred in operating an existing facility. An important tactical feature of the 'as is' model is the division of responsibility for Quality Assurance. The display of the decision-making capability of an organisation can conveniently be made using a GRAI-grid. Such a grid is shown for the 'as is' model in Section 4.4, Figure 4.3. Note that in the node 'To manage materials/Manufacture/H = 12m, P = 3m' there is a reference to the 'Quality Management System' or QMS. The maintenance of quality in the production of health care products is of great importance. The systematic management of quality, a policy of continuous improvement and the controlled issue, review and withdrawal of documents that bear upon product quality come under the heading of the QMS. Many organisations that come from a research background to embark upon production to a GMP standard, for example for clinical trial of an invention, are surprised at the amount of work required to create and maintain the QMS and yet it is central to the accreditation of any unit licensed to produce to GMP standard. At present the creation of the QMS is usually done by each centre as the need arises. As will be shown later (Section 7.2) there is an opportunity to implement a QMS to a common standard in an extended enterprise. This may be a value proposition in itself for an entrepreneurial business because the host operation is likely to be a clinical department and therefore the large burden of overhead associated with running a cleanroom, maintaining regulatory compliance and establishing a training and

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re-training schedule is an unwelcome distraction and expense. If such a service can be provided by a contractor operating on a franchise model then the contractor will have an economy of scale that is not available to the host when it provides a service package to a common format for a number of customers.

Table 4-3: Cost roll-up for ‘as is’ model

	Time/hrs per instance	Instances per parent activity	Cost/\$
A0 (Operate centralised manufacturing)	3284.25	1	520,729,067
A1 (Manage orders)	18.75	1	174,710
A2 (Manufacture product)	351.5	1	518,638,638
A3 (Coordinate materials movement)	893	1	1,792,954
A4 (Manage quality)	60	1	119,786
A5 (Manage operations)	37	1	2,979
A6 (Customer invoice receipt)	1924	N/A	0
A11 (Prepare Master Production Schedule)	14	4	62,608
A12 (Process incoming orders)	2	260	51,740
A13 (Manage customer invoicing)	1.5	260	38,805
A14 (Manage supply invoicing)	0.5	260	8,623
A15 (Order fresh supplies)	0.75	260	12,934
A21 (Prepare for manufacturing campaign)	0.5	24	6,914
A22 (Manufacture product batch)	336	24	518,615,160
A23 (Conduct line clearance)	8	24	2,735
A24 (Take corrective actions in production)	7	12	13,829
A31 (Manage warehousing of supplies)	444	12	883,542
A32 (Manage warehousing of product)	444	12	883,542
A33 (Manage product distribution)	5	52	25,870
A311 (Manage supply quarantine store)	148	1	24,543
A312 (Manage QC-released supplies store)	148	1	24,543
A313 (Manage faulty supplies store)	148	1	24,543
A321 (Manage product quarantine store)	148	1	24,543
A322 (Manage QC-released product store)	148	1	24,543
A323 (Manage faulty goods store)	148	1	24,543
A41 (Determine quality of supplies)	7	52	24,144
A42 (Authorise change in raw material status)	2	52	10,348
A43 (Determine batch quality)	37	24	57,832
A44 (Authorise change in product status)	2	24	4,776
A45 (Corrective and Preventative Action (CAPA))	7	12	16,716
A46 (Produce Quality Documents)	5	12	5,970

4.4 GRAI-grid of 'As Is' Model

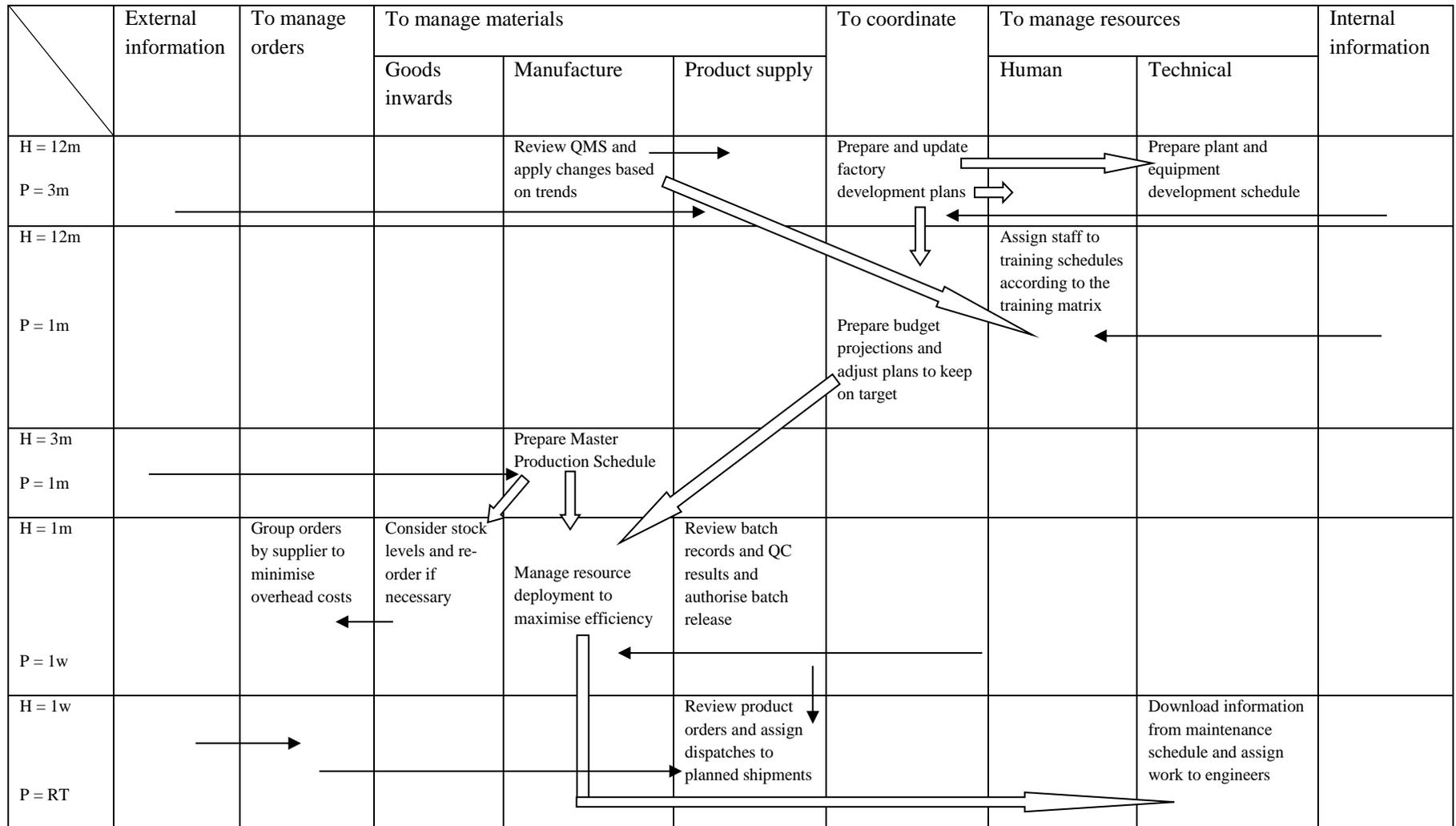


Figure 4.3: GRAI-grid for centralised operation

The GRAI-grid shows several significant features of the organisation that are necessary for the hypothetical centralised business.

Node: ‘To manage materials/Manufacture, H = 12m, P = 3m’: In order to remain compliant with GMP the Quality Management system of the operation must be maintained. Part of this maintenance is the review and continuous improvement of the business processes that are critical to product quality. Typically this is done by quarterly management review. At these reviews, for which detailed records must be kept, the management of the organisation will examine digests of the reasons for process deviations, trends in manufacturing records and records of quality-related activity (e.g. internal audits and supplier audits) over the review interval. From these reviews an action plan is drawn up and implemented. Evidence, often in the form of minutes of meetings and quality reports, is retained in order to demonstrate compliance.

Node: ‘To manage materials/Manufacture, H = 3m, P = 1m’: A Master Production Schedule is maintained based upon projections of demand and plant activity (production and maintenance). The Master Production Schedule in turn influences procurement and training, both of which must be conducted in a timely manner in order to retain compliance and according to authorised procedures.

Node: ‘To manage resources/Human, H = 12m, P = 1m’: Training must be conducted according to prescribed schemes and according to refresher rotas to meet the requirements of GMP. Evidence of training must be provided in documentary form showing both attendance and competence (as a result of a practical and/or theoretical test).

Node: ‘To manage materials/Supply, H = 1m, P = 1w’: Placement of the product on the market is an activity carrying great responsibility and the inappropriate release of unsafe goods can incur criminal penalties. The responsibility for authorising this action in an EU state can only be carried by a ‘Qualified Person’ i.e. an individual authorised by the Competent Authority for the country in question.

The provision and control of these three features is critical to the success of a GMP-compliant operation. Each must be available within any satisfactory business model.

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Responsibility for each must be subject to control by the business 'placing the goods on the market' i.e. the central operation if the supply chain is to be free from risks arising from links where authority is assumed without adopting the appropriate responsibility.

4.5 Costs of Production in the 'As Is' Model

The large operating cost in the roll-up of Table 4-3 must be seen in the light of the product units. In Section 2.7 the target cost of \$300-500 was introduced. With a total operational cost of \$134M and an annual production of approximately 700,000 units per year (688,800 in this example, equivalent to the 2023 projection in Table 3-1) the average direct cost per unit will rise to approximately \$755.99. This exceeds the target range and, in addition, there will be a contribution from the amortised costs of capital required to set up the facility. The capital implications are considered in Chapter 5.

4.6 Summary of the Cost Analysis

The cost analysis of the 'as is' model shows that the unit costs of production using the centralised model are reasonable in the light of the targets discussed earlier when considered in isolation. These unit costs assume that a facility is available in which production can take place. Such a facility must be built around roller bottles (the 'scale-out' model). The next step is therefore to place the unit costs in the context of the size of operation that must be built to give the capacity needed. This is considered in Chapter 5.

Chapter 5

Operability of the ‘As Is’ Model and Alternatives

5.1 Introduction

The point in the thesis that has now been reached is the point at which many technical papers or business proposals for CBTs stop. The market volumes have been estimated, the method of manufacture has been chosen, evidence exists that the cells can be expanded to the required level and the consumption of materials and labour divided by the number of units produced gives an estimated variable cost of production. The disparity between the target range and the estimated variable cost of production may be sustained if the research management concludes that the gap can be bridged during production by a combination of efficiencies of scale and reduction in costs of raw materials due to bulk purchase.

However, it does not follow that a robust investment proposal has been made. There still remains the question of operability and what that implies for the size and cost of the manufacturing plant. This Chapter considers the operability of the ‘as is’ model, describes the shortcomings and proposes an alternative, potentially more practical, arrangement.

5.2 Operability of the ‘As Is’ model

Step 7 in the thesis (see Chapter 1, Figure 1.3) is to establish the viability of the ‘as is’ model. This is informed by capital cost and by operability.

The market figures used in the model are shown in Table 3-1. The number of vessels needed for final Passage is defined by the cells required and the growth area per cell (see equations 5-1 and 5-2).

$$2 \times 10^8 \text{ cells.dose}^{-1} \times 700,000 \text{ doses.year}^{-1} = 1.40 \times 10^{14} \text{ cells.year}^{-1} \quad (5-1)$$

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$$\frac{1.4 \times 10^{14} \text{ cells.year}^{-1}}{31,027 \text{ cells.cm}^{-2}} = 4.51 \times 10^9 \text{ cm}^2 \text{.year}^{-1} \quad (5-2)$$

How can this number of cells be produced? The answer can be calculated by working out the numbers of units of the main classes of plastic ware based upon their usable production surfaces. The results are shown in Appendix 1, Table A1- 3. In that table T-flasks are omitted as the numbers involved are clearly impractical. A manual process is unsuitable for these numbers of roller bottles and cell factories but roller bottles and cell factories differ in how amenable they are to automation.

Cell factories, while popular for intermediate scale or start-up operations, only partially permit automation as they are rich in tube connections and heavy to manipulate. Attempting to base a centralised operation upon them would result in a largely manual operation with very large numbers of units. Incidence of human error would be high [Aldridge 2007].

By contrast roller bottles are free from tubing and more suitable for automatic maintenance; a precedent exists. The largest plant of which the author is aware that employs automated production from roller bottles is the Amgen plant at Boulder, Colorado, which handles a maximum of 40,000 roller bottles at one time and is able to aspirate and re-fill one every 8 minutes on average [Mundin and Fleck 2009].

Calculation of the size of plant that is required if roller bottles are to be used is shown in Table 5-1. The assumptions behind the calculation are:

- a) Each bone marrow aspirate will be expanded to P3 and cryopreserved as a cell bank containing 50 million cells per vial. (The overall yield will be approximately 5.07×10^{10} cells; equivalent to seeding 1,013 campaigns of onward production.)
- b) Each campaign of onward production begins with one vial of resurrected cells seeded to 59 roller bottles and expanded only as far as P6 giving 56,529 roller bottles at the end of the batch. This cycle can occur at most once every two weeks.
- c) No allowances are made for batch losses or sample removal for analysis.

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- d) No allowance is made for the increased processing time due to trypsinisation and cell recovery that a CBT requires [Lepinskas 2010].

Such a plant would produce approximately 7,448 doses every two weeks during uninterrupted operation i.e. 175,503 doses per 47-week year. This yield estimate, scaled on a convenient batch size to P6 rather than committing to culture to P7 and so reducing the cost of a potential lost batch (see Section 4.3) represents a ‘best case’. The vagaries of operation (batch losses, removal of archival and analytical samples) would reduce this number in the real world. In order to deliver 700,000 doses per annum the number of lines required is given by Equation 5-3.

$$\frac{700,000}{175,503} \times \frac{56,529}{40,000} = 5.6 \text{ lines} \quad (5-3)$$

Each line will operate on a minimum of 14 days between the seeding of P4 and the harvest of P6 and can deliver a maximum of 26 batches per year. For a safe operating margin 24 batches per year is more reasonable and the best combination is shown in Table 5-1.

Table 5-1: Automated roller bottle lines based upon current TTP design for Amgen

Numbers per line	
Passage	Roller bottles
P6	40,000
P5	1,290
P4	42
P3	1
P2	<1
P1	<1
Numbers per plant	
Cells per line	1.054 x 10 ¹²
Cells needed <i>per annum</i>	1.40 x 10 ¹⁴
Campaigns per year per line	24
Lines required	7

An accurate capital cost estimation of such a plant is outside the scope of this study but at a first estimate it would be seven times the size of the Amgen facility (allowing one extra

line for redundancy during servicing or breakdown, see Table 5-1) and therefore it is likely to be beyond any business justification for the product line. The other undesirable feature of such a plant will be that the capital costs are all incurred at the start of the product life cycle and therefore incurred 'at risk'. It is a commonplace that technology investors (e.g. venture capitalists) are averse to capital intensive new businesses because in the event of business failure the specialised plant has little or no value as collateral.

Alongside this serious capital cost issue is the question of operability. The Amgen facility was built around a process to harvest a product that is expressed into the growth medium. The harvest cycle is straightforward and consists of aspirating the supernatant liquid from which the product is isolated. By contrast stem cells will need to be recovered using enzyme treatment, repeated rinsing steps and longer manipulation. Process cycle times will be long, more sophisticated bottle handling robots will be needed and the opportunity for error will be large.

It is instructive to examine what is known about the other methods of production that might be used.

5.3 Alternative Technology

At this point an observation must be made about bulk production methods. These are amenable to allogeneic therapeutics in which large, single cell banks are applied. They are unsuitable for autologous therapeutics.

More manageable manufacture can be accomplished, in theory, using suspension culture to achieve a higher intensity process. There is little precedent for this but such precedent does exist. There are large technical hurdles to be overcome; nevertheless an illustration will be made based upon one category of stem cells [Baksh, Davies et al. 2003; Baksh, Zandstra et al. 2007; Baksh and Davies 2008].

As stated in Section 3.2 if a fermenter-based method is to be used then monocellular suspension is preferred because it avoids the need to achieve clean separation of microcarrier debris during downstream stages. Some published work on populations of cells derived from mesenchymal populations has provided an illustration of how this

might be achieved. Employing values of approximately 7.5×10^8 cells per 50mL of medium at harvest (from literature on monocellular suspension culture of specific sub-populations of mesenchymal stem cells) then the capacity needed will be as shown in Equation 5-4.

$$V = \frac{C_G}{I_v} = \frac{700,000(\text{dose}\cdot\text{year}^{-1}) \times 200,000,000(\text{cells}\cdot\text{dose}^{-1})}{7.5 \times 10^8(\text{cells}\cdot 50\text{mL}^{-1}) \times 20(50\text{mL}\cdot\text{L}^{-1})} = 9,333\text{L}\cdot\text{year}^{-1} \quad (5-4)$$

In Equation 5-4: V = fermenter capacity needed (expressed as usable volume *per annum*), C_G = cell requirement *per annum*, I_v = intensity as cells/unit volume.

This capacity could be provided by, say, ten campaigns *per annum* in 1,000 litre reactors. The tanks could be run in fed-batch mode without intermediate Passage. Automation would be largely unnecessary and fill-finish would be conducted in campaigns based upon bulked cell suspensions rather than round-the-clock as each roller bottle is harvested.

However, such technology is not yet ready to use industrially. The culture conditions will need to be proven for each cell type. A strategic decision will be needed about how to proceed. The choices would be either a) to proceed using the familiar tissue plastic culture basis, with the expectation of changing the process later if clinical results justify the investment, or b) to invest in suspension culture before any positive clinical results have been demonstrated. The conditions of suspension culture are different from plastic adherence culture and so the business will need to prove that the Critical Quality Attributes are retained before any switch to suspension culture can be made.

The dilemma facing the new business is that it must decide between the alternatives below.

- a) The process is scaled-out using known, but impractical, plastic ware.
- b) The process is scaled-up using unknown, but potentially more viable, fermenter type methods.

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If choice (a) is taken then it may become necessary to stop at some point once the product has been launched, re-develop the process along more viable lines using the alternative technology and absorb the costs of repeating clinical trials using some of the revenue generated from the initial sales. At least the revenue stream will have been established and confidence will have been gained in the market projections and in the product without committing capital unnecessarily. The risk is that there may not be enough time to increase capacity and market share may be lost during the interval when supply is not maintained.

If choice (b) is taken then there must be enough confidence to justify the expense of what may become a very challenging process development project. There will be no guarantees of success; perhaps the cells will not adjust to such culture.

Neither choice is very appealing. An alternative business model is needed. A suitable alternative would have to feature a smaller capacity for the central manufacturing facility while generating sufficient revenue to make the business proposition attractive. It would be desirable to reduce the number of units of goods in the supply chain so as to make it more manageable.

5.4 Modelling of Preferred Alternative

Against this background an alternative model is proposed. This comprises step 8 of the analysis (see Chapter 1, Figure 1.3). A suitable model will preferably have the following characteristics.

- a) Centralised, well-controlled, low-volume production of high value goods (to address the operability issue)
- b) Smaller numbers of highly-controlled low-temperature shipments to fewer customers
- c) Excellent working relationships with fewer customers each of whom is of high value
- d) Modest initial outlay on capital equipment
- e) Acquisition of capital equipment at a rate commensurate with market growth (to avoid large sunk costs committed at risk prior to launch)

- f) Excellent control of end-product quality
- g) Minimal in-process or inventory losses due to date expiry, loss in transit or human error
- h) Establishment of robust supply arrangements with key opinion leader centres thus ensuring good return on investment
- i) Implementation of a diagnostic (given away free of charge or sold at discount) which enables clinicians to identify patients for whom the therapy is most likely to be effective

These characteristics can be provided if an extended enterprise model is used. The conditions can be met if a decision is made to sell the *capability* to make batches of the final product close to the point of use rather than to sell the final product itself. This could be achieved at ‘satellite’ centres [Browne, Sackett et al. 1995; Davis 2003] under different management from the central facility but involving an oversight mechanism in order to assure quality.

Skill in relationship management will be a key factor for commercial success [Cullen 2000]. The largest risk is that of delegation of control of quality to another legal entity. To mitigate this risk a high degree of control will be needed. A ‘Quality by Design’ approach [ICH 2006] to development will be advisable to provide a robust process. Overbearing control at the satellite centres can be avoided by supplying microfactories. A form of microfactory for regenerative medicine already exists in the Compact Select® from The Automation Partnership [Hogan, Simons et al. 2008; TAP 2010] and the Quantum Cell Expansion System from CaridianBCT. The microfactory will preferably comprise a self-contained work station which has been made to operate as an isolator. The unit would be fully automated and would work to a pre-validated protocol that includes self-sterilisation. It will be preferable for the unit to complete the expansion cycle with cell recovery, washing and dosing to sterile vials without human intervention at any step.

By this mean an organisation will adopt a different value proposition. This will take the form of a service package that enables a customer to operate their own satellite facility. The service package will comprise the following.

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- a) Sale and installation (at a significant discount) of the microfactory (the ‘downstream production module’ or DPM) that can be drop-shipped to the customer’s cleanroom site – this is the durable component
- b) Supply of a kit for manufacturing the end-product at the customer’s facility – this is the consumable component
- c) A standardised series of protocols for production, Quality Control tests, cleaning, periodic re-validation and calibration of relevant equipment – this is the software component
- d) An initial training programme conducted cost-free prior to contract at the central facility (at which a training centre has been set up based upon the exact design of the DPM) in order to convince the potential customer of the benefits of dealing in this way – this is the training component
- e) A periodic re-training module aimed at maintaining the client staff in compliance – this is the compliance component
- f) Templates for all relevant controlled documents, including training records – this is the Quality Assurance component
- g) Call-out cover and preventative maintenance of the DPM – this is the security component

The benefit to the customer will be that the overall costs of applying the CBT will be much lower than if they are purchased outright. The benefit to the central organisation will be that it can charge correspondingly more per unit to sell fewer units of consumable goods. The size of the cold supply network will be reduced. The DPMs will be expensive to supply and so a contract will be needed that commits the customer to the relationship for a specified minimum period.

This model of business has many of the properties of a franchise. The initial development of the product and service will be conducted first at a modestly-sized plant using money supplied at risk by a parent operation. This plant will be identical to all subsequent build projects. This first plant will comprise one central facility and one ‘demonstrator’ satellite facility (later to be used for training). The business plan is illustrated in Table 5-2.

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The satellite facility will most likely be a part of an existing hospital cleanroom. The cost of operational management of the hospital that hosts the satellite manufacturing is not included in the cost model (see Section Chapter 6) on the basis that this would have to be paid for by the host organisation even if the satellite activity were not there.

It is assumed that the key members of staff (dispensing pharmacists, materials movement officers, ward managers) would have been employed even if no satellite operation were in progress therefore only the directly attributable labour is counted into the ‘to be’ model and not the full time salary.

Costs of waste disposal are not examined. Hospital centres will already be sterilising biohazardous waste prior to incineration and the extra cost is not considered important enough to examine in detail.

Table 5-2: Business plan for the extended enterprise

Stage	Title	Activities
1	Process development	Generation of cell bank(s) Process validation
2	Service package development	Simulation of alternatives Exploration of QMSs within clinical centres Optimisation of service model Generation of two-party QMS
3	Creation of pilot facilities	Design of pilot facility Process validation within facility
4	‘Preferred client’ project	Identification of early adopter key opinion leaders Negotiation of terms of agreement with three centres Drop-shipment of facilities to the ‘preferred clients’ Proving batch manufacture
5	Launch	First clinical stock applied Publication campaign conducted on results Snagging of systems and training
6	Sales campaign	Advertising campaign Promotion of concept through existing sales channels of parent company
7	Onward manufacture	Rolling re-training programme Acquisition of new clients Enlargement of number of centres in satellite pool

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The overall format of the business model is illustrated in Figure 5.1. The feature that is immediately apparent is that the division of responsibility referred to in Section 4.4 must be resolved satisfactorily before any other consideration can be worthwhile. In Figure 5.2 the GRAI-grid for the extended enterprise is shown. Focusing on the decision nodes equivalent to those highlighted in Section 4.4 there must be clear accountability.

To manage materials/Manufacture, H = 3m, P = 1m: The Master Production Schedule is now influenced additionally by the node at 'To manage materials/Goods inwards, H = 1m, P = 1w Consider stock levels and re-order if necessary'. This node refers (in the case of the satellite) to the trigger to supply more kits.

To manage resources/Human, H = 12m, P = 1m: Training will still be conducted according to prescribed schemes but now the initial training and refreshment courses will be run by a unit from within the central operation in much the same way that some franchise-based companies mandate compliance through their own brand-oriented standards.

To manage materials/Product supply, H = 1m, P = 1w: The biggest challenge is to retain control of product quality even when the goods are made at a location remote from the central operation. The batch release will be made according to two safeguards. The first safeguard will be the intrinsic mode of operation of the validated DPM. It must be designed to work according to a small number of automated protocols with fixed parts of geometry specific to the module. This is to ensure that no 'off label' use can be made of the device i.e. adaptation with other parts or deviation from the prescribed and validated protocol. The second safeguard will be the provision of production data to the central operation via a web-based data transfer. The Qualified Person at the central operation will authorise batch release based upon two stages of assurance: i) the records of production (asepsis, temperature control, cell number, medium supply) which will be in evidence from the batch records comprising in-process measurements made in real time, and ii) primary analysis by an expert system. This two stage analysis ensures that there will be human oversight without the need for large numbers of QPs (i.e. without each satellite centre having to retain its own QP). It also ensures that the central operation retains control of quality of product released to the market. Data trend analysis will be

conducted by software in real time and compiled into reports for analysis at the Quality Reviews.

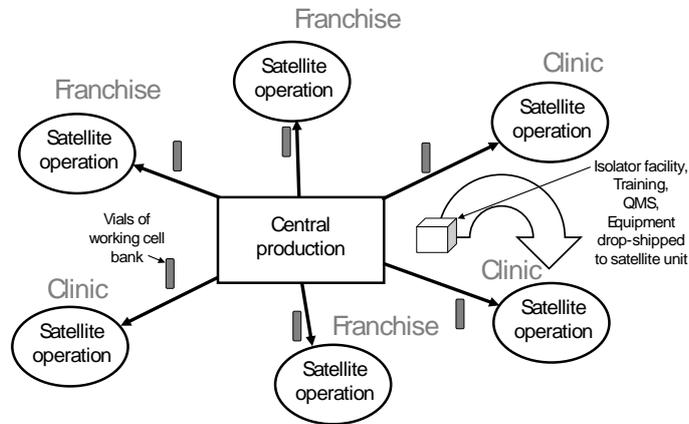


Figure 5.1: Extended enterprise model

At this point a further question arises. If a franchise-style extended enterprise model is adopted is there not a commercial risk that entry by competitors using the same technique, perhaps even providing products that use the downstream processing module, will take the valuable market away from the company that has made the initial investment? The answer to this question, and the risk-mitigating strategy, lies in the following protective measures.

- The equipment should be protected either with a patent or, if that is not possible, with a registered design.
- The disposable components of the system should be made so as to integrate solely with the durable parts, thus preventing a generic use of the durable components.
- Any use of the equipment for purposes other than those which have been registered with the regulatory authority should be prevented by using electronic protocols that are restricted to the approved processes; there should be no operator-adjustable controls other than the choice of protocol.
- The close relationship between central and satellite operation should, in itself, be a barrier to entry for the competition.

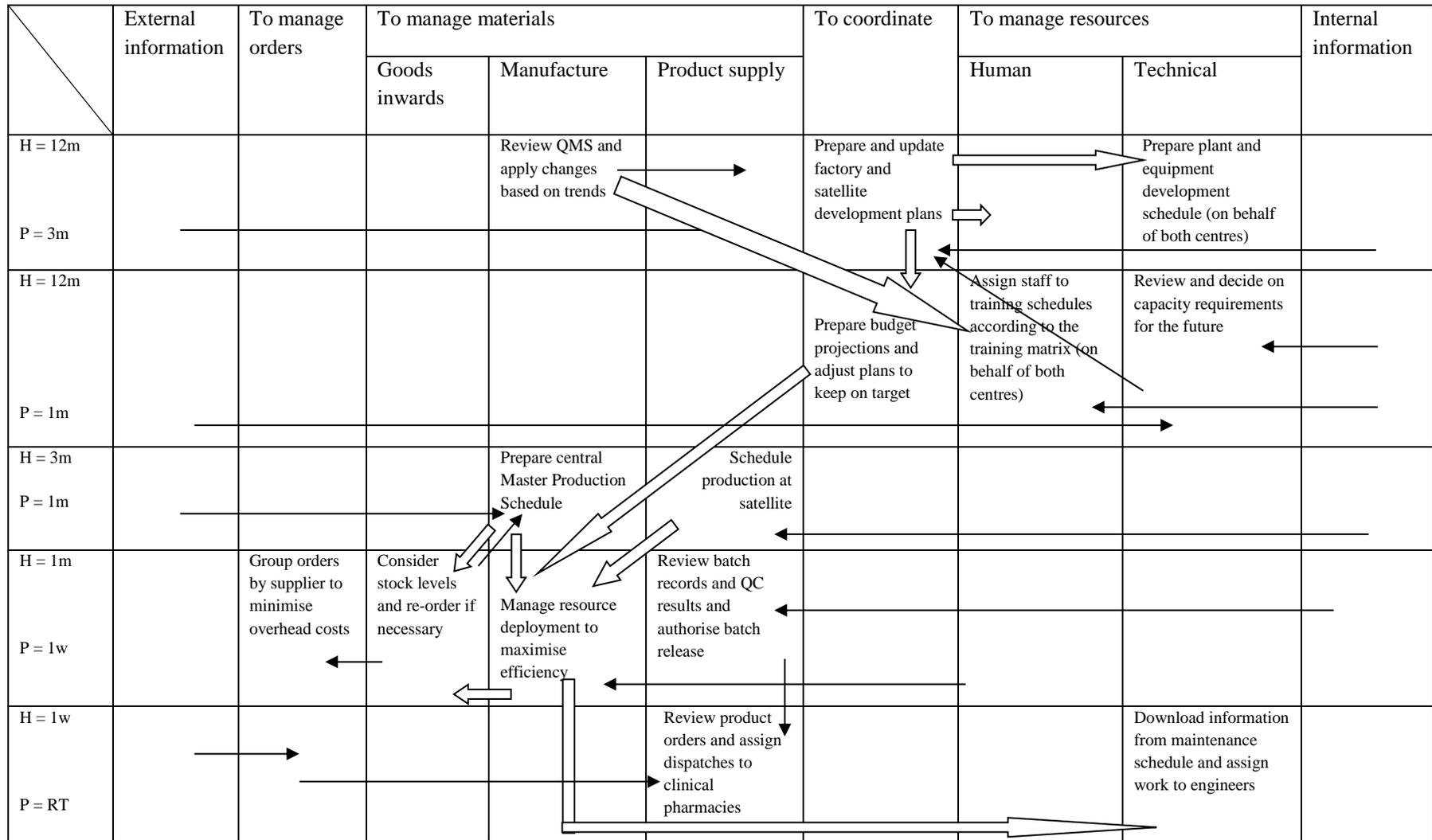


Figure 5.2: GRAI-grid for extended enterprise

5.5 Summary

In this Chapter the deficiency in the centralised model of production for high-dose, medium-value CBTs has been illustrated. Operability at full capacity is not possible without prohibitive levels of capital investment. To avoid this problem by moving to a method with higher process intensity carries with it a big technical risk.

The alternative approach, that avoids the technical risk of scale-up while retaining the operability of a smaller operation, is to scale-out and adopt an extended enterprise model based around a franchise-style approach. There are measures that can be taken by the company that creates the extended enterprise to protect its investment. These include controlled equipment designs, specified electronic protocols and strong customer-provider relationship management.

The value released by this method must justify the investment both from the point of view of the central operation and that of the satellite operation. Chapter 6 addresses this quantification of value release.

Chapter 6

Alternative Business Models

6.1 Introduction

Chapter 5 showed how the central model of manufacture and supply makes for difficulties when operating at full scale even though the initial impression is that scale-up is not a problem. The alternative, the extended enterprise, can resolve the problem in principle but, in order to succeed, the value proposition must be attractive both to the central business and to the host of the satellite operation. Quantification of the value begins with the estimation of the cost of the extended enterprise; this constitutes step 9 in the thesis (see Chapter 1, Figure 1.3).

6.2 Scale of Operation

The first step in the cost modelling is to construct the IDEF0 model for the alternative. This is shown in the diagrams in Appendix 3. Cost analysis is done by making an estimate based upon a reasonable scale for each link in the supply chain. The final link comprises the manufacture of a single batch of vials of cells within the satellite facility. This will be made from one kit therefore the size of the kit from the central facility is determined by the practical scale of each campaign of clinical treatment. It is possible to work back from that value to give the desired scale at each step.

For a global market of approximately 700,000 doses *per annum* and assuming a ten-fold expansion of the cells supplied in a kit at the satellite in one operation it would be convenient to schedule one campaign of treatment from Passage of a vial containing 200 million cells. This scale is equivalent to 76 roller bottles, the limit for an automated device with a capacity equivalent to a conventional Thermo Forma incubator loaded with double rows of roller bottles. This basis requires an annual production capacity at the central facility of 70,000 kits (see Equation 6-1).

$$\frac{2 \times 10^8 \text{ cells.kit}^{-1} \times 10 - \text{fold}}{200 \times 10^6 \text{ cells.dose}^{-1}} = 10 \text{ doses.kit}^{-1} \quad (6-1)$$

A ten-fold expansion will require just less than ten days to culture to confluence (see Equation 6-2).

$$\frac{\text{Ln}(10 - \text{fold})}{\text{Ln}(31 - \text{fold})/14 \text{ days}} = 9.387 \text{ days} \quad (6-2)$$

The production of 70,000 kits *per annum* requires a minimum of nine cycles of production per year at the central facility, each cycle producing 7,448 kits. At a cycle time of 14 days this is easily managed using just one plant unit of the scale described in Section 4.2 so this seems a practical number. The next point to address is whether the size of the campaign of treatment is appropriate.

6.3 Size of the Satellite Operation

Batch size must be matched to patient treatment by linking the final expansion step at the satellite with clinical scheduling. Typically an elective injection of this type of product (c.f. steroid injection to a joint to treat rotator cuff injury in the shoulder) is conducted in sessions with patients timetabled to arrive for the clinic on a particular day. Processing of, say, ten such patients would be feasible in one session. Ideally the clinic will use freshly harvested cells formulated immediately and supplied straight to clinic. As noted in Section 5.4 control of batch quality will be based partly on the confidence generated during validation of the DPM process and partly on the results of in-process analysis for the particular batch which will be conducted by the DPM itself.

The capacity of a fully-utilised satellite facility employing one DPM can be no more than 350 units (Equation 6-3).

$$\frac{47 \text{ weeks.year}^{-1} \times 7 \text{ days.week}^{-1} \times 10 \text{ units.cycle}^{-1}}{9.4 \text{ days.cycle}^{-1}} = 350 \text{ units.year}^{-1} \quad (6-3)$$

It follows that in order to satisfy the projected global demand of 700,000 units *per annum* there must be a total of 1,997 centres (see Equation 6-4).

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$$\frac{700,000 \text{ units} \cdot \text{year}^{-1}}{350 \text{ units} \cdot \text{centre}^{-1} \cdot \text{year}^{-1}} = 1,997 \text{ centres} \quad (6-4)$$

This number of centres will be challenging to find and to manage. The implications of the scale of operation are addressed in Section 6.4. The cost of operating this arrangement was derived by Activity Based Cost analysis and is shown in Table 6-1. (The implications for the cost of capital to the central operation are shown in Table 6-2.)

Table 6-1: Cost of managing the extended enterprise from cost roll-up

	Time	Instances of child act. per parent act.	Cost
A0 (Operate extended enterprise)	2028.25	1	3,883,239,942
A1 (Manage central manufacturing centre)	1984.25	1	41,948,635
A2 (Manage satellite manufacturing centre)	44	1,997	3,841,291,307
A11 (Manage orders)	18.75	1	174,710
A12 (Manufacture central product)	975.5	9	39,851,830
A13 (Coordinate central materials movement)	893	1	1,792,954
A14 (Manage quality of intermediate)	60	1	126,162
A15 (Manage operations)	37	1	2,979
A111 (Prepare central Master Production Schedule)	14	4	62,608
A112 (Process central incoming orders)	2	260	51,740
A113 (Manage central customer invoicing)	1.5	260	38,805
A114 (Manage central supply invoicing)	0.5	260	8,623
A115 (Order central fresh supplies)	0.75	260	12,934
A121 (Prepare for manufacturing campaign)	0.5	1	83
A122 (Manufacture product batch)	960	1	4,426,207
A123 (Conduct line clearance)	8	1	531
A124 (Take corrective actions in production)	7	1	1,161
A131 (Manage warehousing of central supplies)	444	12	883,542
A132 (Manage warehousing of intermediate)	444	12	883,542
A133 (Manage intermediate distribution)	5	52	25,870
A1311 (Manage supply quarantine store)	148	1	24,543
A1312 (Manage QC-released supplies store)	148	1	24,543
A1313 (Manage faulty supplies store)	148	1	24,543
A1321 (Manage intermediate quarantine store)	148	1	24,543
A1322 (Manage QC-released intermediate store)	148	1	24,543
A1323 (Manage faulty intermediate store)	148	1	24,543
A141 (Determine quality of central supplies)	7	52	24,144
A142 (Authorise change in raw material status for intermediate)	2	52	10,348
A143 (Determine intermediate batch quality)	37	26	63,809
A144 (Authorise change in intermediate product status)	2	26	5,174
A145 (Corrective and Preventative Action (CAPA) - central)	7	12	16,716
A146 (Produce Quality Documents - central facility)	5	12	5,970
A21 (Manage orders for final product)	25	12	1,014,941

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	Time	Instances of child act. per parent act.	Cost
A22 (Manufacture final product)	4	35	727,446
A23 (Coordinate satellite materials movement)	7	1	22,884
A24 (Manage quality of final product)	6	1	14,063
A25 (Receive customer invoice for final product)	1	35	0
A26 (Manage satellite operations)	1	1	144,198
A211 (Prepare satellite Master Production Schedule)	7	4	6,965
A212 (Process satellite incoming orders)	7	52	30,183
A213 (Manage satellite customer invoicing)	4	52	17,247
A214 (Manage satellite supply invoicing)	4	52	17,247
A215 (Order fresh supplies for satellite)	3	52	12,936
A221 (Prepare for satellite manufacturing campaign)	1	1	149
A222 (Manufacture final product batch)	1	1	20,419
A223 (Clear final product line)	1	1	66
A224 (Take corrective actions in final product manufacturing)	1	1	149
A231 (Manage warehousing of satellite supplies)	3	12	5,373
A232 (Manage warehousing of final product)	3	12	16,715
A233 (Manage final product faulty goods store)	1	12	796
A2311 (Manage quarantined supplies for final product manufacture)	1	1	149
A2312 (Manage QC-released satellite supplies store)	1	1	149
A2313 (Manage faulty supplies for final product)	1	1	149
A2321 (Manage quarantined final product store)	1	1	464
A2322 (Manage QC released final product store)	1	1	464
A2323 (Manage final product supply to user)	1	1	464
A241 (Determine quality of satellite supplies)	1	12	1,194
A242 (Authorise change in raw material status for satellite)	1	35	3,483
A243 (Determine final product batch quality)	1	35	2,322
A244 (Authorise change in final product status for satellite)	1	35	3,483
A245 (Corrective and preventative action (CAPA) - satellite)	1	12	2,388
A246 (Produce quality documents - satellite)	1	12	1,194

Note that in Table 6-1 the cost of clearing product lines (Activity 223) is much less than the cost in the Activity 123 or in the corresponding row in the previous cost roll-up in Table 4-3. The reason for this is that in the case of the satellite facility line clearance will comprise merely the sanitisation of the culture area and sign-off of batch documents – a quite rapid turnaround. In the central facility a laborious clearance of the bulk production areas, line wash-through and inspection will be required.

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Table 6-2: Cost of capital at the central and satellite operations

Locus of operation	Item	Number needed	Cost/£ unless otherwise stated	Total/\$
Central facility	Centrifuge (bench)	2	20,000	57,676
	Automated culture line	1	6,000,000	8,651,400
	Automated fill-finish line	1	3,000,000	4,325,700
	Incubators	10	80,000	1,153,520
	BSC (4 off)	4	50,000	288,380
	Cleanroom	1	2,000,000	2,883,800
	Centrifuge (production)	2	25,000	72,095
	Fill station	2	15,000	43,257
	Controlled rate freezer	4	25,000	144,190
	Minus 70°C freezer	4	12,000	69,211
	Waste holding tank	1	25,000	36,048
	Ancillary equipment	1	50,000	72,095
	Guava flow cytometer	2	120,000	346,056
	Pump (2 off)	4	30,000	173,028
	Invert microscope	2	60,000	173,028
	Liquid nitrogen supply	2	120,000	346,056
	Total			18,835,540
	Installation (Lang factor)			1.7
	Installed			32,020,417
	Validation	0.75	years	
	6	FTEs	450,000	
Grand total			32,470,417	
Satellite facility	-70°C freezer	1	40,000	57,676
	Automated workstation	1	500,000	720,950
	Incubator	1	20,000	20,838
	Total			807,464
	Installation (Lang factor)			1.7
	Installed			1,372,689
	Validation	0.25	FTEs	25,000
Proxy capital outlay for the central facility	Satellite set-up	1,997	1,397,689	2,741,259,933
Total capital outlay for satellites+centre			Used in Table 6-3	2,823,654,951

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A broad estimate of the capital outlay needed is included in Table 6-2. Note that in this assessment the DPM would need to be donated by the central company along with, arguably, the installation cost. Estimates for these figures were included in the calculations. The cost implications are shown in Table 6-3. Note that the cost to manufacture one kit after the first year is around \$7.5k and that this cost is dominated by the capital costs for setting up the satellites.

Table 6-3: Five year P&L forecast for the central operation (the ‘product’ here is the kit, not the final therapeutic product, and therefore the Cost per unit and the Margin per unit relate to the price of \$10,000 per kit)

All currency in USD	Year 1	Year 2	Year 3	Year 4	Year 5
Capacity - required (kits)	44,104	67,065	67,971	68,880	69,786
Value of sales of kits/\$	441,040,000	670,650,000	679,710,000	688,800,000	697,860,000
Amortised capital plant cost - central/\$	282,365,495	282,365,495	282,365,495	282,365,495	282,365,495
Plant operational costs - central/\$	2,685,865	2,685,865	2,685,865	2,685,865	2,685,865
Variable cost of production of cells/\$	32,743,819	49,790,591	50,463,226	51,138,089	51,810,724
Amortised extraordinary costs/\$	822,000	822,000	822,000	822,000	822,000
Kit production/\$	2,713,948	4,126,858	4,182,609	4,238,545	4,294,295
CoGs ex factory/\$	321,331,128	339,790,810	340,519,196	341,249,994	341,978,380
Transport costs/\$	110,260,000	167,662,500	169,927,500	172,200,000	174,465,000
Total production costs	431,591,128	507,453,310	510,446,696	513,449,994	516,443,380
Cost per unit/\$	9,786	7,567	7,510	7,454	7,400
Margin per unit/\$	214	2,433	2,490	2,546	2,600
% margin	2.14%	24.33%	24.90%	25.46%	26.00%

In Table 6-3 the variable cost of production of cells is based upon the unit cost in Section 4.5 while the ‘Amortised Extraordinary Costs’ (10-year amortisation) refer to the estimated cost of conducting regulatory work, clinical trials and marketing work up to the point of launch.

On paper the value to the business is large and the value to the end user is large as well. However, implementation of such a strategy would be prohibitively expensive in terms of

capital outlay. Small deviations in efficiency and in particular poor utilisation of the equipment supplied to the satellite would quickly destroy the value chain. The strategy would be exquisitely sensitive to market penetration. The central operation will take too high a moral risk and in order to adopt the supply model the satellite must take a strategic decision that will result in much upheaval. The model in this form is therefore unrealistic mainly because of the capital investment required.

A refinement is needed that incorporates the benefits of the extended enterprise while avoiding the pitfalls of high capital costs. This is addressed in the next section.

6.4 A Lower Risk Alternative

The features that militate against take-up of the ‘to be’ model can be summarised as:

- a) High implementation costs
- b) High front-end investment
- c) Large business risk

These features can be avoided if the ‘to be’ model is modified so as to avoid the capital-intensive aspects. In order to retain the benefits of tight process control while removing the high capital and training costs the microfactory concept may be exchanged for simpler, compact apparatus designed to do the same job but in a less ambitious manner. For such an approach to succeed the apparatus must be much smaller, must be capable of use within a conventional incubator and must still be self-contained so as to remove operator variability from the production cycle. As noted above a ten-fold expansion in one Passage is expected for the satellite facility. Given that a full-height Thermo Forma incubator is the largest incubator format conventionally seen in modestly-sized cleanrooms and will require complete occupancy to accommodate just one cycle with the DPM it will be necessary to abandon the roller bottle concept at this point in favour of better space utilisation. The microfactory concept must be conserved in order to remove errors due to human intervention. Something more compact, predictable and independent is needed.

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This requirement can be met by applying a compact culture system in a small, easy-to-use format based upon a 'fixed bed' bioreactor. Fixed beds are monolithic structures capable of supporting cell growth and through which culture medium can permeate [Anli Ouyang 2007]. A cartridge filled with a porous three-dimensional scaffold can deliver considerably more surface area per unit volume than can a roller bottle. A realistic figure of $150 \text{ cm}^2 \cdot \text{cm}^{-3}$ for the fixed bed is chosen as a representative figure for this study [Chiou 1992]. Each of the roller bottles of the size considered in this thesis will have a surface area for cell growth of 850 cm^2 . The hypothetical 76 roller bottles of Section 6.2 would therefore have a combined surface area as shown in Equation 6-5.

$$850 \text{ cm}^2 \cdot \text{bottle}^{-1} \times 76 \text{ bottles} = 64,600 \text{ cm}^2 \quad (6-5)$$

The equivalent volume of a single fixed-bed cartridge offering a growth surface equal to 76 roller bottles is shown in Equation 6-6.

$$\frac{64,600 \text{ cm}^2}{150 \text{ cm}^2 \cdot \text{cm}^{-3}} = 430 \text{ cm}^3 \quad (6-6)$$

Such a compact system will easily be managed even in more common, smaller incubators. The key to maintaining quality under these circumstances will be to ensure that the system operates under automatic control as a closed system. Admission of medium and cells will be by attachment of cartridges so as to avoid batch variation or infection due to differences in handling techniques. A single injection moulded cartridge with captive impeller, sensors and batch monitoring would be a suitable embodiment. This arrangement prevents the risk of leakage from any tubing unions and ensures uniformity of culture. A topological drawing of such a device is shown in Figure 6.1.

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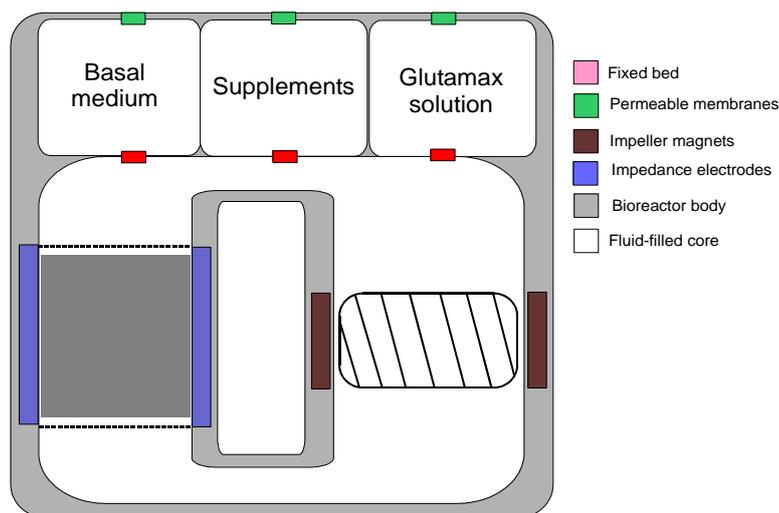


Figure 6.1: Topological drawing of the cartridge device

The device in Figure 6.1 will be a form of micro electromechanical device and can be likened to the ink cartridge of a printer but with more than one liquid component and with sensors for feedback control. On the left can be seen the fixed bed: a scaffold upon which the cells will be grown. The scaffold is bridged by impedance electrodes which will be low cost conductive foils embedded in the cartridge body. The purpose of these electrodes is to enable growth monitoring in real time using scanning impedance tomography. On the right is a captive magnetic impeller driven by embedded electrodes so as to re-circulate the medium through the bed. At the top are three reservoirs capable of controlled addition of medium, supplements and glutamine via electromechanical valves. Compensation for loss of pressure (which would otherwise prevent accurate dosing from these reservoirs) is arranged via permeable film ports at the top.

The items that are not shown in Figure 6.1 but which will be needed are:

- a) Connection to the controller module
- b) A dispenser cartridge for enzyme detachment of cells
- c) A device for dosing cells to vials ready for use
- d) Sensors for monitoring and control of medium composition
- e) A waste reservoir (similar to the dosing reservoirs but towards the base of the unit)

The purpose of the impedance scanning electrodes is to give advance notice of the time of harvest. Information about medium consumption will be used as well to make this prediction. Data from the tomographic sensors and from the medium sensors will be sent to the central organisation for the purposes of verification of product quality prior to release of goods.

This arrangement lends itself to cost containment because the cartridge will be housed in a durable, reusable control module with more than one station thus allowing comfortable overlap of episodes of culture and thus more flexible scheduling. A version of such a device already exists in the product ACTES from Millenium Biologix, Inc. [Wendt, Jakob et al. 2005] which was designed to produce neo-tissue. More recently CaridianBCT has released a device called Quantum® that is aimed specifically at stem cell manufacture but which employs a hollow fibre bioreactor cartridge and extensive tubing sets. Neither ACTES nor Quantum is intended for supervisory control from a remote authority or for providing the cells ready for clinical use; both are intended for use in standalone cultures. What is proposed in this thesis is a dedicated format which will guarantee the specified quality by means of recipe-driven control followed by automatic cell detachment ready for dispensing into a series of equivalent dosage forms. The dispensing step will require rinsing and counting of cells. There are already devices on the market, capable of operation within a conventional centrifuge, which will permit such rinsing.

The advantages of this method lie in the cost containment. The initial manufacturing run of the cartridges will be relatively expensive but onward production will be much cheaper as it is based upon known technology (injection moulding with inclusion of electronic sensors and valves). The capital-intensity of the business model will be greatly reduced and the space requirements for the process are much lower making the unit accessible even for quite small facilities on constrained budgets.

6.5 The Economics of the Lower Risk Alternative

A quantitative comparison is now made between the costs of the smaller unit and the previous model of extended enterprise. It is reasonable to assume that the durable part of

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such a compact unit (the control module) would be much cheaper to produce than an enclosed microfactory. A cost of, say, \$50k may be assumed for the purposes of analysing the consequences. This value is not unrealistic and may be compared with the cost of items such as bench-top spectrometers. We can make the further assumption that the portable unit will require no special utilities other than a single phase electricity supply and a connection to the internet for data monitoring by the central business. Installation will consist merely of plugging the device into position within an incubator. Under these circumstances the Lang factor (see Table 6-2) will reduce to 1.0. If the device is arranged such that a minimum of two usable stations may be used at any one time then the number of satellite centres to be serviced decreases proportionally. This will make oversight and supply much easier. Supply may then be restricted to those better-equipped centres that possess the requisite freezers or who intend being supplied on a just-in-time basis. A reworking of Table 6-2 and Table 6-3 now takes on the appearance of Table 6-4 and Table 6-5. This raises the possibility of a price reduction for the kits and faster market penetration. The product kits in this lower risk model will comprise the cartridge containing the cells and the sterile, hard-shell disposable reactor body pre-charged with media. The cartridge will clip into position in the control module (the durable device).

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Table 6-4: Cost of capital at the central and satellite operations with the smaller automated finishing unit

Locus of operation	Item	Number needed	Cost/£ unless otherwise stated	Total/\$
Central facility	Centrifuge (bench)	2	20,000	57,676
	Automated culture line	1	6,000,000	8,651,400
	Automated fill-finish line	1	3,000,000	4,325,700
	Incubators	10	80,000	1,153,520
	BSC (4 off)	4	50,000	288,380
	Cleanroom	1	2,000,000	2,883,800
	Centrifuge (production)	2	25,000	72,095
	Fill station	2	15,000	43,257
	Controlled rate freezer	4	25,000	144,190
	Minus 70°C freezer	4	12,000	69,211
	Waste holding tank	1	25,000	36,048
	Ancillary equipment	1	50,000	72,095
	Guava	2	120,000	346,056
	Pump (2 off)	4	30,000	173,028
	Invert microscope	2	60,000	173,028
	Liquid nitrogen supply	2	120,000	346,056
	Total			18,835,540
	Installation (Lang factor)			1.7
	Installed			32,020,418
	Validation	0.75	years	
	6	FTEs	450,000	
Grand total			32,470,418	
Satellite facility	-70°C freezer	0	40,000	0
	Automated workstation	1	50,000	72,095
	Incubator	0	20,000	0
	Total			72,095
	Installation (Lang factor)			1.0
	Installed			72,095
	Satellite set-up	998.5		72,095
			Used in Table 6-5	104,457,275

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Table 6-5: Five year P&L forecast for the central operation with the smaller automated finishing unit (first five years of sales but with ten year amortisation of capital costs) at a sale price for the kit of \$5,500

All currency in USD	Year 1	Year 2	Year 3	Year 4	Year 5
Capacity - required (kits)	44,104	67,065	67,971	68,880	69,786
Value of sales of kits/\$	242,572,000	368,857,500	373,840,500	378,840,000	383,823,000
Amortised capital plant cost - central/\$	10,445,727	10,445,727	10,445,727	10,445,727	10,445,727
Plant operational costs - central/\$	2,685,865	2,685,865	2,685,865	2,685,865	2,685,865
Variable cost of production of cells/\$	32,743,819	49,790,591	50,463,226	51,138,089	51,810,724
Amortised extraordinary costs/\$	822,000	822,000	822,000	822,000	822,000
Kit production/\$	2,713,948	4,126,858	4,182,609	4,238,545	4,294,295
CoGs ex factory/\$	49,411,360	67,871,042	68,599,428	69,330,226	70,058,612
Transport costs/\$	110,260,000	167,662,500	169,927,500	172,200,000	174,465,000
Total production costs	159,671,360	235,533,542	238,526,928	241,530,226	244,523,612
Cost per unit/\$	3,620	3,512	3,509	3,507	3,504
Margin per unit/\$	1,880	1,988	1,991	1,993	1,996
% margin	18.80%	19.88%	19.91%	19.93%	19.96%

6.6 Advantages and Value of the Lower Risk Model

As shown above (Sections 5.2 and 5.3) a new business with plans to manufacture a CBT must address the difficult issue of how to scale-up, or out; both unattractive alternatives. The lower risk model proposed in this thesis offers a way to escape the horns of this dilemma. The extent to which it can do so can be assessed by comparing it with the central model on the grounds of operability, cost and risk.

The question of operability is crucial: without satisfying this criterion nothing else can take place. The manufacturing and materials movement burden for the 'as is' model has been described above (Section 5.2). The impact of switching to the lower risk extended enterprise model in terms of the reduction in processing burden at the central facility is shown in Table 6-6.

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Table 6-6: Operability comparison of ‘as is’ with ‘to be’ models (values refer to the perspective of the central business)

	‘As Is’ model	‘To Be’ model
No. of roller bottles handled <i>per annum</i>	5.5 million	0.5 million
No. of product units shipped <i>per annum</i>	700,000	70,000

From the point of view of operability at the central facility this ‘to be’ model is a big improvement. No longer is it necessary to supply such large numbers of individual units at low temperature over long distances. The number of units in production at any one time is also greatly reduced.

At the satellite facility the important feature is whether business systems are available to permit the satellite to operate smoothly. The right utilities and the availability of controlled low temperature storage will be at the top of this list. At the operational level the important issue is the overall ratio of central to satellite facilities. For the ‘to be’ model to work on the franchise basis there must be enough suitable centres to supply the market. The arithmetic is challenging: there must be about 1,000 satellite operations willing and able to take part unless some of these centres adopt the role of regional suppliers to other clinics that lack manufacturing capability. Taking the UK as an example: there are approximately fourteen accredited cleanroom centres within the National Health Service that are suitably equipped to make CBTs. If we assume that the European Union has, on average, half that number per member state then 7×27 or 189 such centres may be available. The population of the EU is approximately 500 million. The US population is approximately 310 million. If we assume that access to the rest of the world will be at most only as much as for the EU then the number of such centres can be estimated at a further 306 giving about 500 centres. While this figure will provide a viable business the number of franchises achieved may be considerably less. Full market capacity can only then be achieved if multiple stations are fitted on each durable unit and the centres were prepared to act as regional supply hubs. Such modification of the durable units would be reasonable as the volumes involved are small and the engineering will be simple. The more sensitive point is whether the centres that adopt the equipment

will be motivated to act as regional centres for such treatment or as suppliers for neighbouring clinics.

In addition to these operational caveats commercial success with the 'to be' model also depends upon the value proposition. The advantages for the central operation have been discussed above (Sections 6.4 and 6.5). The practical success of the 'to be' model also relies upon the creation of satisfactory value release from the point of view of the clinic. The clinic will be asked to establish a relationship with the central business that requires some business practices, training schedules and production techniques that are tightly prescribed; is the value sufficient to justify this commitment?

This question can be answered in two parts. The first part of the value argument arises from the value release of the product: is it worth using the product at all? If the answer to this question is "Yes" then the second part of the answer arises from the question, "Is it worthwhile for the satellite to adopt the business relationship that is necessary to make the end product this way?"

A fully developed case for demonstrating the value of the CBT can only be made using a detailed health economics analysis. In this thesis an abbreviated argument is used to show the general principle and order of magnitude of the value. The approximate value can be derived by comparing the cost of treatment following the most usual patient pathway with the cost of treatment if the new therapy is used instead. The normal patient pathway comprises drug treatment, starting at age 40 to 70 and lasting for five to ten years, followed by total knee arthroplasty. The patient pathway with the CBT will comprise treatment with the cells instead of the drug followed by total knee arthroplasty. Value arises from two sources: i) the cost difference in treatment with the CBT instead of the drug, and ii) the value of the delay for total knee arthroplasty. There are many ways of calculating the value and these include variations in the time horizon that is considered, assumptions about whether patient pathway includes some people who will revert to drug treatment before arthroplasty and how much allowance should be made for infection, revision surgery and non-responders.

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In the interests of conciseness a base case only is considered here by way of illustration. The base case contains the assumptions below which are broadly derived from a Smith & Nephew market analysis.

Age of patient at first intervention	55	
Age of patient at arthroplasty	60	
Discount factor	0.97	
Cost of pre-operative assessment	\$426	
Annual cost of complications	\$700	
Incidence of complications	0.2	
Complications requiring hospitalisation	0.07	
Cost of hospitalisation	\$6,000	
Annual cost of drug therapy	\$2,000	
Patient population considered	700	i.e. no. of units/centre made per annum

Using these assumptions the discounted five year total cost of therapy will be \$9,592. The discounted cost of primary and secondary total knee arthroplasty revisions to the five year horizon will be \$14,511. The total cost of primary total knee arthroplasty, revisions to the five year horizon and drug costs over five years will be $\$14,511 + \$9,592 + \$426 = \$24,529$.

In addition to the patient based assumptions above the following assumptions are made about the product.

Purchase price of kit	\$5,500
Cost of arthrocentesis	\$70

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Cost of clinical evaluation	\$60 (initial referral, administration)
Responder rate	60%
Maximum duration of effect	5 years (i.e. repeat injection or alternative resolution after this interval)

In this case the cumulative cost of therapy over five years will be \$22,944.

This means that the value release will be on average \$24,529 - \$22,944 per patient or \$1,585. For 700 patients per year the total value release will be \$1,159 x 700 or \$1,109,500.

If the responder rate is increased to 100% (e.g. by the use of a diagnostic to identify those who will respond) the cost per patient reduces to \$19,368 with a value release of \$24,529 - \$19,368 or \$5,161 per patient. A lot then depends on what proportion of the population will respond. If we assume, say, 80% then the value to the average centre is $700 \times 0.8 \times \$5,161$ or \$2,890,160.

An additional observation on this evaluation is that the developed world has an aging population. The market may confidently be expected to grow. An advantage of the adoption of this model is that the number of units made at the satellites is flexible. Increase in demand can be managed by increasing the number of stations on the DPM.

Having shown that the treatment will pay its way and comparing the difference in value release between supply by the centralised, 'as is' model and supply from the extended enterprise it is possible to look at the cost savings to the clinical centre when changing to the lower risk model. This difference equates to the difference in cost to set up the supply (amortised over some suitable interval) plus the difference in unit cost for supply of units over the same interval.

For a working comparison let us assume a ten year interval from the point of view of the clinical centre and the satellite operation. In acquiring the kit in the simplified model the setup is of minimal cost, especially if the durable components are given away free by the central business and the supervisory data collection is web-based. The cost at the clinic is

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mainly due to time spent in training. If we assume a ten day programme for each of four people (i.e. a two-person shift with back-up) the costs may be estimated as shown in Table 6-7.

Table 6-7: Five year P&L forecast for the satellite operation with the smaller automated finishing unit (first five years of sales but with ten year amortisation of capital costs by the central operation) sales price of kit \$5,500

All currency in USD	Year 1	Year 2	Year 3	Year 4	Year 5
Capacity - required (final product)	441,040	670,650	679,710	688,800	697,860
No. of satellite facilities	314	478	484	490	497
No. of culture stations	628	956	968	980	994
Capacity, actual	441,400	671,940	680,374	688,808	698,648
Training costs	2,672,340	4,068,085	4,119,149	4,170,213	4,229,787
Plant operational costs - satellites/\$	68,234,398	103,872,746	105,176,588	106,480,430	108,001,579
Variable cost of production of doses/\$	242,769,797	369,566,762	374,205,675	378,844,588	384,256,654
Dose form production/\$	27,161,615	41,347,936	41,866,947	42,385,959	42,991,473
CoGs ex factory/\$	340,838,150	518,855,528	525,368,359	531,881,190	539,479,493
Transport costs/\$	11,034,991	16,798,489	17,009,349	17,220,209	17,466,212
Total production costs	351,873,141	535,654,018	542,377,708	549,101,399	556,945,704
Cost per unit/\$	797	797	797	797	797
Saving per unit/\$	1,203	1,203	1,203	1,203	1,203
% Saving	60.14%	60.14%	60.14%	60.14%	60.14%

However, the feature most likely to inhibit adoption of the ‘to be’ model will be the commercial risk (real or perceived). Although savings can be made by the satellite operation by adopting the relationship with the central facility there is a risk due to the

large commitment needed and the changes in operating practices. There is already evidence that cost arguments alone do not readily change buying practices within the health services sector. A radical change such as the one proposed here faces big hurdles to adoption unless multiple benefits are perceived.

6.7 Model Sensitivity

Step 10 in the thesis comprises an analysis of the sensitivity of the model. Table 6-8 shows the impact of changing each of the main independent variables by 10% in the direction likely to increase costs. For clarity several of the variables that made negligible difference have been omitted. The reason why the sensitivity analysis is not illustrated with 10% perturbation in both directions is that as the model cost values decrease so the results of changes are damped by normalisation to an asymptote. This is not true in the direction of cost increase. Also the important question is what features are most likely to exert an influence upon cost *increase*. Hence the analysis is unidirectional.

Transport costs for cold supply chain are the most important for supply of the kit. The values used for transport costs will be subject to negotiation in real life but serve in this study to illustrate the direct impact of distribution costs. The significance of cold chain supply cost in the sensitivity analysis prompts further investigation of this subject.

Next in significance for the kit are the fold-increase in cells per Passage and the initial seeding density of cells. These variables are related insofar as they impact directly on process intensity and therefore on both variable costs of production and on turnaround time. Each campaign of cell expansion begins with a bone marrow aspirate. The size of the batch will be defined by the level of expansion at which the cells lose their desired properties (allowing a margin for variability in the properties of the aspirate). The cost of making each batch comprises fixed costs of production (pre-qualification of donors, Quality Control costs for the batch) and variable costs of production (medium consumption, plastic ware, reagents, packaging, cold chain supply).

If the yield per bone marrow aspirate is low the CoGs for one unit will be disproportionately high because the fixed costs are spread over fewer units.

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For the final product the most important feature that exerts an influence on the final product cost is the fold-increase per Passage. This is followed by the cells per dose, the price of the kit and the average transport distance for the product plus the cost of low-temperature transport respectively (the last two features have equal influence).

In the tables that follow (Tables 6-9 and 6-10) the impact of interaction between the four most important variables for the central and satellite operation respectively are shown. The figures in bold represent the direction in which any modification must move in order to minimise CoGs.

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Table 6-8: Sensitivity analysis of main variables (Order is by decreasing impact on central costs and then by satellite costs. Analysis conducted on first year of production.)

Variable	Base value	Incremental value (10% in the direction to increase costs)	Cost per unit (kit)/\$	Percentage change in kit production cost	Cost per unit (final product)/\$	Percentage change in final product production cost
Cost of low temperature transport	\$5/mile	\$5.50	3,870	6.92	800	0.31
Average transport distance (kit)	500 miles	550	3,870	6.92	797	0.00
Fold increase per passage from P0	31	28	3,702	2.27	797	0.00
Seeding density at P1 to P6	1,000 cells.cm ²	900 cells.cm ²	3,703	2.29	797	0.00
Cells per kit	200 million	220 million	3,695	2.06	797	0.00
Medium per roller bottle	200mL	220mL	3,683	1.75	797	0.00
Intervals of medium change (average)	4	3.6 days	3,675	1.51	797	0.00
Time to harvest P1-P10	14 days	15.4 days	3,669	1.36	797	0.00
Amortisation interval	10	9	3,649	0.79	797	0.00
Cells per dose	200 million	220 million	3,620	0.00	868	8.91
Fold increase during Passage at satellite	10	9	3,620	0.00	876	9.90
Price of kit to satellite	\$5,500	\$6,050	3,620	0.00	852	6.90
Average transport distance (product)	5 miles	5.5 miles	3,620	0.00	800	0.31
Labour rate per FTE p.a.	\$100k	\$110k	3,620	0.00	798	0.08
Staffing at satellite	4	4.4	3,620	0.00	798	0.08
Time to harvest P0	14 days	15.4 days	3,620	0.00	797	0.00
Seeding density at P0	1.8 x 10 ⁵	1.98 x 10 ⁵	3,620	0.00	797	0.00
Initial yield of cells from aspirate	8,180	7,360	3,620	0.00	797	0.00
Fold increase per passage: asp to P0	208	187	3,620	0.00	797	0.00
QC cost per cell batch	\$85,000	\$93,500	3,620	0.00	797	0.00
Surgeon rate per FTE p.a.	\$300k	\$330k	3,620	0.00	797	0.00
Labour rate per QP p.a.	\$120k	\$132k	3,620	0.00	797	0.00
Usage of QP	10%	11%	3,620	0.00	797	0.00
Satellite facilities per central facility	Variable according to year	+10%	3,620	0.00	797	0.00

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Table 6-9: Relationship between the four leading variables in their impact on CoGs of the kit (COLTT = ‘Cost of low temperature transport’)

All values are percent increase		Initial seeding density = 1,000 cm ⁻²		Initial seeding density = 900 cm ⁻²	
		COLTT = \$5.50	COLTT = \$5.00	COLTT = \$5.50	COLTT = \$5.00
Average transport distance (kit) = 500	Fold-increase from P0 = 28	\$3,952 (9.2%)	\$3,702 (2.3%)	\$4,044 (11.7%)	\$3,794 (4.9%)
	Fold-increase from P0 = 31	\$3,870 (6.9%)	\$3,620 (0.0%)	\$3,953 (9.2%)	\$3,703 (2.3%)
Average transport distance (kit) = 550	Fold-increase from P0 = 28	\$4,227 (16.8%)	\$3,952 (9.2%)	\$4,319 (19.3%)	\$4,044 (11.7%)
	Fold-increase from P0 = 31	\$4,145 (14.5%)	\$3,870 (6.9%)	\$4,228 (16.8%)	\$3,953 (9.19%)

Table 6-10: Relationship between the four leading variables in their impact on CoGs of the final product (COLTT = ‘Cost of low temperature transport’)

All values are percent increase		Cells per dose 200 million		Cells per dose 220 million	
		Price of kit to satellite = \$5,500	Price of kit to satellite = \$6,050	Price of kit to satellite = \$5,500	Price of kit to satellite = \$6,050
COLTT = \$5.50	Fold-increase at satellite = 9	\$879 (10.2%)	\$940 (17.9%)	\$958 (20.1%)	\$1,025 (28.6%)
	Fold-increase at satellite = 10	\$800 (0.3%)	\$855 (7.2%)	\$871 (9.2%)	\$931 (16.8%)
COLTT = \$5.00	Fold-increase at satellite = 9	\$876 (9.9%)	\$937 (17.6%)	\$955 (19.8%)	\$1,022 (28.2%)
	Fold-increase at satellite = 10	\$797 (0.0%)	\$852 (6.9%)	\$868 (8.9%)	\$929 (16.5%)

6.8 The Requirement for Automation

Automation has often been suggested as one of the most likely tools for increasing the commercial viability of regenerative medicine. The earliest introductions of automation in this sector were for improved unit handling on the culture pathway, e.g. the CellMate® from The Automation Partnership [Christopher, David et al. 2004]. The reasons for this are:

- Re-feeding cells during culture involves repetitive aseptic fluid handling and there is a risk of infection from human operators
- The number of units handled is greatest during culture and this introduces a risk of repetitive strain disorder or operator fatigue

The initial bone marrow aspiration is not a concern because this will be infrequent as long as a high Passage number is attainable. It is the large numbers of culture units in central production that will benefit from automation. The user requirements will be

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somewhat different for T-175s, roller bottles and cell factories but there are common elements. The manipulations in the central facility or in the satellite unit will be:

- a) Cell seeding
- b) Cell feeding/re-feeding
- c) In-process QC testing
- d) Trypsinisation and harvest of cells
- e) End of process QC testing

For each operation the general principles to be observed are:

- a) Operations must be conducted in an aseptic environment when the vessels are open.
- b) As far as possible only gentle movements must be applied to the vessels so as not to splash the insides of the lids where filters are fitted to allow gas exchange.
- c) Full batch traceability will be required so individual vessels must be uniquely labelled. Radio frequency identification labelling or bar coding will be preferred.
- d) Each vessel in production will be examined optically to confirm the absence of microbial growth. (Optical sensors can be used if necessary.)
- e) Multiple parallel lines are preferred in production above single, large lines so as to allow for continual production in the event of breakdown in one section.
- f) Maintenance of the drive unit parts must be possible without interrupting production.
- g) The machinery must produce minimal dust and aerosols (e.g. oil aerosols) and so drives should be held inside sealed housings.
- h) The equipment must be capable of sterilisation and must be easy to clean.
- i) The apparatus must contain its own incubator or be capable of operation within a warm room or incubator at 37°C.
- j) The apparatus must be resistant to corrosion in conditions of high humidity and warmth (37°C, 90% relative humidity, 5% CO₂).

Automation is no substitute for good system design. Many early production systems for engineered tissue relied upon large numbers of hoses and connections. This led to high

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rates of in-process failure. Such unions can deform during sterilisation and will then leak when assembled. The hoses are easy to snag and muddle up during production unless they can be assembled in only one way. To facilitate good system management and high yields the process units must be as simple as possible; preferably with a minimal number of unambiguous connections and comprising self-contained flasks or cartridges wherever possible.

A consideration of sources of automated equipment is not strictly necessary for this thesis but is given in Appendix 4 as a source of reference.

The relationship between the central and the satellite facility in the 'to be' model must be carefully managed in order to ensure timely delivery of kits, appropriate scheduling of harvest and the required quality of product. The data communication and control must have two features. The first feature relates to consumables: the central operation will preferably supply the satellite with a software application to manage the ordering process based upon look-up tables of consumables and reagents. Part numbers will preferably be linked to inventory at the supply depot (part of the central business) ensuring minimal delay in re-ordering. The second feature relates to the mechanism for release of goods that was described in Section 2.6. As described above the DPMs will carry on-board monitors to predict harvest point. The data supplied by the monitors will be sent in packets to the central business. Data collection at the centre will fulfil three purposes.

The first purpose is to provide an archive of records of batch release. This will be needed during regulatory inspections and audits.

The second purpose is to permit a history of performance to be built up by the central business. As the satellite will operate under a license that will be maintained by the central business it would be the prerogative of the central business to revoke that license in the event of high levels of out-of-specification products, any attempts to circumvent the standard operating procedures and any failure to comply with equipment maintenance schedules or training courses.

The third purpose will be to provide the trigger that initiates the batch release process. The product will be subject to batch release protocols at the satellite and, in addition, it

will be used only on the authority of the central business. This can be achieved, for example, by issue of special labels at the satellite from commands at the centre or by means of a lock-off upon batch completion that can only be released by a command trigger from the centre. A Qualified Person based at the central business will hold the authority for batch release.

In summary: in the alternative business model the monitoring both of raw materials inventory and of product quality is subject to oversight from the central facility. Real-time culture data will be relayed to the centre and operational controls will allow for intervention in the event of deviations in the process.

6.9 Validation of the Model

So far this thesis has introduced the problem with a centralised business model, the advantages of using an extended enterprise model and how shortcomings in the extended enterprise model may be overcome. The thesis is theoretical and contains many aspects derived from the point of view of several different disciplines. While the validity of the thesis can ultimately be demonstrated only by starting an enterprise based upon the 'to be' model it will be helpful to attempt validation of the model in theory. This has been achieved using three separate mechanisms: sensitivity analysis, scrutiny by independent experts and evidence from initiatives in the regenerative medicine community.

In the sensitivity analysis above (Section 6.7) those features of the model were identified that exert the most influence over the model cost predictions. The combinations of variables that exert the most influence over costs are shown in Tables 6-9 and 6-10. In the base case the costs are acceptable relative to the target. Any large increase in expected costs may affect the viability of the business model and so the combinations that provide the largest increases are of relevance. In Table 6-9 it is the combination of an increase in average transport distance and in the related variable of the cost of low temperature transport that gives the largest increase: 19% of the base case. The fold-increase at Passage 0 level and the initial seeding level at each succeeding Passage both contribute as well but the dependence is less significant for these two features.

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The cost of the cold supply chain was so important that the author sought first hand information from a provider of these services: Biostór Ireland, a company specialising in this service based in County Wexford. The most robust transit uses liquid nitrogen chilling in re-usable shipper containers. This gives temperature security up to three weeks and confers IATA-approved status to the goods. If the goods kits are bulked up into larger shippers using cassettes to support any sensitive components then a maximum price of \$2.50 per mile would apply [MacGabhann 2010 (2)].

The model discussed in this thesis was constructed using values of \$5.00 per mile transit rate, an average transit distance of 500 miles for a kit and 5 miles for the final product. While the transit distance for the final product seems reasonable the transit distance for the kit will probably be too low. (Note that these comments are based on the idea of a global operation. If the model were to be restricted to Europe then the distance of 500 miles would be too much.) The lower-than-expected cost per mile (which will probably fall still lower if orders are grouped as the business grows) introduces a cost reduction factor of at least 0.5. This will counteract to an extent any increase in the value representing the average transit distance per kit. Furthermore, it should be remembered that most businesses will use a combination of distribution hubs and aggregated deliveries for cold distribution. These features, which are under-represented in the model, will reduce any inaccuracies due to the average transit distance of the kit – overall the model is slightly conservative in this respect.

As noted above the thesis was also validated by subjecting the results to scrutiny by experts. An opinion regarding the calculations of aspirate harvest, cell expansion and scale of operation was obtained from two consultancy sources: Dr Mark Pittenger and Dr Scott Burger. Dr Mark Pittenger (at one time VP of Research at Osiris Therapeutics and now Chief Science Officer at Pearl Lifesciences Partners of Baltimore MD) was presented with the data shown in Table A1- 1 to A1- 3 (Appendix 1) and invited to comment on the realism of the volume-and-operability argument in Section 5.2. Dr Pittenger verified the overall calculations and compared the values with his own work with mesenchymal stem cells. When Dr Pittenger's calculation of area yield in plastic ware was compared with the calculation in this thesis the difference was less than 10%. In addition Dr Scott Burger (Principal at Advanced Cell & Gene Therapy, a consultancy

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in North Carolina) was presented with the argument, scale calculations and rationale for the inoperability of the plastic ware approach at full scale he agreed with the findings of this thesis.

To validate the health economic argument the work was subjected to the scrutiny of Dr John Posnett (formerly Professor of Health Economics at the University of York, UK, and Vice President of Health Economics at Smith & Nephew). Dr Posnett made some helpful observations on the calculation of the value release by a diagnostic. These observations have been incorporated in Section 2.7. Dr Posnett confirmed that overall the argument was sound.

From this scrutiny the author can confirm that the model is representative of the real case.

The other feature of the thesis that requires validation is the realism of the proposed alternative business model. During the time that the thesis has been under construction the author has taken steps to confirm the practical validity of combining private sector supply with an operation within hospital-run cleanrooms. In this connection meetings were held with Simon Ellison (Regenerative Medicine Contract Manufacture Specialist at National Blood Service). There is currently a project under way from the UK National Health Service to find ways of increasing value from the cleanroom network within the NHS. There are a total of fourteen such centres with, on average, utilisation of around 50% of capacity. The Service is seeking ways of generating additional value from them. At the time of writing this initiative is gathering momentum; it seems that a service offering that would give an appropriate structure together with demonstrable value would be welcomed. The cleanrooms are already GMP-compliant and the members of staff have the right know-how to execute such work. Activity-Based Cost analyses have been constructed for the cleanrooms but are not available to the author without non-disclosure agreement. In 2011 the author and Simon Ellison put forward a proposal to initiate a scoping study to provide the business case for a full project based on this thesis but this could not be pursued for reasons of commercial sensitivity.

The work was also examined, under confidentiality agreement, by David R. Williams, Professor of Healthcare Engineering at the Wolfson School of Mechanical and

Manufacturing Engineering, Director of the Research School of Health and Life Sciences and Director of the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine at Loughborough University, UK. His comments are shown in full in Appendix 5 and his comment on the challenge of imposing a uniform Quality Management System is explored further in Chapter 7.

The third method of validation was by comparing the findings in this thesis with the trends in the regenerative medicine business sector. During 2009 the author made a bid for funding from the UK's Technology Strategy Board for the funding call entitled 'Regenerative Medicine - Value Systems and Business Modelling'. The bid was aimed at verification of the type of business model described in this thesis for a selection of therapeutic targets. It was to be based around collaboration between Smith & Nephew with a regenerative medicine centre of excellence, a cost analysis and software specialist in the bioprocessing area, a regulatory consultant in regenerative medicine and a large pharmaceutical company active in CBTs. The bid was successful at Stage One but changes in the economic climate prevented the bid being progressed to Stage Two. Nevertheless, the fact that the various parties were each willing to enter into such a project is testimony to the robustness of the idea at this early stage.

In addition, since work on this thesis began another project has started (funded by EPSRC) entitled 'Automating stem cell bioscience: from GMP to the clinic.' Other new initiatives have begun that relate to the supply chain from business to bedside for cell therapeutics, a recent example being "Manufacture of Advanced Therapies: Academia meets Industry" Newcastle, UK, 04 March 2011. A register of UK cleanrooms has been assembled by eXmoor Pharma, Ltd. with the intention of encouraging contract use by interested parties.

6.10 Summary

The cost of setting up the extended enterprise can be reduced to more realistic levels by changing the nature of the DPM to a more compact system. Inclusion of remote monitoring equipment will make it possible for the required level of oversight to be maintained from the central operation.

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The costs of production of the CBT are most strongly influenced by the costs arising from cold chain supply. The values for this have been investigated with a service provider and a better picture of the likely value for these variables has emerged. The findings will not significantly affect the conclusions of the thesis.

The content of this thesis is regarded as commercially sensitive by the author's employer. This has made it impossible to explore the thesis further by validating it with health care professionals. The three-fold approach of validating by means of sensitivity analysis, expert opinion and corroborating evidence from the regenerative medicine community is the limit of what can be done in this respect without authority to work with a hospital. However, the evidence from the three-fold approach supports the validity of the extended enterprise model for products of this type.

The thesis has provided the basis for studies to verify the commercial approach for specific case studies. Areas of uncertainty, particular challenges and subjects for further study are discussed in Chapter 7.

Chapter 7

Conclusions and Further Work

7.1 Introduction

This thesis shows that the development of cell-based therapeutics to a commercial scale of production presents serious technical challenges to the operability of the process at full scale. The unique regulatory constraints upon products of this kind and the expense of clinical trials mean that a business must make an early decision regarding technology for manufacture. For a centralised business neither of the main choices, scale-out or scale-up, is attractive when the required capacity is large.

The thesis shows that the problems of scale-out can be avoided if the final stages of cell expansion are derogated to satellite manufacturing operations using an extended enterprise model. Such a model carries commercial risks in the form of control of quality and especially asepsis. The market will benefit from the creation of the tools and communications hardware and software to operate downstream processing kits under supervisory control from a central operation.

This thesis has provided the opportunity to explore the possibility of turning the perceived disadvantages of manufacturing a regenerative medicine, the difficulty in scaling up, into an advantage by scaling out manufacture in a distributed manufacturing model. The thesis has also provided the test bed for a systematic approach to business reengineering for this type of high value biotechnology product.

In Chapter 1, Section 1.5, three main aims of this thesis were introduced. These aims have been addressed and the results are summarised here.

To generate alternative business models

The shortcomings in the current, centralised model of production and supply of cell-based therapeutics have been demonstrated. If the decision is made to scale out

production then the capital investment required for operation at full scale will be very large. If the decision is made to scale up to bulk production then there is no guarantee that the desired cell phenotype will be retained or that such culture will be technically feasible. If the scale up is successful the business may well be required to repeat early development work to demonstrate that the basis of comparability of the product has been conserved during the change in process.

The model proposed in this thesis offers a means of avoiding this dilemma. It provides an incremental means of growing the business in which much of the capital cost is incurred in line with market share rather than up front. This alternative model offers a means of building and exploiting mutually beneficial relationships with 'early adopter' centres. Furthermore the alternative model offers an opportunity for an entrepreneurial company to build a business based upon management of the clean environment of production, its Quality Management System and the operation of the downstream processing equipment.

To provide a method for technology appraisal

The method that is demonstrated in this thesis is applicable to other examples of new technology in regenerative medicine. The combination of flowsheeting, IDEF0, Activity Based Cost modelling, operability analysis and GRAI analysis makes it possible for a team exercising due diligence to ensure that the future integration of the technology into the business can be performed with confidence.

To initiate a library of partial models

The work conducted in this thesis has resulted in the creation of reference models of the central and the satellite operations. These models can be adapted and the costs can be adjusted to allow enterprise modelling studies to be carried out. The results of such studies can inform investment decisions in advanced healthcare.

7.2 Significance for Business and Health Care

The significance of this thesis to commerce lies in the acceleration of take-up of the products of regenerative medicine and the potential cost savings to health care. Health care providers are facing mounting pressure to make improved use of resources [HFM

2004]. This has already led to more flexible networks of provision of services. In many cases health care providers have begun to act as though they are commercial operations with cost-based targets. Dramatic changes in medicinal product reimbursement patterns have driven down margins on many products and this has exacerbated the pressure still further. In the UK there are now moves afoot to consolidate health care provision around integrated practice units that give higher rates of success through specialisation. While this may not be popular with patients initially, because travelling distances for patients and relatives may be greater, the benefits in terms of increased success rates and higher value in health care provision will emerge over time. Some Health Management Organisations, e.g. the NHS Blood and Transplant service, are now in a position to engage with industry in an extended enterprise. Such engagement requires common Quality Management Systems and some common working practices.

As has been observed by Professor Williams (see Appendix 5) the obstacles in constructing the common Quality Management Systems must not be underestimated. The provision of a 'boiler plate' QMS and procedures, a training package and IT support may emerge as a good opportunity for entrepreneurs because it can be a business in its own right. Since a common, effective structure is needed for IT services, training, QMS, SOPs and complaints handling there may be a niche for a service provider who can deliver the whole package to a common standard and link the central operations to the clinics.

The relationship management must be good in order for the extended enterprise concept to work in this context [Buchanan 1997]. The creation of one or two demonstrator projects with informed clinical centres that have a practice of early adoption will probably be the strongest incentive for the model to be adopted.

The results of the thesis highlight an important risk when assessing the commercial viability of regenerative medicine innovations: operability must be considered at an early stage. At present this is the exception rather than the rule and the complexity of such an assessment is off-putting to investment analysts. As a result the issue of operability at full scale has been neglected, especially since it is not apparent to investors and relatively few products in this sector have reached production. There is an opportunity to create a community of practice specialising in this subject and sharing learning on a pre-

competitive basis. Most entrepreneurs in regenerative medicine focus on the intellectual property surrounding the product (cell sub-populations, control of cell expression etc.) and it would not be threatening to their business proposition if they were to join with other such organisations in creating the market within which a new business could provide the management of the satellite operations on their behalf.

Many of the features of regenerative medicine lend themselves to a modular approach to capital acquisition and the capacity to drop-ship complete operations to different locations on a franchised basis could be an attractive model for growing a new business.

7.3 Summary of the Modelling Method

The method used in this thesis can be applied elsewhere. The combination of GRAI-grid and SADT that was proposed by Doumeingts has found an application here. Specifically this comprises the use of process flowsheets together with GRAI-grids, SADT and Activity-Based Cost analysis to create an ‘as is’ model, to examine the shortcomings of the model and to identify a potentially viable alternative.

Taken together these techniques comprise an approach to business reengineering that can be applied to other high-value enterprises, especially in fields where little direct operating experience is possible prior to making decisions about organisational structure and the capital expenditure to support it.

Although the prescriptive method was described in outline in Section 1.6 it is re-stated here in a format that enables it to be followed as a practical framework (see Figure 7.1).

Chapter 7

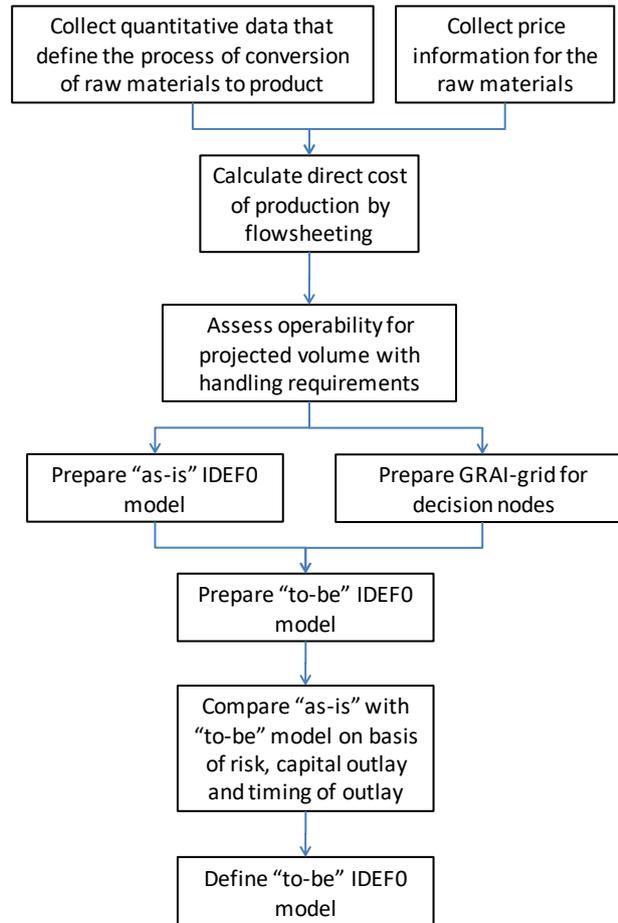


Figure 7.1: Summary of the method

Accurate information is vital to give the right context for the technique [Hicks 1998]. Unless the data used are appropriate to the model it is possible to draw very misleading conclusions. In this thesis, for example, it is the combination of scale of operation (dictated by market projections) combined with the behaviour of the cells and the expected dose that draws attention to the operability issue. If a more physiologically active cell sub-population were to be found or a more restricted sub-population of patients were to be targeted then the issue would not arise. Under these circumstances the total rate of production and delivery of cells will be much less than in this thesis and more amenable to normal production methods.

It is useful to draw a distinction regarding the concept of ‘stratified medicine’. In stratified medicine the patient population is sub-divided, perhaps along genetic, age-related or immunological axes. The large volume of uniform dose units would be

replaced with customised formats. However, this is not the same situation that obtains with reduced patient populations because the total capacity required, albeit with various cell types, may be similar to the case presented in this thesis. The extended enterprise model would still be valid with terminal customisation of products based upon a limited range of alternative kits.

The value of the product influences the model and higher value products may justify the investment needed to make higher productivity processes. In this thesis an example of a 'mid-price-range' cell-based therapeutic product was selected. Such a product will not command the high value of one aimed at, for example, a life-threatening condition such as a stroke or cardiac failure.

The products of regenerative medicine are dramatic and this must not hide the fact that for such products to be of value they must compete successfully against current 'gold standard' treatments (where they are available). For non-life-threatening conditions there is probably no continuum of value for regenerative medicine but instead there are probably local optima in the value space.

When working on such mid-range products new businesses in regenerative medicine must pay sufficient attention to the production and distribution methods in the context of the desired capacity to arrive at a viable business model. In the future the emergence of effective, well-characterised bulk production methods will make the allogeneic product sector more economically viable. In the meantime it is important for investors to remain vigilant about the viability of the high-volume-manufacturing cost features in the business plans presented to them.

The features which exert the most influence over the costs in the model of this thesis, mainly those related to cold product supply, will continue to dominate costs until improvements in shipping arrangements can be made either by developing cheaper transport systems or by reducing numbers of units in transit. The obvious way of reducing transit costs is a social, rather than a technical, innovation. Currently there are few specialist couriers who have the knowledge, the capacity and the reach to supply such products globally. An extended enterprise might include several different businesses all providing their own kits for different indications to a common format and the clinical

centres might then specialise in providing treatments based upon this model. A more fully-utilised satellite operation would give the biggest cost reduction. This economy of scale would be accompanied with the kind of improvement in expertise and efficiency that comes from specialising in the treatment mode. The cold supply chain will be more economical as well under these circumstances because a specialist provider in this product type can manage rapid transit of multiple products in single consignments through regional hubs.

7.4 Possible Improvements to the Method

Some of the numerical features in the model can be improved. For example a growth factor is assumed to be needed for cell expansion; if the growth factor proves unnecessary then this can be deleted; if it is required then discount for supply at scale should be added to the spreadsheet. Quality Control has been represented in the model using a global approximation. A firm cost for the Quality Control will contribute to accuracy in the model at low Passage number and at low cell yields per batch. During the work in this thesis it was quite difficult to get an accurate picture of the business processes behind current clinical practice at the point of care; the author understands that this can be quite variable. Due to the commercially-sensitive nature of the thesis it was not possible to conduct collaborative work on this topic. Information received by the author suggests that ABC models have been constructed for some relevant parts of the NHS but access to these was not possible during the thesis work.

In this thesis costs for labour, materials etc. were derived from primary data. Commercial databases are now available that offer these details as part of a service that includes annual updates e.g. BioSolve® from BioPharm Services. Inclusion of such values along with more work to provide accurate capital costs will greatly improve model accuracy. In the meantime reliance has been placed upon the sensitivity analysis to show just how important these factors can be.

It would be quite powerful to assemble a library of partial models representing the key elements of the operation. In this way a more accurate calculation could be made of the

value release on the basis of changing administration, communication, procurement of Quality Control and transport aspects of the model.

The other feature that could be improved is the robustness of the model to variations in operation. As was remarked in Section 2.15 a weakness of IDEF0 is that it cannot represent dynamic information e.g. scheduling, consequences of batch failures, inventory management decisions and the like. Such information is stochastic in nature and a possible improvement would be to conduct Monte Carlo simulations of the production and supply events using a combination of IDEF0 and Petri Nets in order to identify points of weakness in the supply chain and to look at consequences for distribution hubs, clinical inventory and any hold-ups in supply e.g. due to customs controls. Such probabilistic studies would increase the understanding of the points in the manufacture and supply where combinations of events could threaten delivery. It would also improve knowledge of the realism of the supply chain with respect to supply of goods just in time for clinical application. This information would provide insight into how robust the model is with respect to changes forced upon it by real-world events.

7.5 Further Research

There are some items that require a larger investment of time and effort than could be accomplished in this thesis. The sensitivity analysis of the model responses does not address two features of the overall situation that exert a strong influence upon the viability of the putative business. The first of these is the capital requirement for the business. This will bear more careful examination, in particular the design of any DPM and its control system. Success depends upon economical design of this device, especially in the 'lower risk' model. The concept warrants a project in its own right.

The second feature is the subject of suitable automation and monitoring hardware. This will be of vital importance to any realisation of the 'to be' model enterprise. The two highest scoring companies, TTP and TAP (see Appendix 4), could be approached to explore opportunities for obtaining scoping estimates and concept designs for automation of the satellite units and automation of cell handling in the upstream processing. The results could be applied in revised cost projections and in a study of operability.

Chapter 7

There have recently been several positive signs that the industry will be able to make the transition to this kind of business model. One of these signs is the development of reactor systems by Beckman alluded to earlier (Section 2.6). Another sign is that the subject of link-up between health care providers and businesses in new enterprise models has begun to feature in professional meetings.

It is essential that robust, validated methods of production can be created if the satellite DPM is to be applied successfully. Regenerative medicine products are naturally complex and therefore a suitable control strategy must be found to ensure a commercially meaningful success rate in production. A new project from the University of Loughborough is now examining methods of making regenerative medicine products in a way that will integrate smoothly with the clinical process. It is hoped that Quality Control at 'six sigma' level will be attempted.

Regarding the specifics of the product in this thesis it is important to confirm a commercially meaningful level of expansion (with a margin for error) and the likely rate of failure of donor batches in order to be confident that average yields will meet the cost criterion. This can be done by conducting a study of, say, three batches of human bone marrow aspirate from different donors by expanding them to a level equivalent to eight levels of Passage. The expected fold-expansion and duration at each Passage can be confirmed. (Note that it would not be necessary to expand using the projected total number of roller bottles or T-flasks, the cells could be split at each Passage and only a representative portion need be carried forward.) A clear potency criterion will be needed to permit definition of the maximum practical level of expansion before that feature is lost from the cell phenotype.

Regarding the variables in the model the staff and plant values make less difference to the outcome than the direct costs but they do contribute and an accurate plan to manage materials movement would enhance the model to the point where it could be used as a business proposal. Such a study can be carried out by working through the method with a multidisciplinary team to identify staffing levels, schedules and plant. The cost estimates for the plant, installation and validation can be refined using the results.

Some commercial opportunities are apparent from the results of the thesis. These are as follows.

- a) Commercial development of the hardware and software for cost-effective multipurpose downstream modules
- b) Entrepreneurial value creation from the local clean facilities in- or near-clinic, probably on a franchise basis
- c) Advanced technologies and business processes for management of the cold supply chain

There are signs that these opportunities may be taken up. If so we may see the widespread use of advanced therapeutics on a different basis from that of the current supply.

7.6 Conclusions

Regenerative medicine offers the possibility of resolving conditions that are currently not amenable to any treatment except palliative care. In time regenerative medicine may replace conventional drug- and surgical treatment for a variety of disorders. With an aging population and higher expectations of activity in later life there is a clinical need for the products. However, it does not follow that *any* such product will be viable economically. While products aimed at life-threatening conditions may command margins high enough to allow high overheads and customised delivery (c.f. transplant organs) the resolution of non life-threatening conditions will command a lower price. Therapeutics that are required at large volume but for a relatively modest price pose problems in development because of the technical and operational challenge of full scale manufacture. These challenges can too easily be overlooked during the research stages of the work leaving commercial risks unresolved until late in the development pathway. This issue is one of the main reasons why regenerative medicine has not so far delivered the degree of commercial success that was initially expected of it.

This thesis examines the technical and operational risks in building a business in regenerative medicine. This thesis has established a hybrid method for appraisal of business proposals in regenerative medicine that goes beyond the normal flowsheet and

profit-and-loss analysis in which a centralised operation is always assumed. Examination of the ‘overhead’ arrangements and inspection of materials movement issues is vital if blunders are to be avoided in planning for operation at full-scale.

The main issue that must be addressed if the proposed model is to be realised concerns the mechanism of Quality Control and the view of the regulatory authorities. The intervention of an entrepreneurial business that will handle the manufacture within the host site would ensure consistency of training, methods, quality systems and reporting.

The extended enterprise model of production has the capability to meet the cost and scheduling requirements of clinics provided that the right hardware and software can be assembled to permit supervisory control from the central operation. The approach may be applicable to other biological therapies.

In Section 1.5 two research questions are posed:

1. “Is it possible to construct a model of business for regenerative medicine that avoids both the technical challenge of bulk cell manufacture and the high capital investment that is needed for a conventional supply chain?”
2. “Does a business model exist that can be used as a platform for the delivery of more than one cell-based or tissue-based therapeutic by terminal customisation of the product?”

This thesis has shown that the answer to question 1 is “Yes”. The validation of a cell-based therapeutic production method can, in principle, be conducted at a scale similar to that of the research. This effectively bypasses the need to build bulk production equipment provided that the last stages of cell expansion are derogated to a satellite facility.

The incremental construction of a network of satellite manufacturing units in an extended enterprise offers a new way forward in advanced medicinal products. Provided that the units are capable of operating to a menu of culture protocols then the answer to question 2 is “Yes” as well.

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Appendices

Appendix 1: Values used in the Cost of Goods Model

Table A1- 1: Values of important variables in model of cell expansion

Item	Value	Source of data
Initial yield of cells from aspirate	8,176	Vunjak-Novakovic and Freshney 2006
Seeding density at aspirate stage (P0)	10^9 mesenchymal stem cells.cm ⁻²	Bonab, Alimoghaddam et al. 2006
Seeding density P1 and higher	1,000 cells.cm ⁻² (2,800 cells.cm ⁻² can be used but leads to lower rate of expansion)	Bonab, Alimoghaddam et al. 2006; Sensebé 2008
Fold increase from P0 to P1	208	Bonab, Alimoghaddam et al. 2006
Fold increase per Passage at Passages higher than P0-P1	31 (a combination of the average harvest observed from Bonab <i>et al</i> but adjusting to start from the seeding level given by Sensebé)	Bonab, Alimoghaddam et al. 2006; Sensebé 2008
Average time to Passage	14 days	Bonab, Alimoghaddam et al. 2006
Interval between feeding	4 days	Bonab, Alimoghaddam et al. 2006
Medium fill level in roller bottle	200 mL	Bellett 2010
Dose per unit	200 million cells	Analogy with Prochymal® [Caplan 2008]
Composition of medium (% v/v)	MEM (89), HIFCS (9), L-Glutamine 200 mM (1), NEAA Sigma-Aldrich M7145 100x (1) FGF as occasional supplement	Bellett 2010

Appendices

Table A1- 2: Unit costs of raw materials

Item	Price per unit/\$
Alpha MEM	0.03
Aspirate extraction device	100.00
Cell strainer	1.00
Centrifuge tubes - 15 mL	0.29
Centrifuge tubes - 200 mL	4.26
Centrifuge tubes - 50 mL	0.23
Cryogenic Vials - 2mL	0.40
Dual barrelled syringe	11.54
Hyaluronic acid dose	50.00
Eppendorff	0.10
Ethanol - 70%v/v	0.02
FGF2 (25mg/1mL)	291.26
HIFCS	0.10
Gilson tip	0.10
L-Glutamine	0.06
MSCM-sf (a serum-free medium from ScienCell)	0.43
NEAA	0.04
PBS	0.12
PBS	0.11
Pen/Strep	0.04
Pipette - 1 mL	0.15
Pipette - 10 mL	0.24
Pipette - 2 mL	0.17
Pipette - 25 mL	0.48
Pipette - 5 mL	0.23
Pipette - 50 mL	1.84
Roller bottle	9.17
T175 Flasks	1.99
Trypsin	0.17
Trypsin-EDTA	0.18
Wipe	0.25

Appendices

Table A1- 3: Comparison of vessel numbers needed to meet demand (approximately 700,000 units per annum in this illustration)

Vessels needed per annum, US only	Area for culture/cm²	No. of vessels needed p.a. (2024)
Roller bottle	850	5,292,298
10-layer Cell Factory	6,320	711,781
40-layer Cell Factory	25,284	177,917

Appendices

Appendix 2: IDEF0 Diagrams for Centralised Production

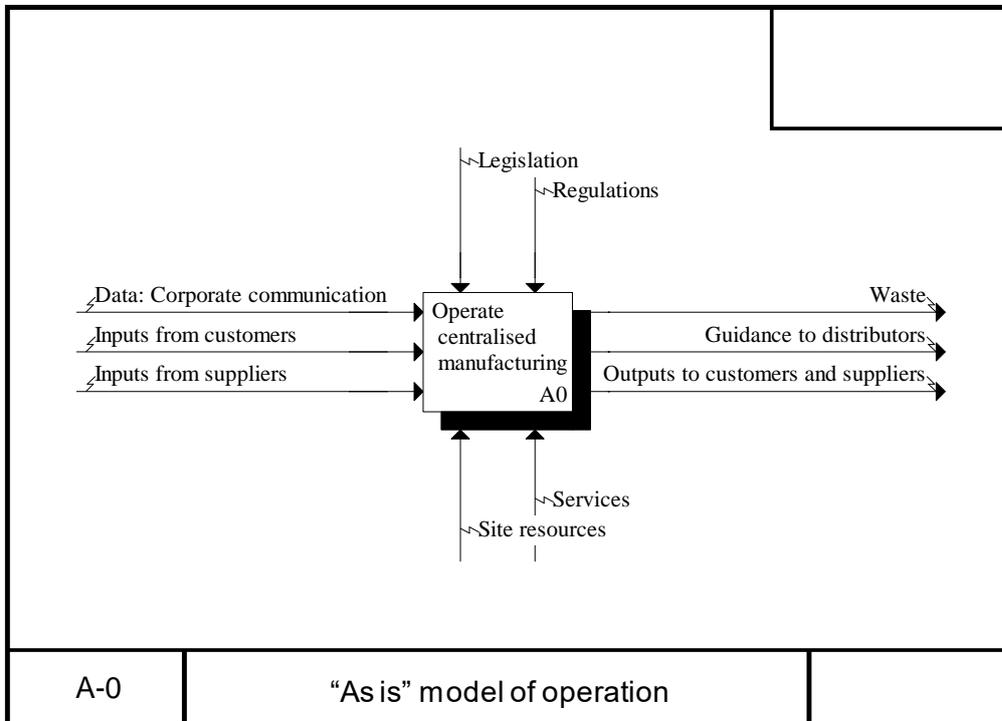


Figure A2. 1: A-0 Model of ‘as is’ operation

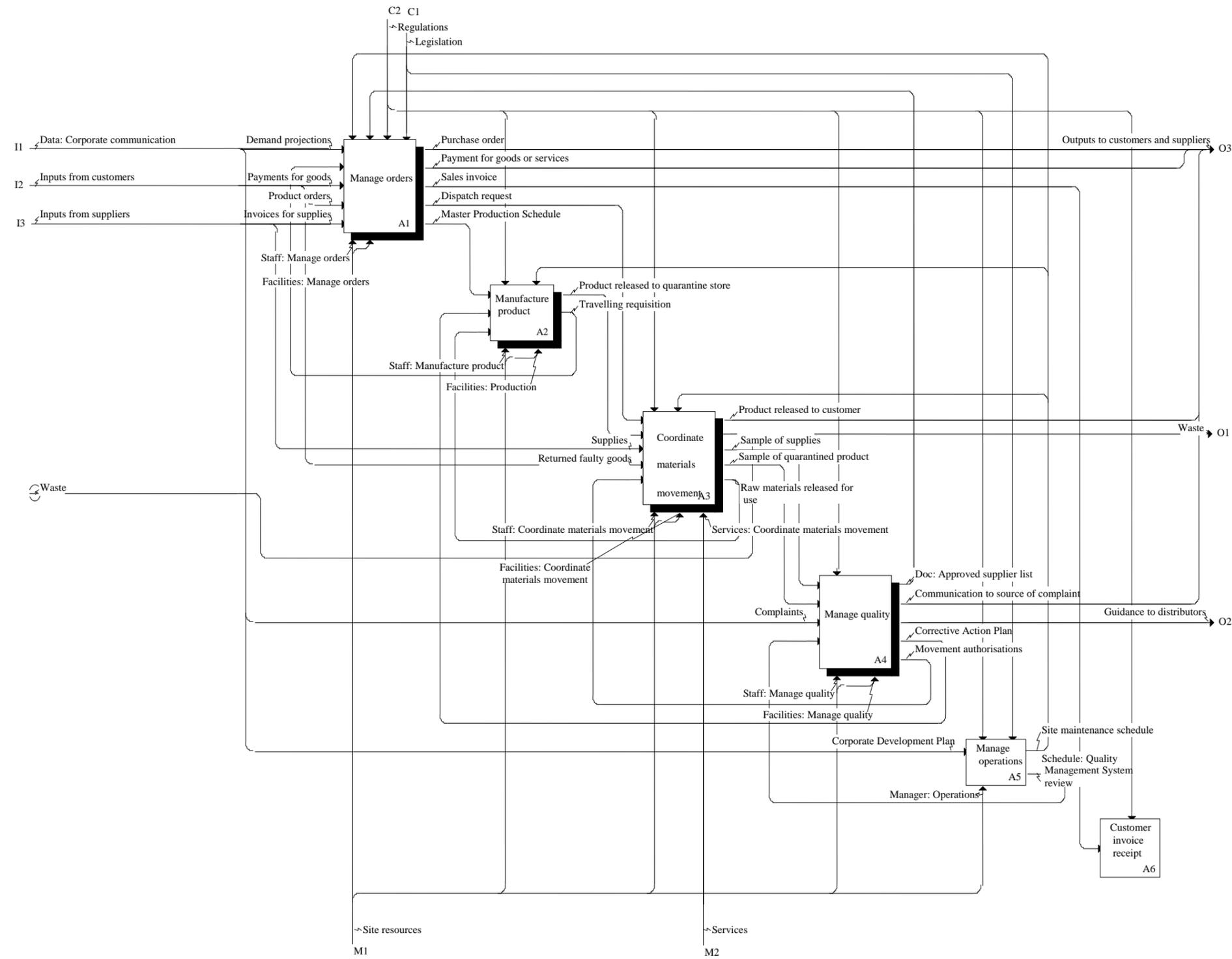


Figure A2. 2: A0 Model of 'as is' operation

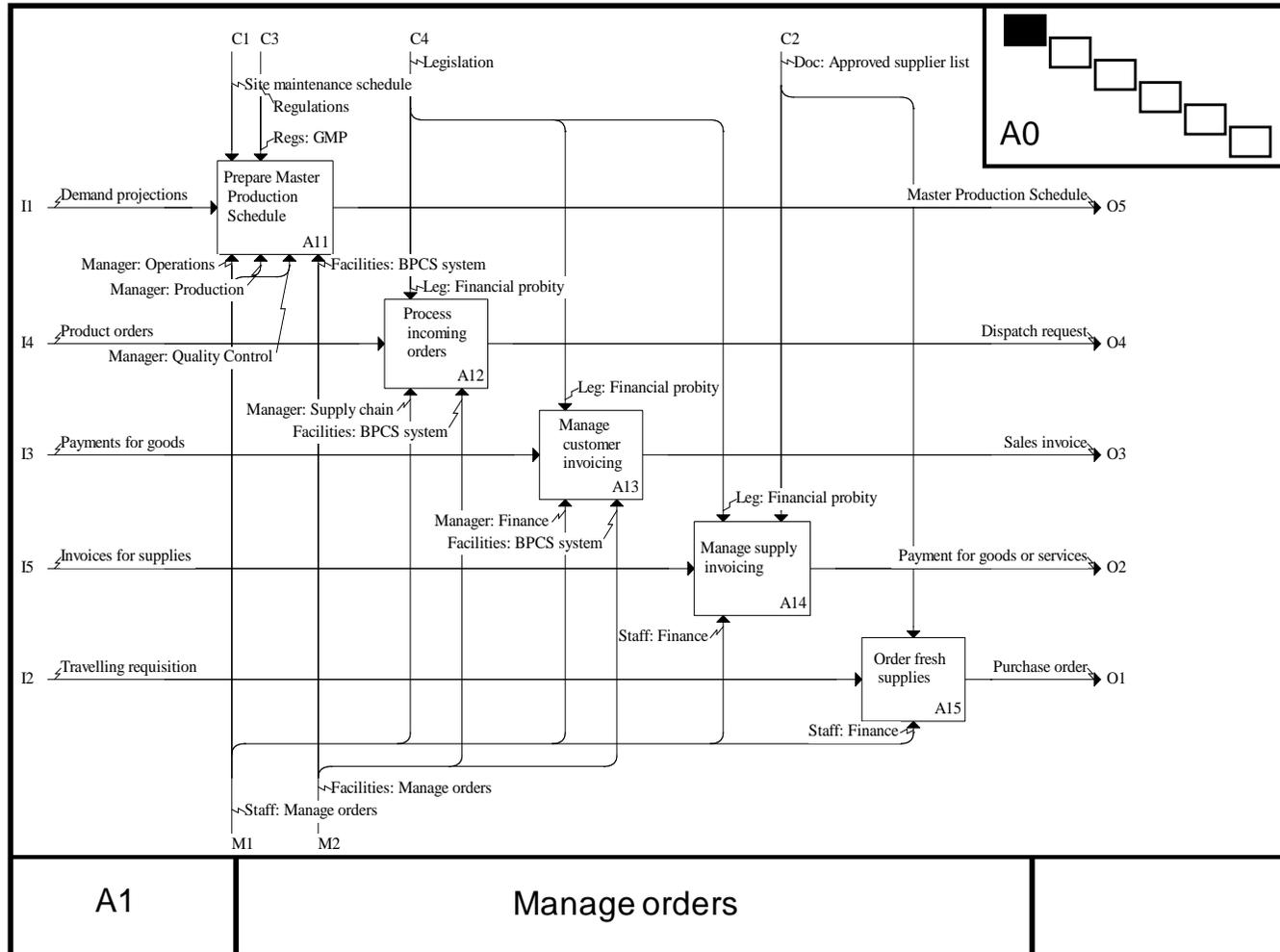


Figure A2. 3: A1 Model of 'as is' operation

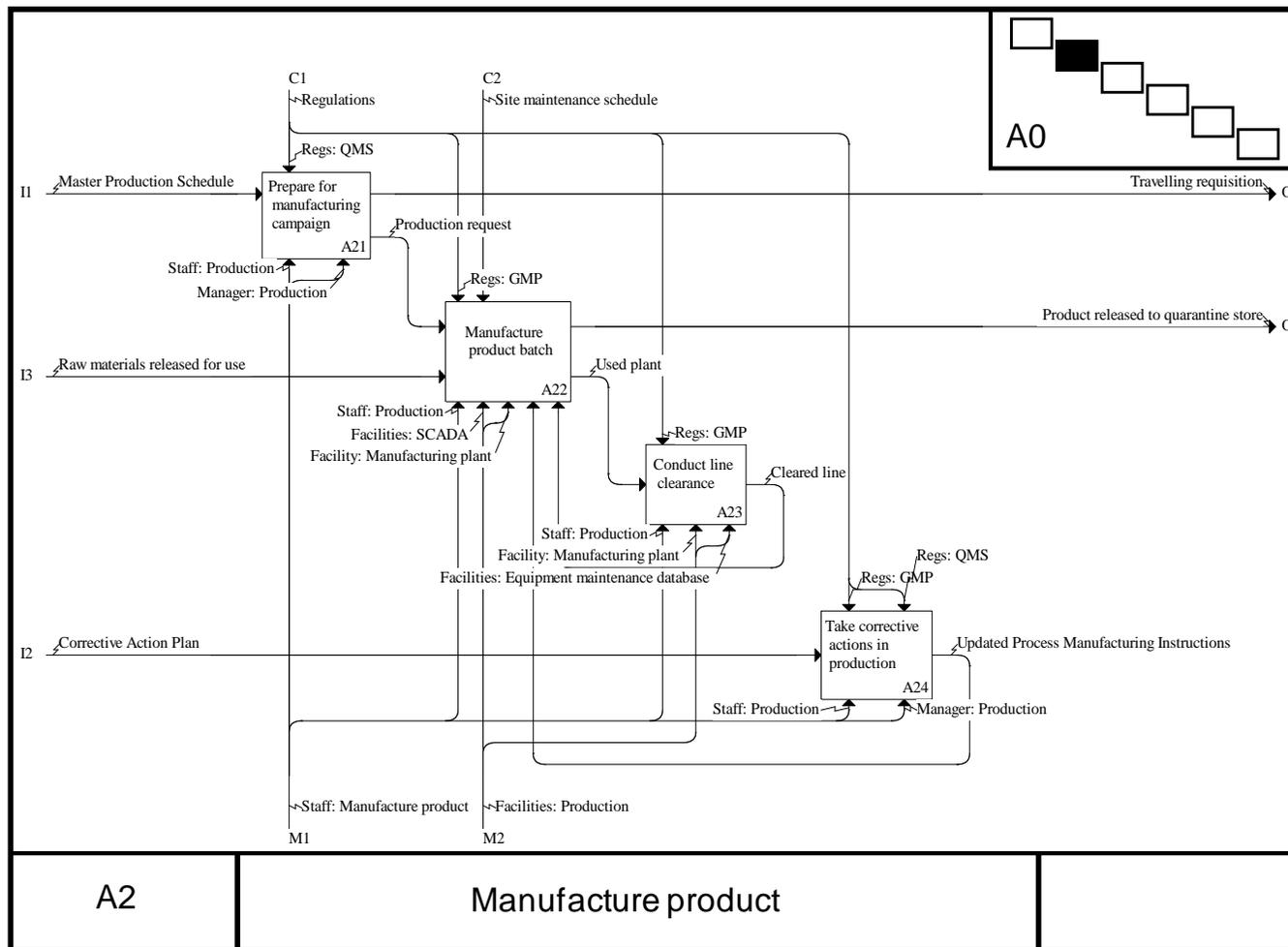


Figure A2. 4: A2 Model of 'as is' operation

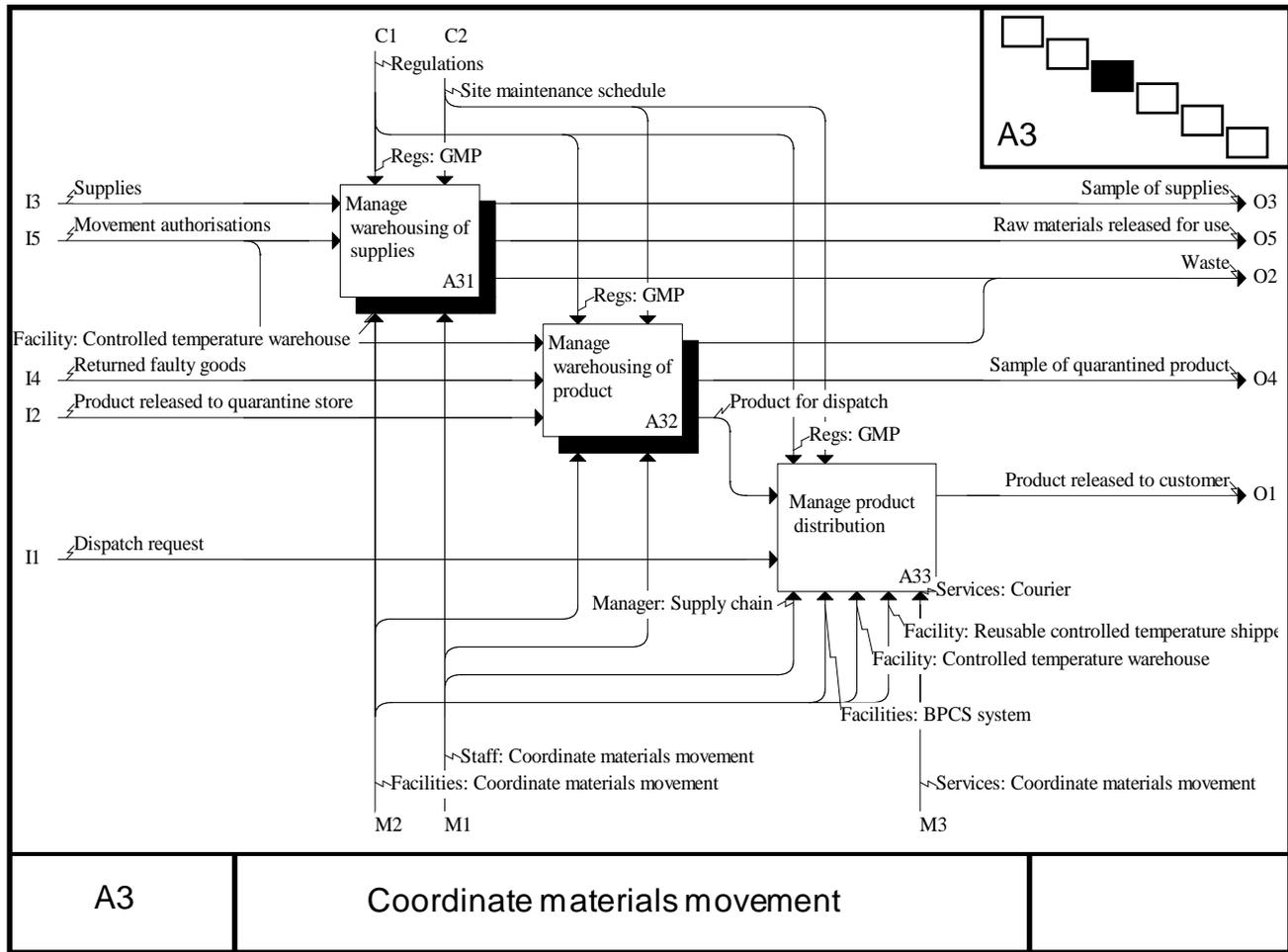


Figure A2. 5: A3 Model of 'as is' operation

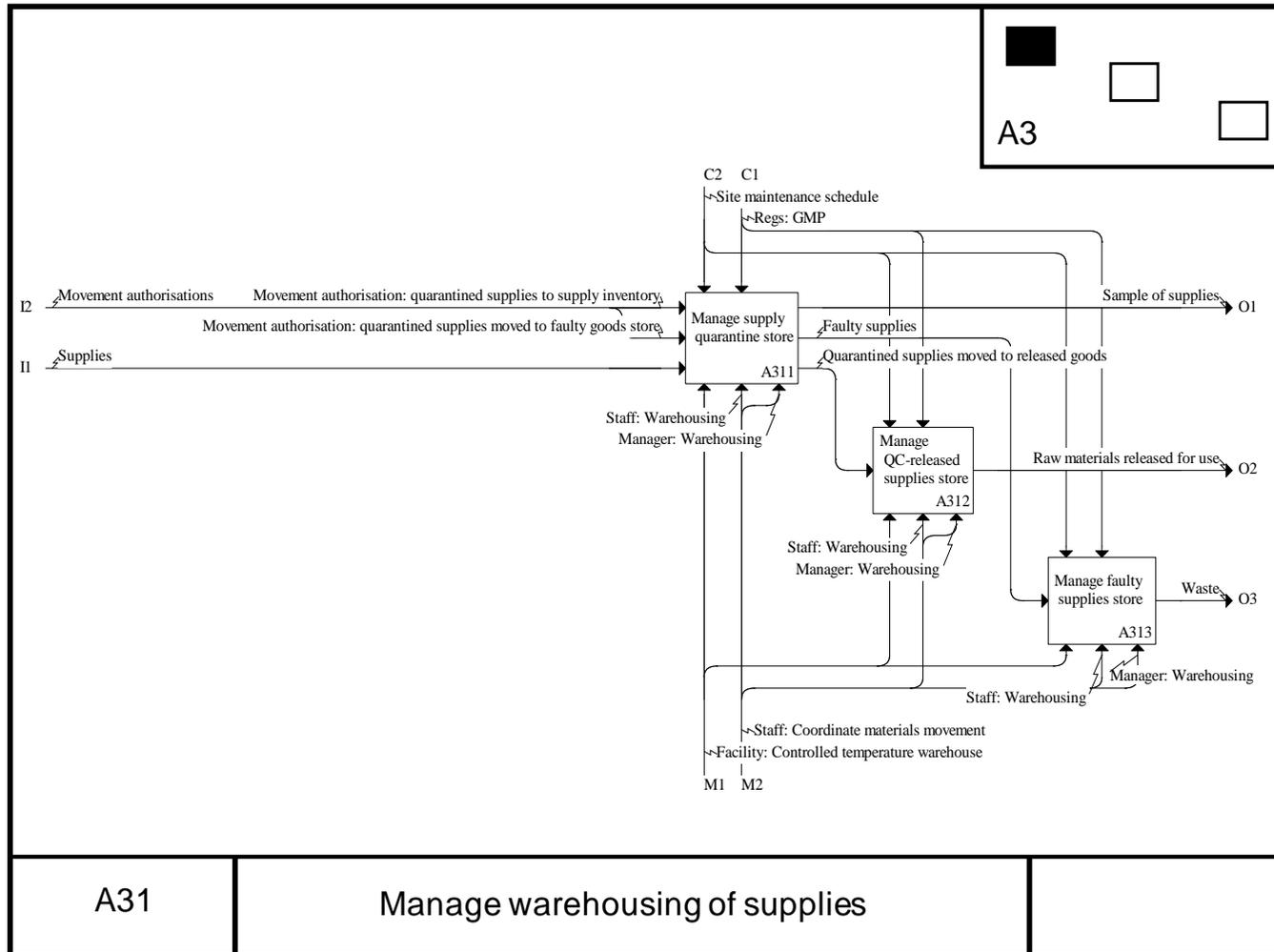


Figure A2. 6: A31 Model of 'as is' operation

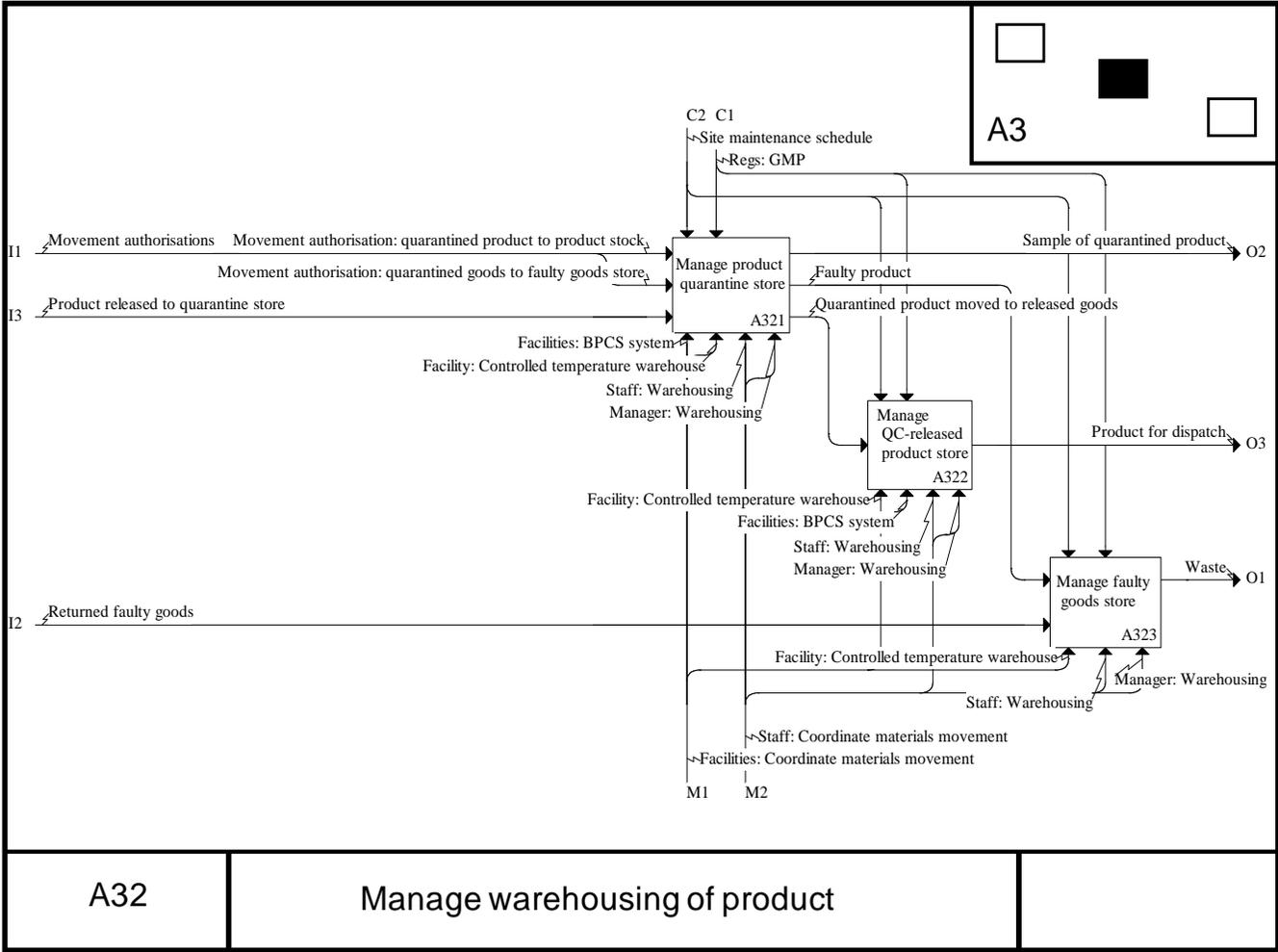


Figure A2. 7: A32 Model of 'as is' operation

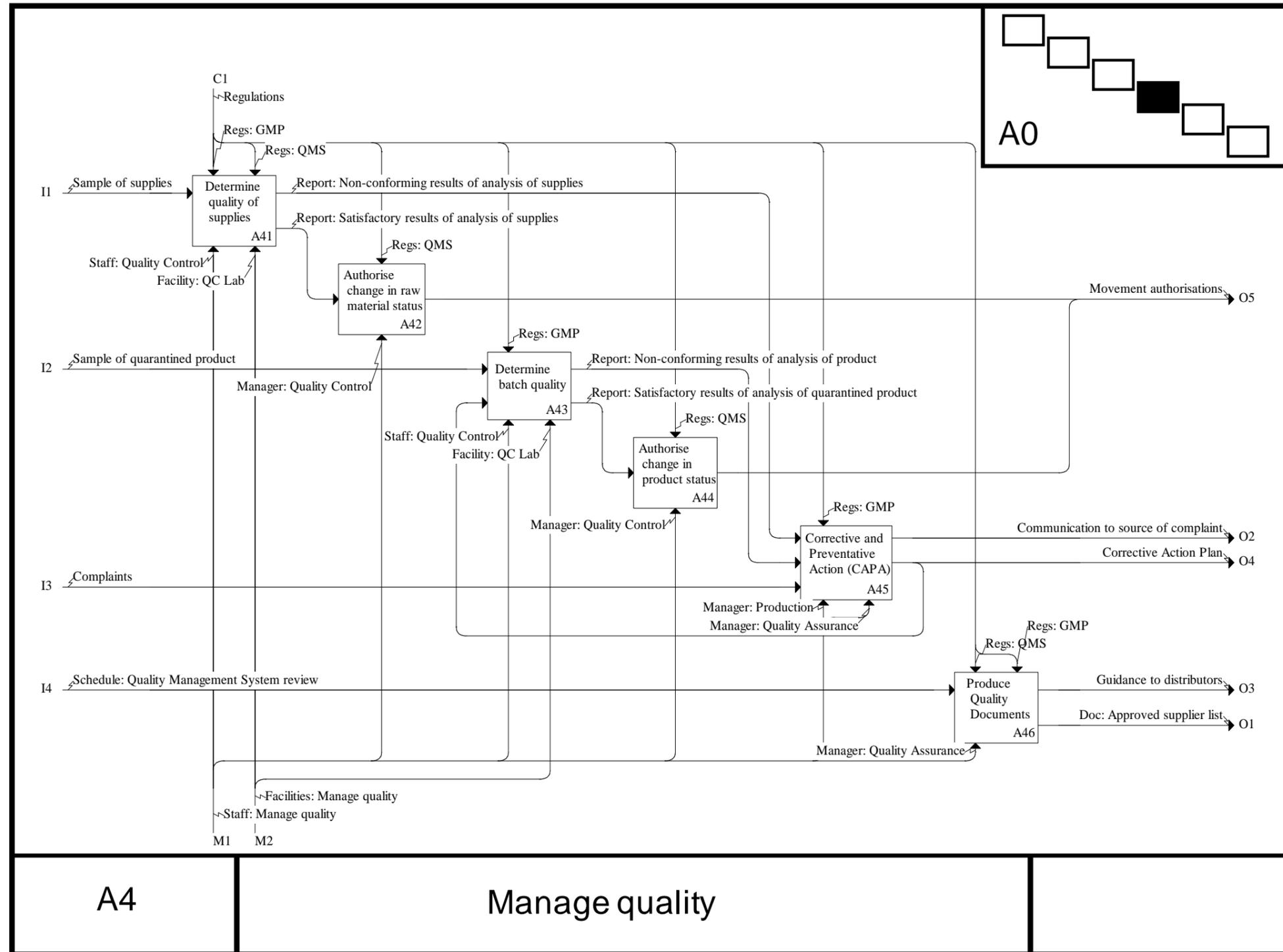


Figure A2. 8: A4 Model of 'as is' operation

Appendix 3: IDEF0 Diagrams for Decentralised Production

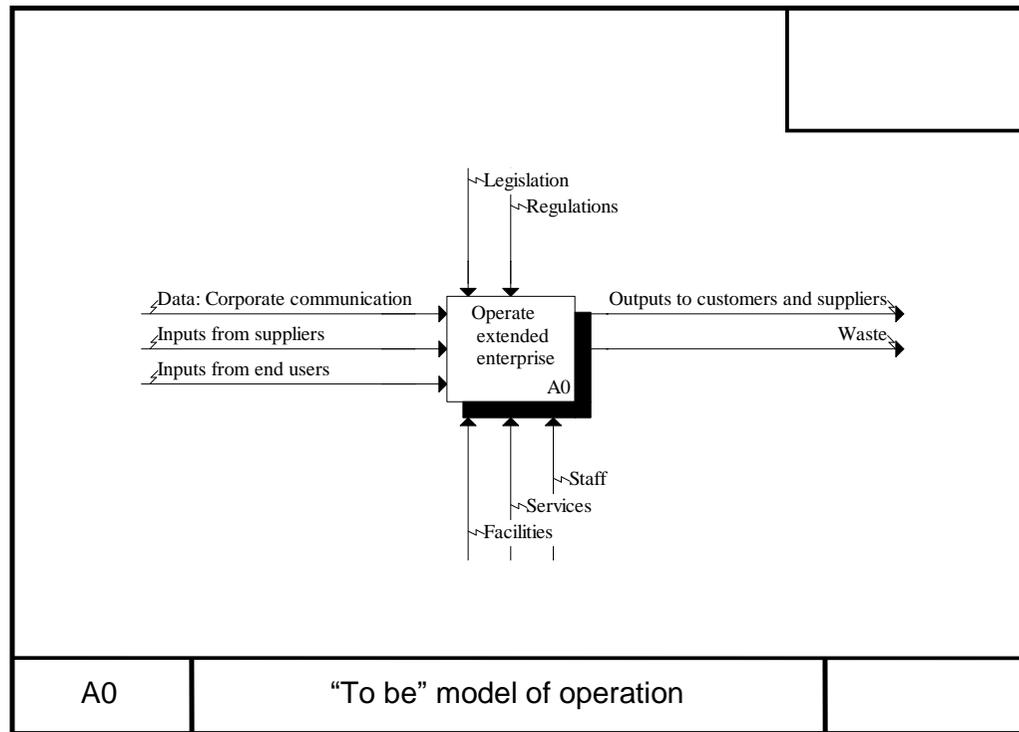


Figure A3. 1: A-0 Model of 'to be' operation

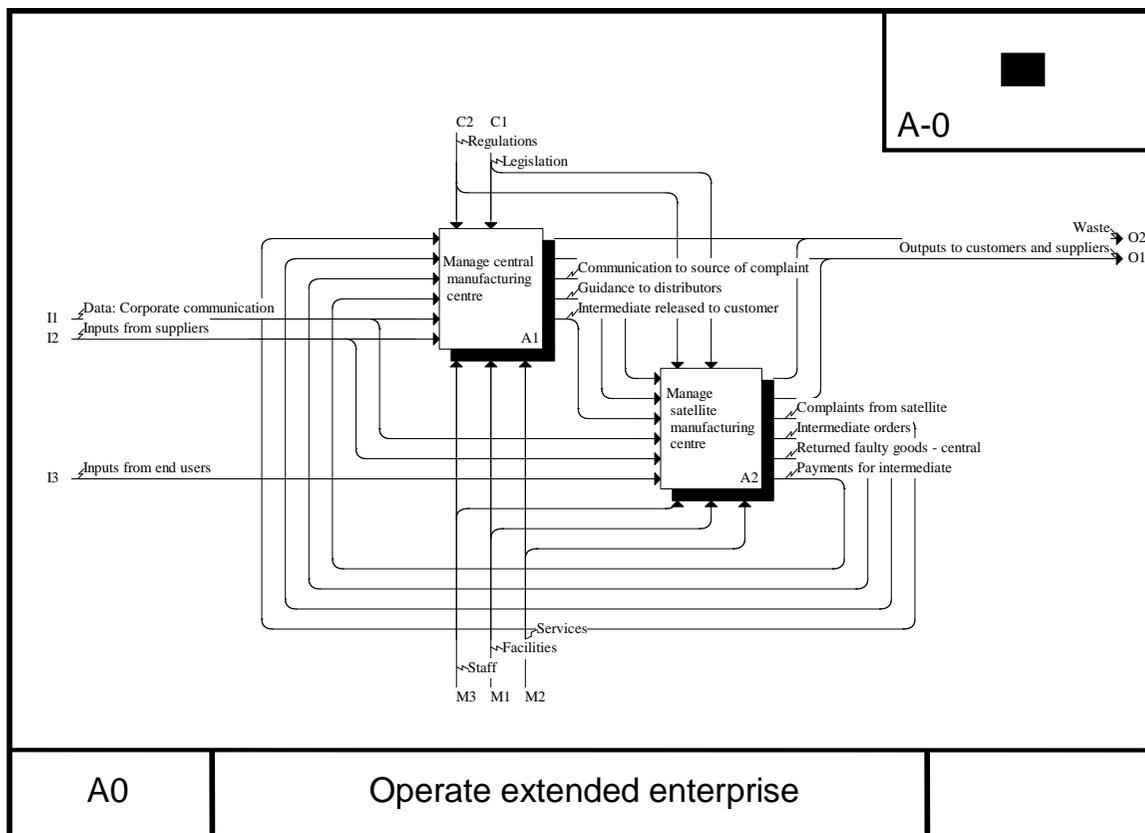


Figure A3. 2: A0 Model of 'to be' operation

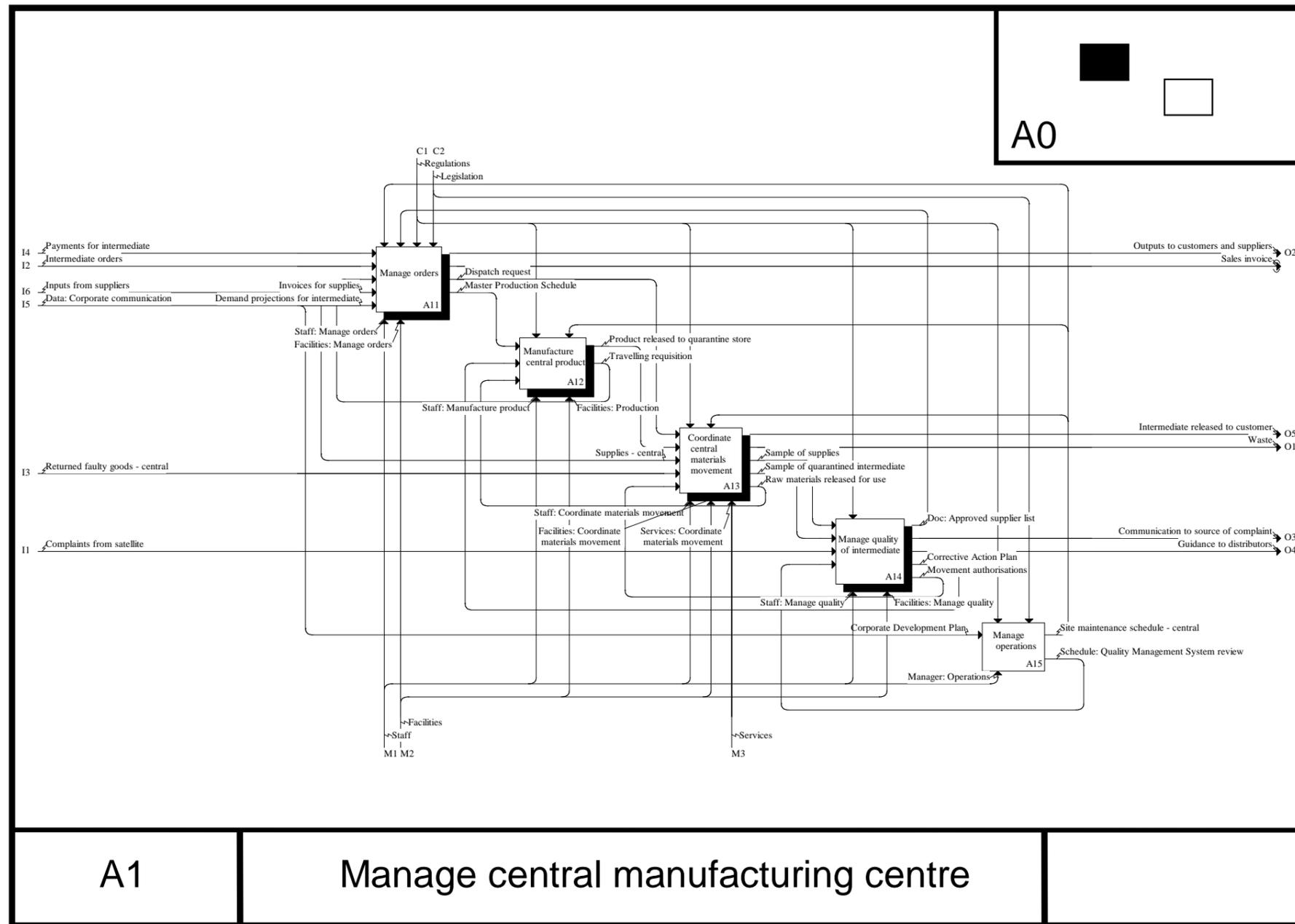


Figure A3. 3: A1 Model of 'to be' operation

Appendices

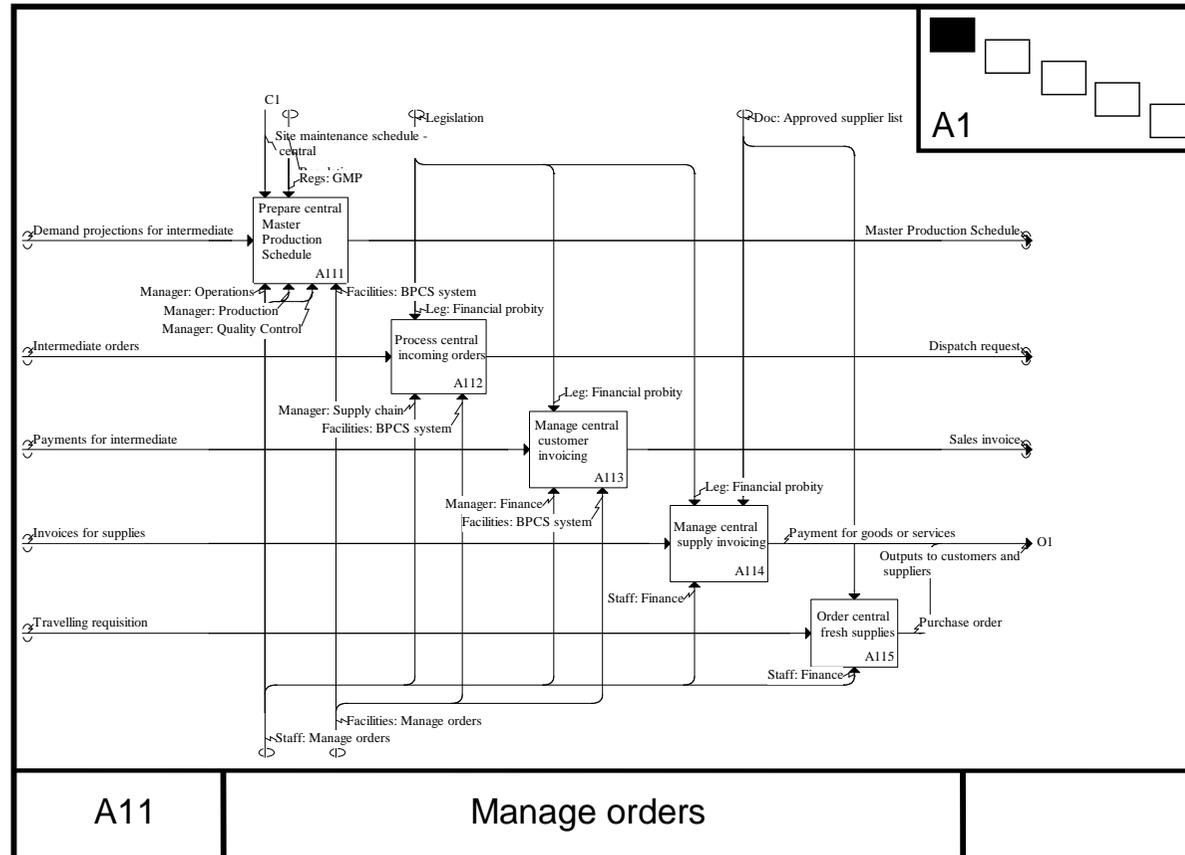


Figure A3. 4: A11 Model of 'to be' operation

Appendices

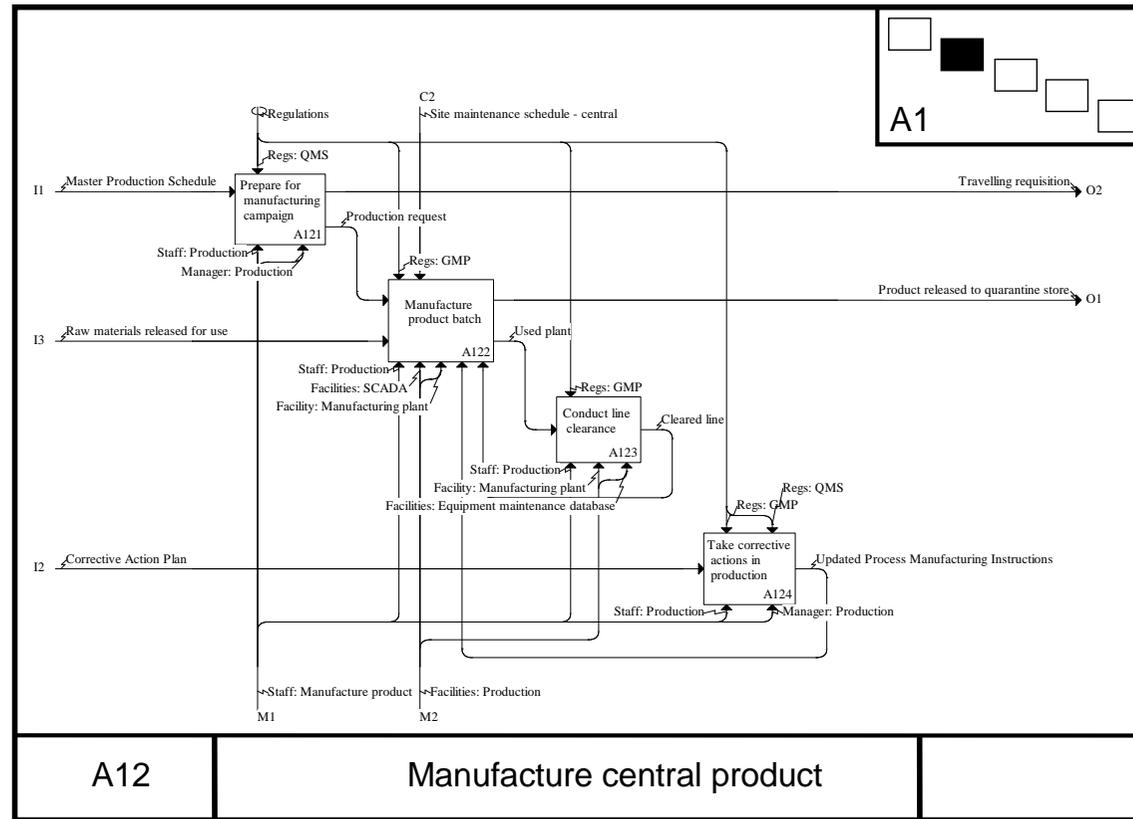


Figure A3. 5: A12 Model of 'to be' operation

Appendices

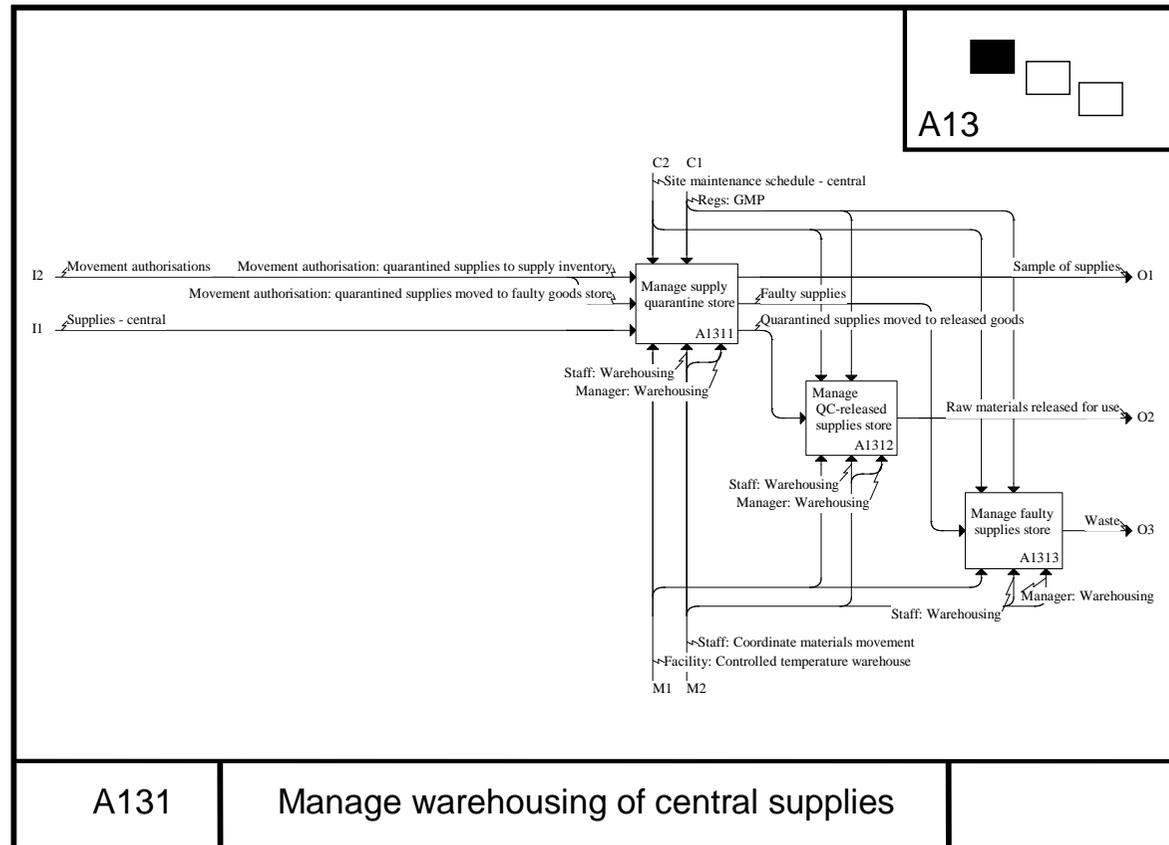


Figure A3. 7: A131 Model of 'to be' operation

Appendices

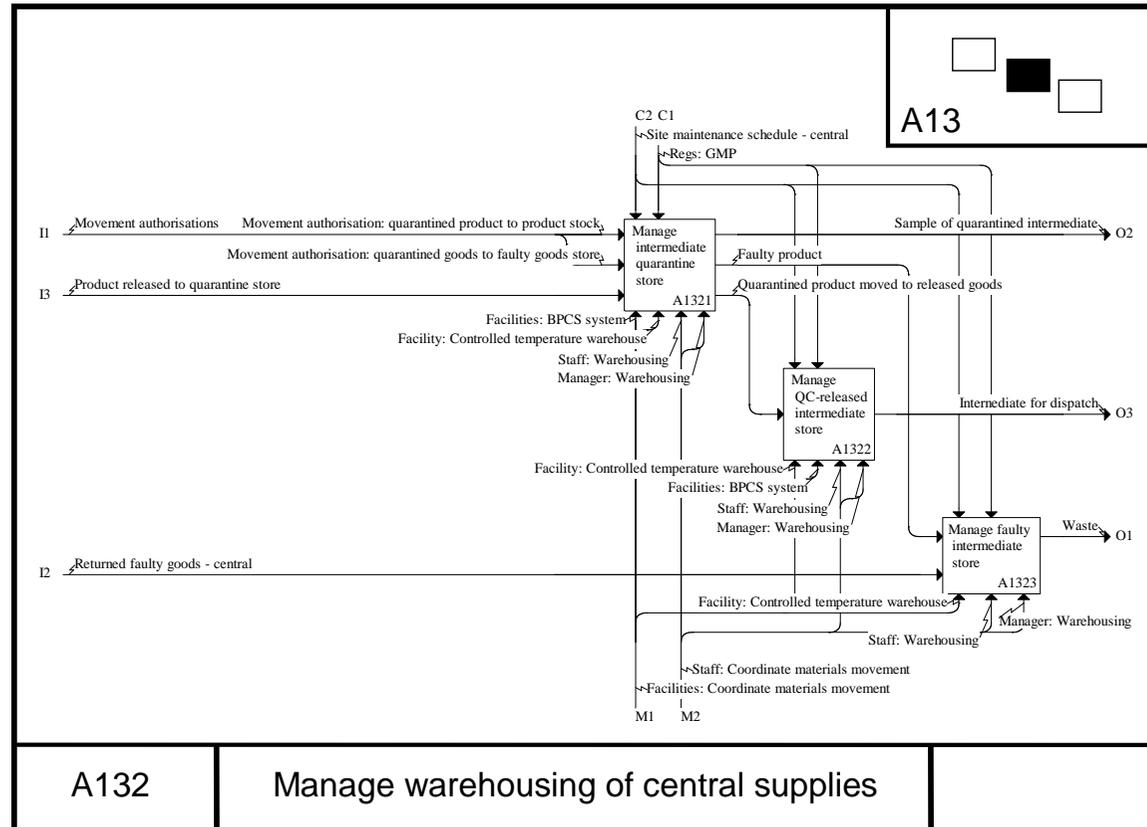


Figure A3. 8: A132 Model of 'to be' operation

Appendices

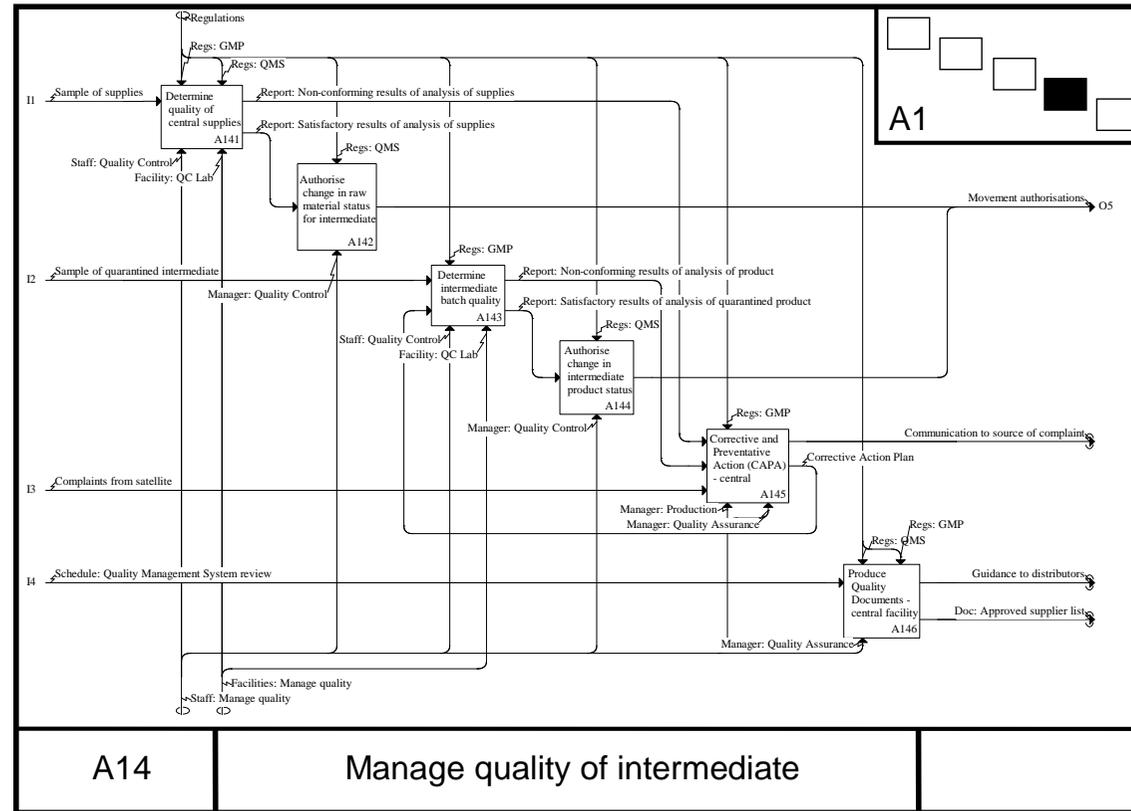


Figure A3. 9: A14 Model of 'to be' operation

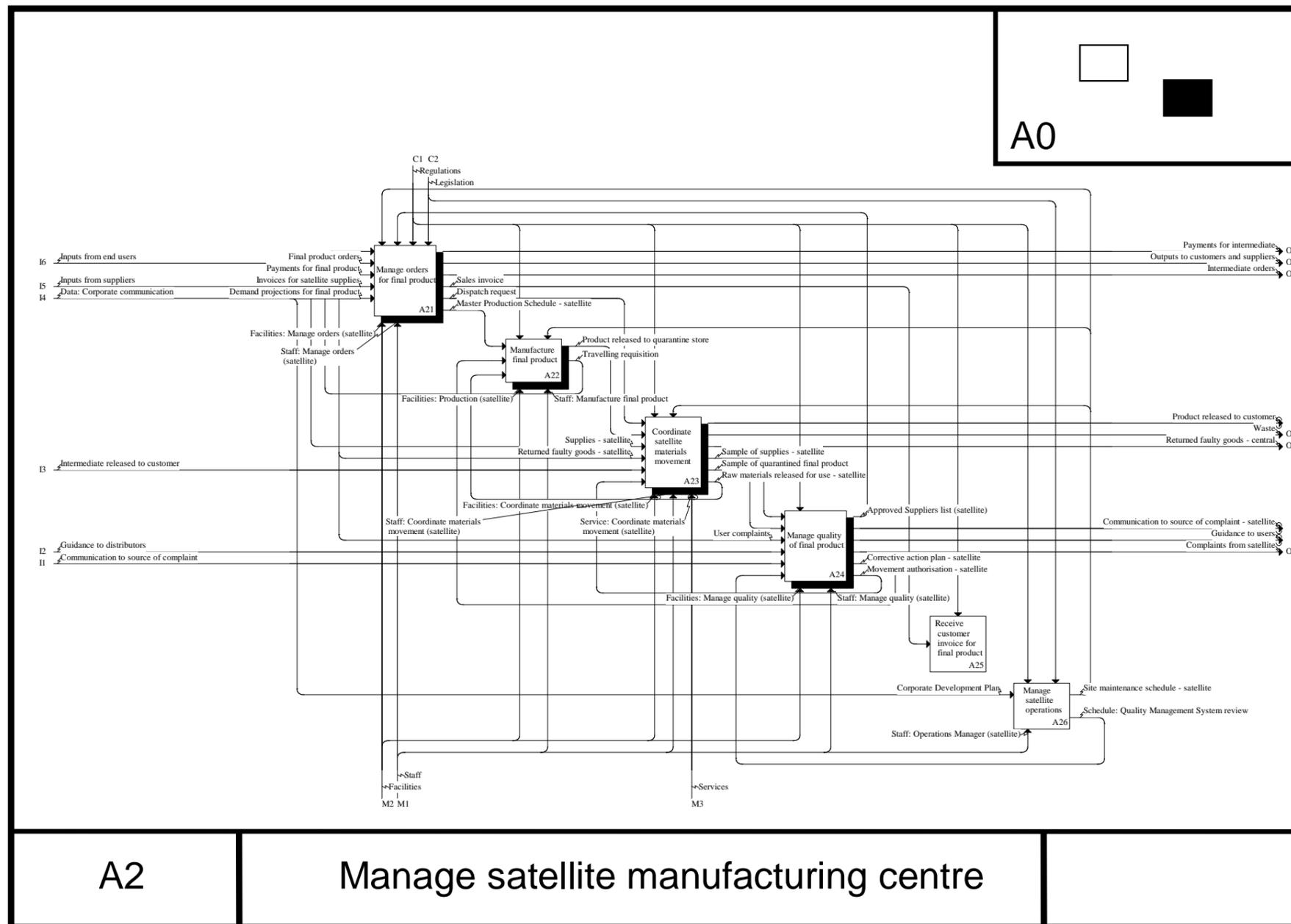


Figure A3. 10: A2 Model of 'to be' operation

Appendices

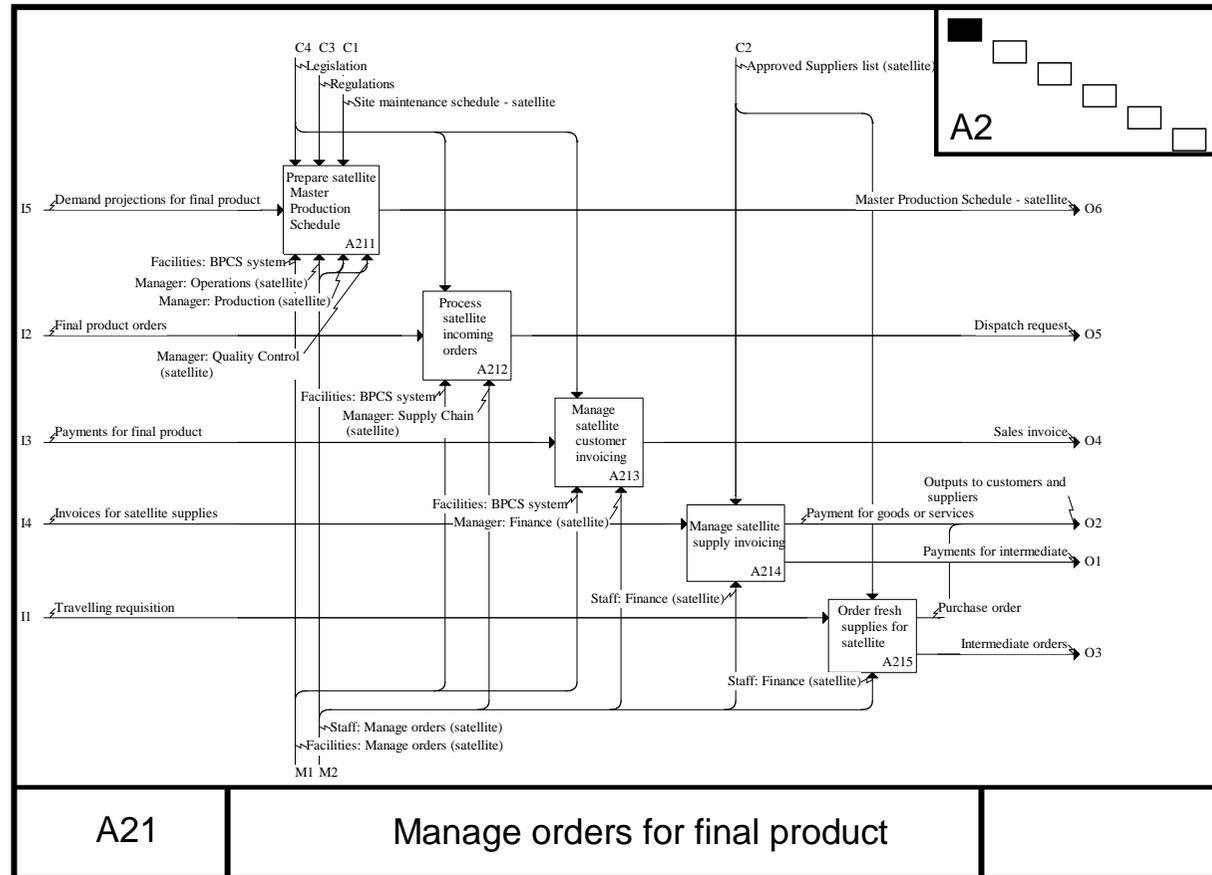


Figure A3. 11: A21 Model of 'to be' operation

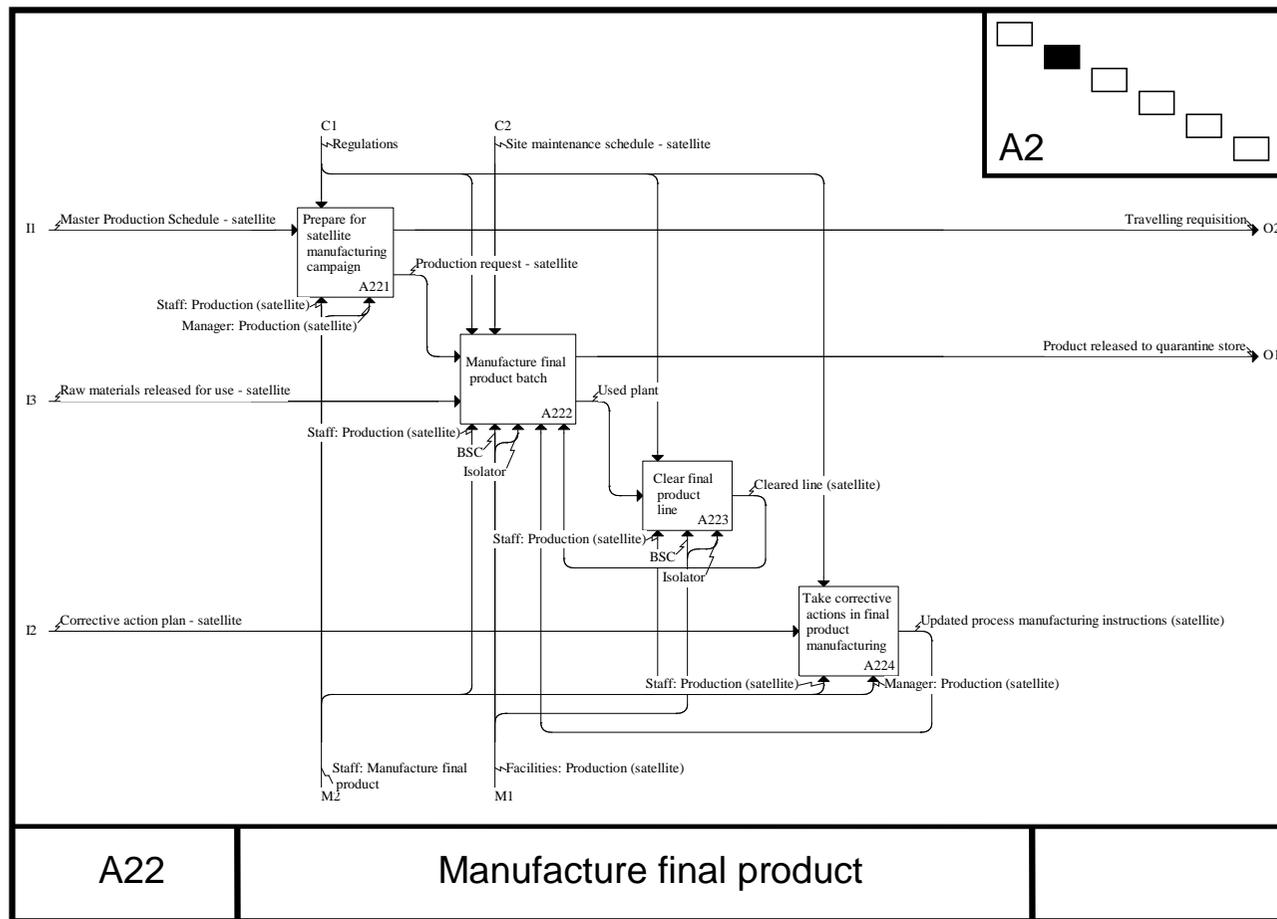


Figure A3. 12: A22 Model of 'to be' operation

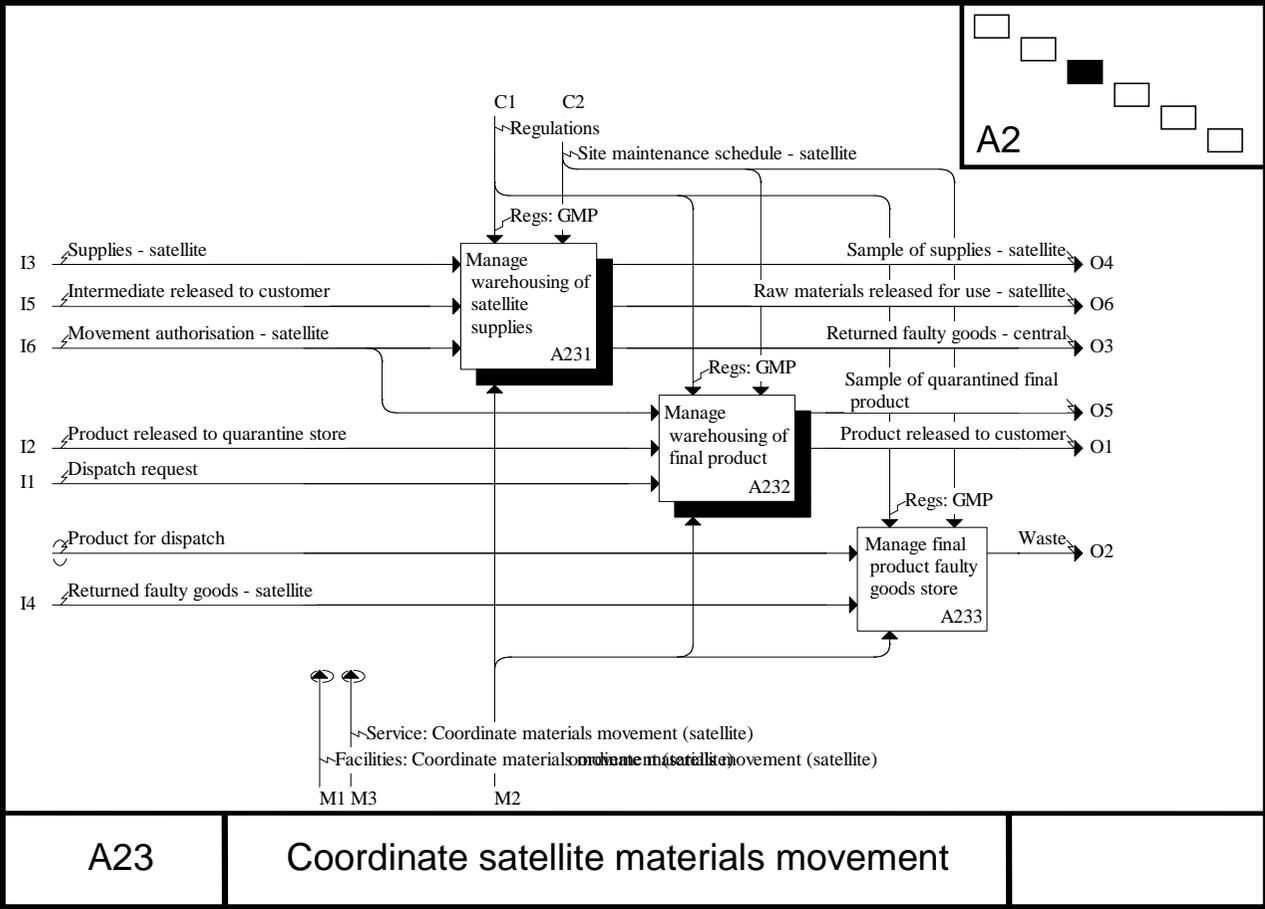


Figure A3. 13: A23 Model of 'to be' operation

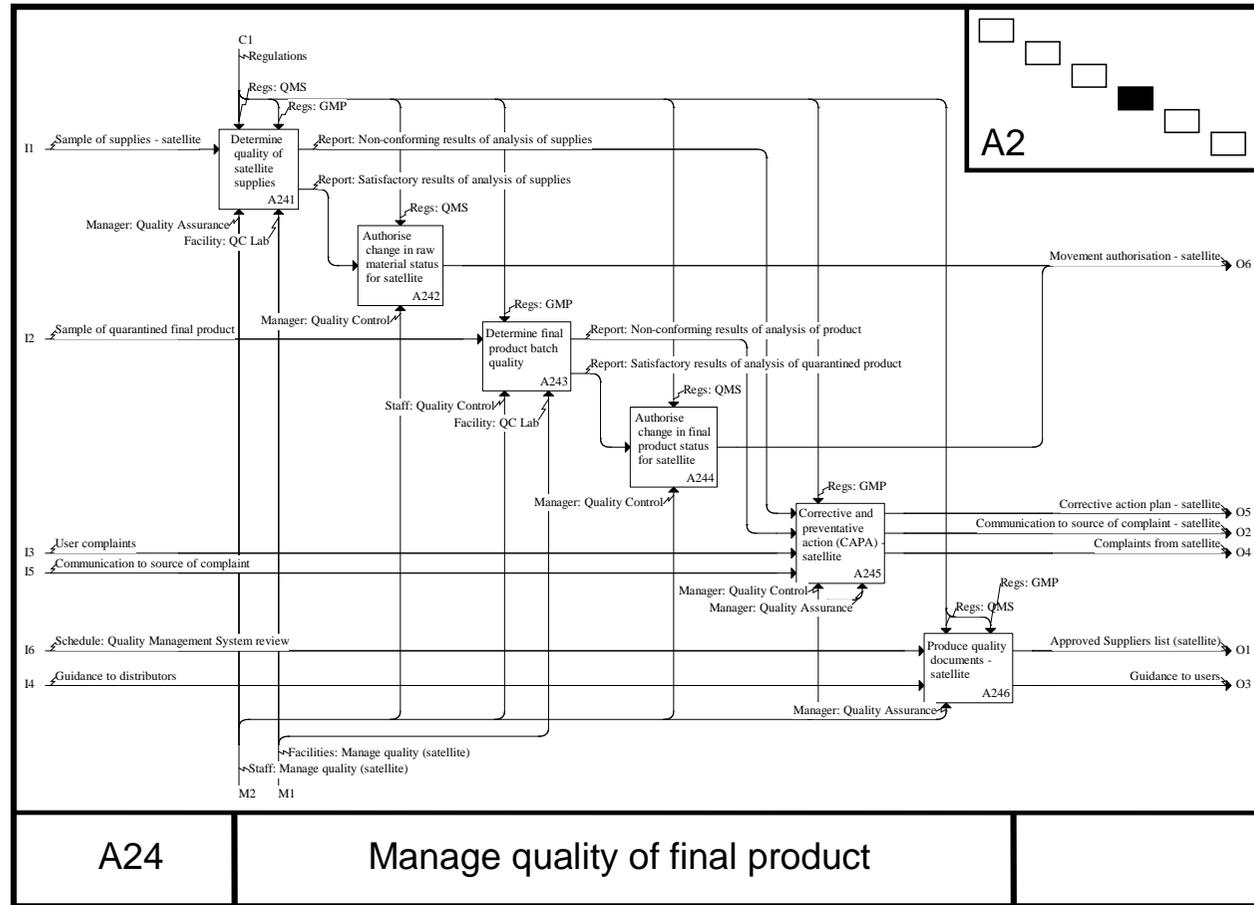


Figure A3. 14: A24 Model of 'to be' operation

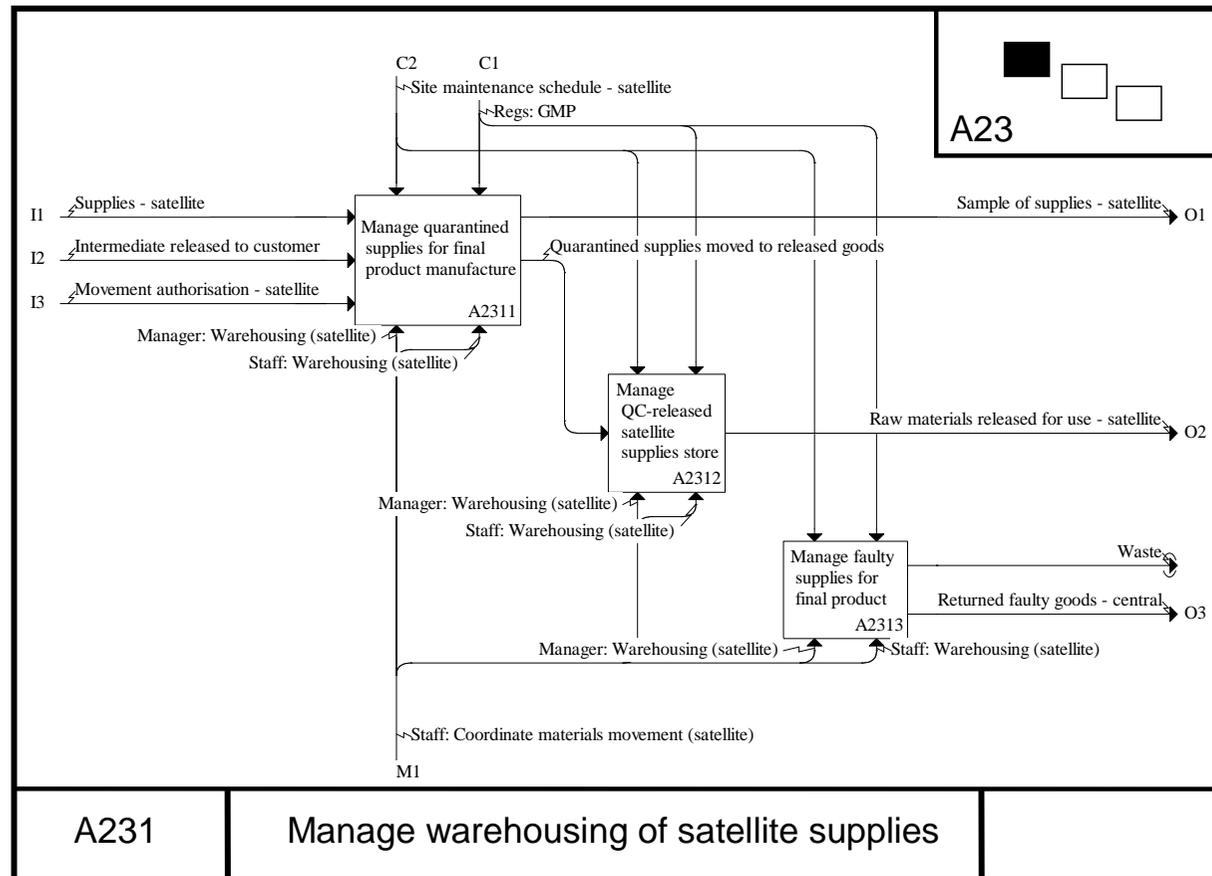


Figure A3. 15: A211 Model of 'to be' operation

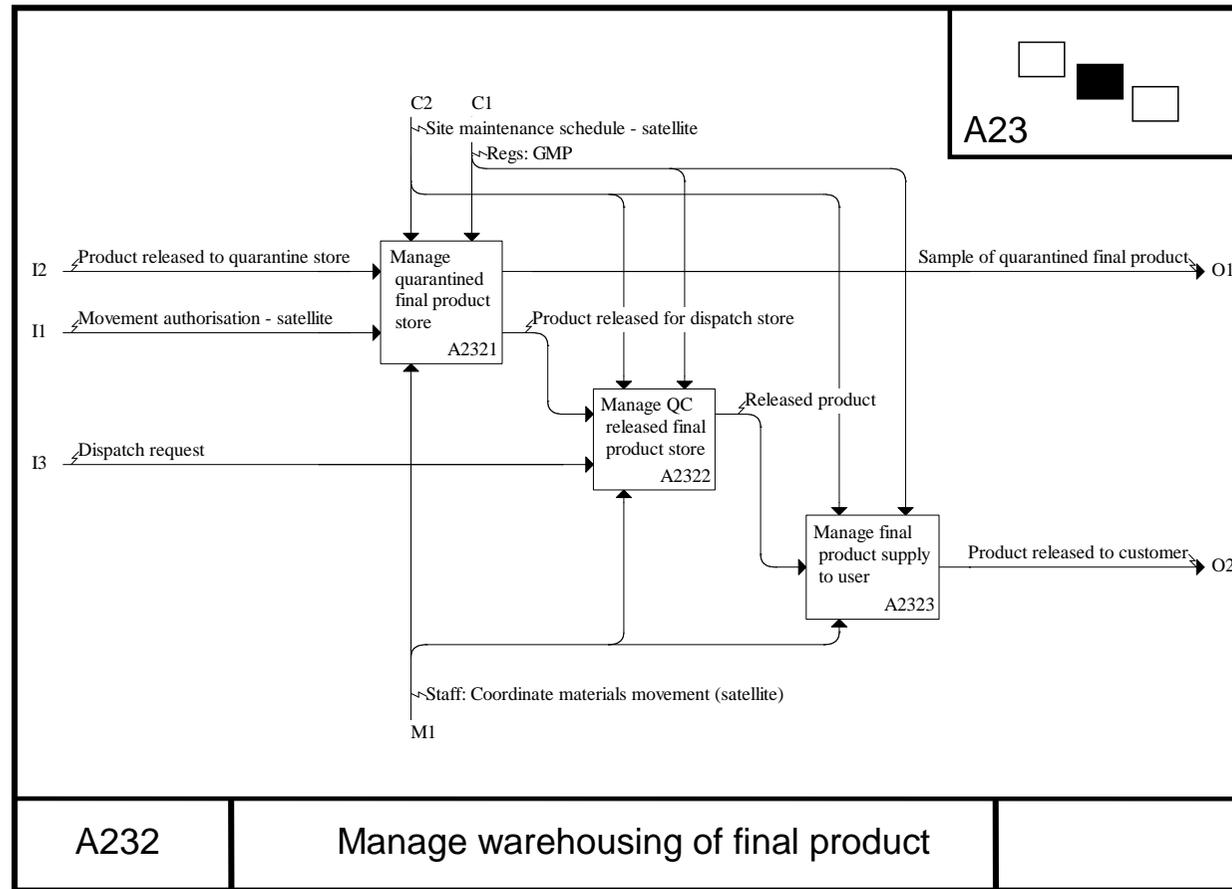


Figure A3. 16: A232 Model of 'to be' operation

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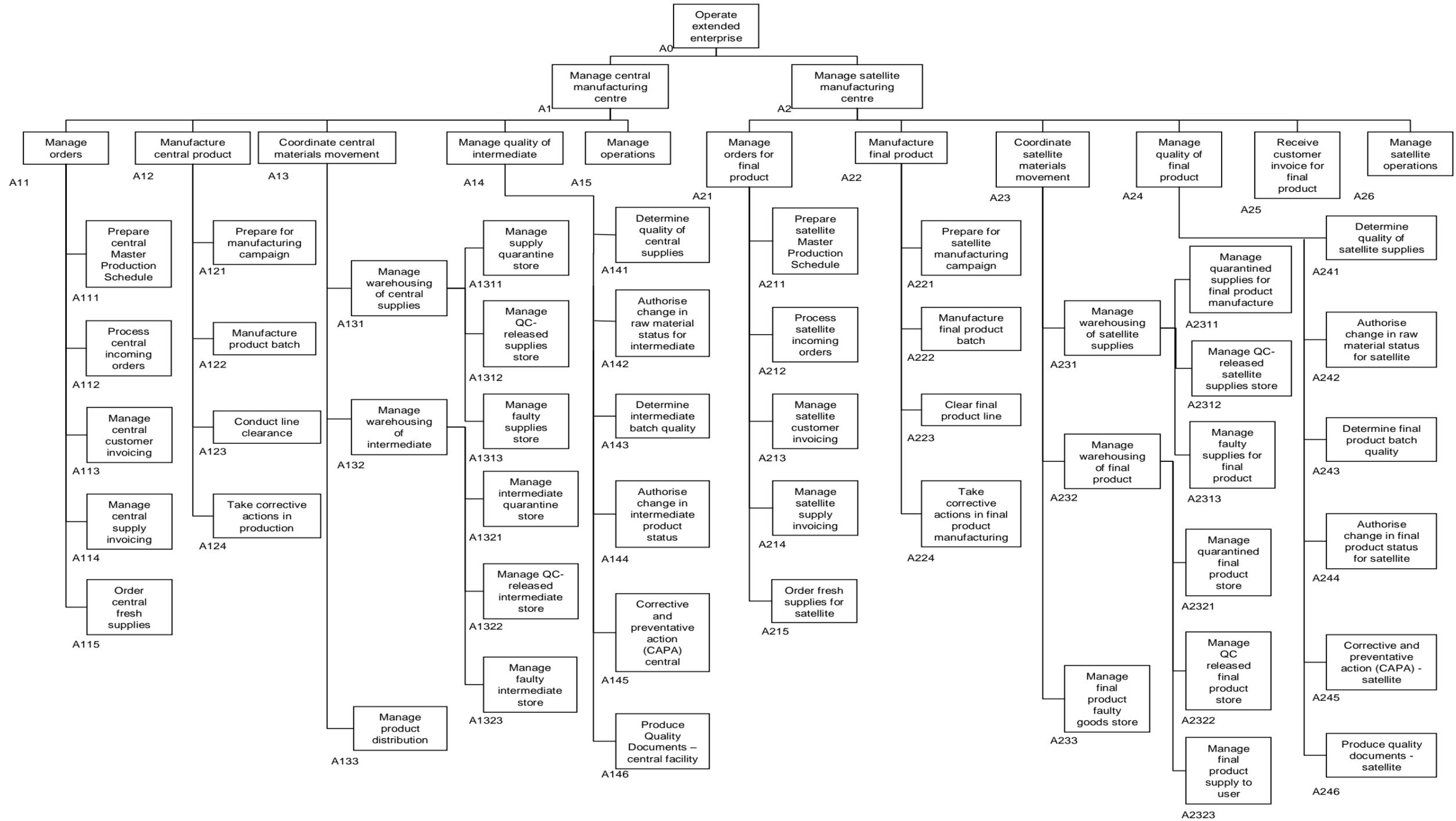


Figure A3. 17: Overview of IDEF0 'to be' model (for exposition only)

Table A3- 1: Node table

A0: Operate extended enterprise

- A1: Manage central manufacturing centre
 - A11: Manage orders
 - A111: Prepare central Master Production Schedule
 - A112: Process central incoming orders
 - A113: Manage central customer invoicing
 - A114: Manage central supply invoicing
 - A115: Order central fresh supplies
 - A12: Manufacture central product
 - A121: Prepare for manufacturing campaign
 - A122: Manufacture product batch
 - A123: Conduct line clearance
 - A124: Take corrective actions in production
 - A13: Coordinate central materials movement
 - A131: Manage warehousing of central supplies
 - A1311: Manage supply quarantine store
 - A1312: Manage QC-released supplies store
 - A1313: Manage faulty supplies store
 - A132: Manage warehousing of intermediate
 - A1321: Manage intermediate quarantine store
 - A1322: Manage QC-released intermediate store
 - A1323: Manage faulty intermediate store
 - A133: Manage intermediate distribution
 - A14: Manage quality of intermediate
 - A141: Determine quality of central supplies
 - A142: Authorise change in raw material status for intermediate
 - A143: Determine intermediate batch quality
 - A144: Authorise change in intermediate product status
 - A145: Corrective and Preventative Action (CAPA) - central
 - A146: Produce Quality Documents - central facility
 - A15: Manage operations
- A2: Manage satellite manufacturing centre
 - A21: Manage orders for final product
 - A211: Prepare satellite Master Production Schedule
 - A212: Process satellite incoming orders
 - A213: Manage satellite customer invoicing
 - A214: Manage satellite supply invoicing
 - A215: Order fresh supplies for satellite
 - A22: Manufacture final product
 - A221: Prepare for satellite manufacturing campaign
 - A222: Manufacture final product batch
 - A223: Clear final product line
 - A224: Take corrective actions in final product manufacturing
 - A23: Coordinate satellite materials movement
 - A231: Manage warehousing of satellite supplies
 - A2311: Manage quarantined supplies for final product manufacture
 - A2312: Manage QC-released satellite supplies store
 - A2313: Manage faulty supplies for final product
 - A232: Manage warehousing of final product
 - A2321: Manage quarantined final product store
 - A2322: Manage QC released final product store
 - A2323: Manage final product supply to user
 - A233: Manage final product faulty goods store
 - A24: Manage quality of final product
 - A241: Determine quality of satellite supplies
 - A242: Authorise change in raw material status for satellite
 - A243: Determine final product batch quality
 - A244: Authorise change in final product status for satellite
 - A245: Corrective and preventative action (CAPA) - satellite
 - A246: Produce quality documents - satellite
 - A25: Receive customer invoice for final product
 - A26: Manage satellite operations

Appendix 4: Criteria and Suppliers for Automation

In order to select suitable target companies a set of criteria was needed against which to screen the prospects. The list that follows is the result of personal brainstorm.

Table A4- 1: Criteria and loadings for company selection (1 = low, 3 = high)

Criterion	Requirement	Loading
Previous experience	Installations in health care Installations for cell based manufacturing	3
Ability to install, validate and support in the US as well as the EU	Previous work to 21CFR11 Documentation in support of product registration	3
Work to GMP	Compliance with EU directive 2001/83/EC	3
Service support	Ability to provide ongoing repair, maintenance and preventative maintenance	1

The following companies were identified from a search based upon the internet, personal contact and networking. The groups used here are natural groupings by target market.

Table A4- 2: Companies concentrating on drug screening applications

Company	Product offering	Website (or other contact)
RTS Life Science International(Harding, Bradford et al. 2002; Timoney and Felder 2002)	This company is one of the earlier ones to access the market. Most of the automation solutions revolve around assay automation and are clearly aimed at drug discovery. However, RTS also offer customised automation. Their base in liquid handling puts them in a good technical position to address cell culture needs.	http://www.rtslifescience.com Northbank, Irlam, Manchester M44 5AY, UK
Zymark Corp. [Bal 2008]	A wholly owned and privately held subsidiary of Berwind Corp. Becoming a leader in microfluidics. Concentrates on drug discovery applications and pharmaceutical testing. Acquired by Sotax in 2008.	http://www.sotax.com
Essen Instruments	Based around high throughput cell screening the FLIPR and IncuCyte products are aimed as off-the-shelf systems for drug discovery companies.	http://www.essen-instruments.com

Table A4- 3: Companies concentrating on automation involving cell culture

Company	Product offering	Website (or other contact)
CRS Biodiscovery (Burlington, MA)	This company became CRS Robotics Corp. in 1994 and went public in 1995. It was renamed Thermo CRS in 2002 when it was taken over by the Thermo Electron Corporation. Their robots played a large part in the work on the human genetic code: Cytomat range of incubators, stackers, software solutions, cellular imaging.	http://www.thermo.com/com/cda/article/general/1,,352,00.html
Integra Biosciences	A well-known supplier offering a wide range of liquid handling solutions and accessories to cell culture.	http://www.integra-biosciences.com/index.html
Sterogene Bioseparations, Inc.	As the name suggests this company concentrates on one aspect of production: cell product separation only.	www.sterogene.com
Greiner Bio-One	Plates and scanners for drug discovery and/or cell screening.	http://www.greinerbioone.com/en/start/
Beckman Coulter	Flow cytometry using the Vi-Cell XR is an example of the main interest in automation. This device for live cell determination is fitted with an autosampling apparatus. (Primary screening using the Biomek® system is another example.)	http://www.beckman.com/eCatalog/CatalogItemDetails.do?productId=13068
Molecular Devices	Part of MDS Analytical Technologies. Product offering is mainly in rapid imaging, patch-clamp analyses and electrophysiology.	http://www.moleculardevices.com

Table A4- 4: Companies able to address many different automation jobs

Company	Product offering	Website (or other contact)
Labman Automation Ltd.	Bespoke and system based automation. wide variety of projects. None specifically for cell culture.	http://www.labman.co.uk
The Automation Partnership [Christopher, David et al. 2004]	A company that sun out from The Technology Partnership. Famously introduced liquid handling for roller bottle manufacture of cells for Advanced Tissue Sciences in the form of the CellMate® manipulator. Support remedi (Univ. of Loughborough) with CompactSelect® apparatus.(Thomas, Chandra et al. 2008)	http://www.automationpartnership.com
The Technology Partnership [Fleck 2007]	Parent company of The Automation Partnership. Created arguably the world’s largest roller bottle manufacturing plant for Amgen.	http://www.ttp.com
Agilent Technologies	Agilent offers a variety of standalone systems through to complete workstations. The biggest arrangements are most closely likened to microfactories i.e. automated input/output to set-ups within enclosures e.g. for screening or reagent manipulation.	http://www.chem.agilent.com/en-US/Products/Instruments/automation/Pages/default.aspx
Maxon Motors	An international organisation with an emphasis on drives and high performance computer integrated manufacturing. Surgical robotics is one important field and Maxon Medical manufactures to ISO 13485: 2003 (ceramics).	http://www.maxonmotor.co.uk
Zinsser Analytic	Zinsser offer a wide variety of automated platforms for e.g. liquid handling, blending, tissue homogenisation, cell harvesting. They do not appear to invite enquiries about custom automation. they also supply consumables and reusable flasks (e.g. glass roller bottles) for cell culture.	http://www.zinsser-analytic.com
Tecan	Tecan offers a range of sample handlers and liquid handling devices. They have built bespoke apparatus for e.g. Abbott Laboratories.	http://www.tecan.com
Millipore	Millipore supports conventional bioprocessing through automation of the stages typically found in a fermentation system development pathway. This means that they work with multiwell plates, seed and feed systems, recovery and in-line analysis.	http://www.millipore.com

Table A4- 5: Companies that exploit specific technology concepts

Company	Product offering	Website (or other contact)
Cytogration	Cytogration is owned and operated by Brandel, Inc. The Company created automated equipment that would facilitate use of the Caco-2 cell line to make membranes that are used in assessment of novel pharmaceuticals.	www.cytogration.com BRANDEL 8561 Atlas Drive Gaithersburg, MD 20877 USA
Sarstedt	Founded in 1961. Manufactures nearly all its own stock. Mostly consumables, diagnostics and analytical equipment. Markets and sells its own products. Sample processors such as the AutoMate®	http://www.sarstedt.com/php/main.php?newlanguage=en
Nikon	BioStation CT and BioStation IM are examples of Nikon's stock-in-trade which is live cell imaging during culture.	http://www.nikoninstruments.com/Products/Cell-Incubator-Observation/BioStation-IM
Eppendorff	Contribution is largely restricted to liquid handling automation at a small scale e.g. dispensing, plate handling and PCR management.	http://www.eppendorf.de/int/index.php?l=131&action=products&contentid=52
Matrical Biosciences	With a focus on high-throughput systems the company offers cell culture automation e.g. through their product MACCS®.	http://www.matrical.com

From the tables above a short list was derived containing only those companies with a cell culture history and the ability to produce more than a restricted set of products.

These are tabulated and scored in Table A4- 6.

Table A4- 6: Scoring of shortlisted companies_(Scores w.r.t. prospects of -1 = poor, 0 = neutral or no evidence, +1 = good)

Criterion (on appearances, subject to verification)	Loading	Companies with score + (loaded score)				
		RTS	TAP	TTP	CRS	LabMan
Previous experience	3	0 (0)	+1 (+3)	+1 (+3)	+1 (+3)	0 (0)
Ability to install, validate and support in the US as well as the EU	3	+1 (+3)	+1 (+3)	+1 (+3)	0 (0)	0 (0)
Work to GMP	3	0 (0)	+1 (+3)	+1 (+3)	0 (0)	0 (0)
Service support	1	+1 (+1)	+1 (+1)	+1 (+1)	0 (0)	0 (0)
Totals (loaded)		4	10	10	3	0

Appendix 5: Feedback on the thesis

Page 1 of 1

Medcalf, Nick

From: David Williams [D.J.Williams2@lboro.ac.uk]

Sent: 11 February 2011 08:42

To: Medcalf, Nick

Subject: Thesis Overview and Precis Review

Dear Nick,

Many thanks for the opportunity to overview your thesis and to review the précis that you handed over to me. This of course covered by the NDA we have in place with S&N.

I do strongly endorse your distributed "empowered clinic" model, it echoes many of my own thoughts as a consequence of our work in large scale stem cell culture automation – one of our unique capabilities - with the TAP Compact Select and in suspension culture, and transport of cells and consequent potential damage. This is one of the reasons I regard our collaborative project with TAP on Near Patient Cell processing as so important.

It is appropriate to briefly record some of the background thinking that has driven me to this thinking. This of course includes the scale of investment required from Pfizer to install the supply chain for inhaled insulin before launch. This is widely thought to have significantly contributed to their recent issues. You will recall that I was responsible for building one of the two device supply plants while at Bepak. At the time it was the largest medical device cleanroom in Europe. Also Pfizer built TWO such plants, one in the EU and one in the US for security of supply, doubling the capital requirement.

We are also thinking very hard about the business model for our own facility and talking hard with the Gene Therapy GMP unit of UCL which is managed by one of my old PhD students Eugene Arulmuthu. Eugene is effectively an outstation of NHSBT at Bristol and falls under their Quality System and QP. This very strongly echoes components of your model and is strongly influencing our thinking as we progressively move our GMP automated facility out of shelter.

We have a Business Plan competition as part of our Doctoral Training Centre in Regenerative Medicine, this allows me to rapidly explore business models that may be viable. One of the most interesting ones that arose this year was for an empowered clinic model based around adipose stem cell treatments for pelvic floor issues prepared using the Cytori device and scaled out clinic by clinic. This is very close to your model.

One of the things that does strike me however that is an area where perhaps your model could be improved is to explore the costs and risks associated with the imposition of a uniform Quality System across many multiple sites that are not used to operating in a regulated manufacturing culture and that do not have the kind of experience that you and I have in Quality Engineering and process design and improvement for cell culture. I think this will be a real challenge.

I hope all goes well with the closing stages of writing the thesis and that you enjoy the oral.

With best wishes

David

David J Williams FEng DEng PhD
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Wolfson School of Mechanical and Manufacturing Engineering
Director of the Research School of Health and Life Sciences
Director of the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine
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15/03/2011

Figure A5- 1: Feedback from Professor David Williams