CHAPTER 22

Decisions in the Development Lifecycle of Cell and Gene Therapies*

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INTRODUCTION

Since the approval of Transcyte in 1997 (Parenteau, 1999), the field of regenerative medicine has witnessed a wave of products achieve regulatory approval. The diversity of these products has varied widely, evolving from tissue-engineered products mostly for wound care to a mix of tissue-engineered and cell- and gene-based therapies. Remarkably, the investment into cell and gene therapies by large pharmaceutical companies has been increasing, and several multi-billion transactions were implemented between 2017 and 2018 in the field of chimeric antigen receptor (CAR) T cells.

However, historically very few advanced therapeutic medicinal products (ATMPs) have achieved commercial success. Table 22.1 shows the ATMPs that have been approved in the European Union (EU) up until May 2018. Out of the 10 regenerative medicine products approved in the EU, three (ChrondroCelect, Glybera and Provenge) were withdrawn because of commercial reasons and one (MACI) was suspended by the European Medicines Agency (EMA) due to the closure of the authorised manufacturing facility. The company did not seek renewal of its marketing authorisation (MA) (European Medicines Agency, 2014). Moreover, multiple products, including Strimvelis (Yano et al., 2015), were divested after launch by their original developers. A few of the indications targeted by the developers of the new products were so rare that these emerging products had high commercial prices, and the number of commercial patients remained very small. For example, Strimvelis only secured its first commercial patient 10 months after its approval (Yano et al., 2015), whereas Glybera, which was introduced at a price of about €1 million, recorded only one sale in 3 years and thus was removed from the European market in 2017 by uniQure B.V. (Amsterdam, the Netherlands) (Regaldo, 2016).

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Table 22.1 Table Showing Approved Advanced Therapeutic Medicinal Products in the European Union (Until May 2018) (European Medicines Agency, 2018a).

#	Product	Marketing Authorisation (MA) Holder	Date of Approval	Withdrawn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2	ChondroCelect	TiGenix N.V. (Leuven, Belgium)	November 2009	MA withdrawn at request of MA holder on November 30, 2016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

These commercial challenges highlight the importance for ATMP developers to make, given the risk and uncertainty, better and more informed investment and manufacturing decisions. Strengthening these approaches will lead to stronger business plans, where efficiency gains can be used to derive increased cost benefits, thus enhancing the sustainability of the emerging biotechs supporting their developments.

Decisional tools or decision-support tools are tools that can be used to support complex decision-making and problem solving. It is worth noting that the refinement of decision-making processes through repeatable models allows continuous feedback and subsequent continuous improvement. These tools are widely used by strategists, for example, at consulting firms, as a methodical and quantitative approach to address common biases in human judgement and decision-making (Rosenzweig, 2014).

As a relatively new therapeutic modality, whilst cell and gene therapies face different obstacles, similar decision-support techniques can be applied to support complex decision-making in investment, product development and subsequent manufacturing. Models tailored to industry requirements should be designed with reasonable and industry-relevant assumptions, especially considering regulatory needs, to realise the power of decision models.

In this chapter, we discuss the challenges in the commercialisation of cell and gene therapies and the decisions made along the development pathway, to inform a proposed systematic approach to facilitating these decisions.

Challenges in the Commercialisation of Cell and Gene Therapies

Since the approval of Transcyte in 1997, the field of regenerative medicine has seen a wave of products achieve regulatory approval (Fig. 22.1), with an increasing diversity of products from only tissue-engineered products to an array of tissue engineering and cell- and gene-based therapies.

The cost of treatments range from $308 for 56 cm^2 of wound care treatment in South Korea (information provided by Tego Science, South Korea) to €1.1 million for UniQure's Glybera, a niche gene therapy indicated for lipoprotein lipase deficiency (Ylã, 2012). As these therapies are significantly more expensive to produce than conventional therapeutics, the loss of a batch can result in a substantial financial loss for the manufacturer. Ensuring a robust process for the manufacture and delivery of a therapy thus constitutes a critical success factor.

Reimbursement for cell and gene therapies has been cited as one of the biggest hurdles for the clinical adoption of these therapies (Caplan et al., 2017; Couto et al., 2012). Similarly, in the multistakeholder assessment of barriers to adoption of cell therapies conducted by Davies et al. (2014, 2017), reimbursement has been found to be recognised as one of the biggest barriers to adoption by researchers, clinicians and commercial experts worldwide. Whilst it is possible to implement a value chain that follows a more traditional pharmaceutical drug-development approach for allogeneic therapies, autologous therapies require more innovative pricing strategies (Majewski, 2018; Abou-El-Enein et al., 2016).

Autologous Versus Allogeneic Products

Autologous therapies are based on patients' own tissues or cells. The first step constitutes harvesting target cells from the patient, processing them, and subsequently administering them to the patient. In contrast, allogeneic therapies are derived from healthy universal donors and can be produced in large batches. Autologous therapies, including mesenchymal stem cells (MSCs), represent a large proportion of approved therapies, as researchers and clinicians initially focused on autologous treatments for safety and ethical reasons (Le Blanc and Pittenger, 2005). From Li et al.'s stem cell clinical trial landscape

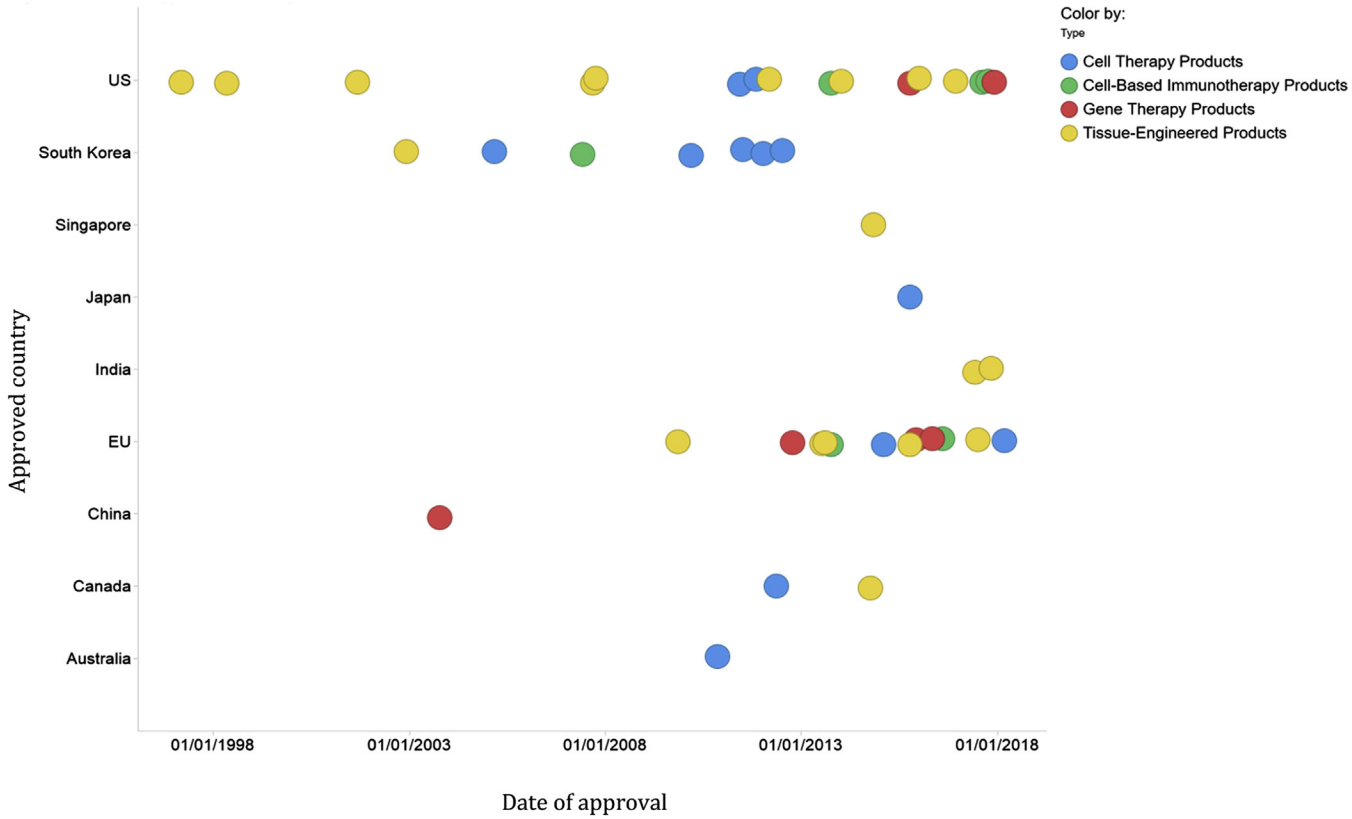

Figure 22.1 Regenerative medicine approvals from 1997 to present.

exercise published in 2014, the number of autologous therapy trials is consistently greater than the number of allogeneic ones from 1992 to 2012: out of the 907 trials with identified graft donor source at the time of that analysis, around 65.4% where conducted using autologous cells or tissues (Li et al., 2014). Autologous therapies cannot benefit from economies of scale in the same way that antibodies and small molecules do. The two types of therapies each have their own unique set of challenges.

Using the conceptual framework proposed by Mason and Hoare (2007) for regenerative medicine bioprocessing, a summary of the commercialisation challenges for autologous and allogeneic therapies is presented in Table 22.2.

A second critical success factor can be derived here, whereby off-the-shelf components and service components of the new therapies need to be well identified and optimised by having them provided to the market by the party most adapted to providing them. In many ways, autologous cell therapies depend on both creative and innovative business strategies, implementing innovative manufacturing and service models for commercial success.

Product Withdrawal and Divestment

The number of cases of product withdrawals and divestment in the ATMP industry are to this date significant. Several companies, from large and midsize pharmaceutical companies (Shire plc (Dublin, Ireland) (Anon, 2014) and GlaxoSmithKline plc (London, United Kingdom) (GSK, 2017)) to small enterprises (Dendreon (Seattle, United States), Advanced Tissue Sciences (San Diego, United States) (Pangarkar et al., 2010)), have experienced bankruptcy or experienced difficulties in product development. For Dendreon, the lack of a sound reimbursement strategy is just one of the many reasons for its inability to achieve commercial success. Clinicians were deterred from administering the drug, not only due to the logistical complexity but also due to cost-effectiveness and reimbursement considerations (Staton, 2011). As emphasised earlier in this chapter, 3 out of 10 regenerative medicine products approved in the EU were withdrawn due to commercial reasons and one was suspended by the EMA due to the closure of the authorised manufacturing facility, which drove the company into deciding not to renew its MA (European Medicines Agency, 2013). This is not surprising, as a similar trend was experienced at the launch of the monoclonal antibodies (mAb). Because of lack of understanding of the biology and mechanism of action, early mAb products experienced serious safety issues and subsequently investment backlash (Marks, 2012). Vertès and Dowden (2016) summarised the learnings from the mAb development that can also be applied to stem cell therapeutics. Generating meaningful impact through the development of transformational treatments to meet unmet medical demands and meeting demand through robust logistics and manufacturing platform technologies whilst recognising clinical adoption and regulatory barriers are a key to the successful translation of novel therapies from benchtop to bedside (Vertès and Dowden, 2016).

Table 22.2 Challenges of Commercialisation of Autologous and Allogeneic Therapies.

	Challenge	Allogeneic	Autologous
Scientific	Donor source	**Ethical issues** Cell and tissues (such as umbilical cord) must be 'ethically sourced' (Corsano et al., 2015). **Establishing cell banks** A two-tiered cell banking system and cryostorage space is required. Immunophenotyping, differentiation potential and karyotyping are required (Cooper and Viswanathan, 2011). **Risk of transferring pathogens from donor to recipients** (Malik, 2012)	**Regulated sites of collection** Tissue/ cell procurement can only be done in regulated sites, hence limits the widespread use of autologous therapies (Ram-Liebig et al., 2015). **Variability between patients** Intrinsic variability in the cells/tissues collected impacts the cell expansion phase and final product quality (Calmels et al., 2018; Harrison et al., 2018). Novartis recently reported that the cell variability impacted the final viable cell percentage causing it to fail, meeting the stringent commercial specifications (Palmer and Sagonowsky, 2018).
	Product understanding	**Complex therapies require more product understanding for definition of critical process parameters and quality attributes** Use of a target product profile approach for aligning the process with the desired product to overcome process development–related issues such as high cost of goods (COGs), poor product characterisation, process inconsistencies and product limitation (Campbell et al., 2015; Lipsitz et al., 2016).	
	Safety and efficacy	**Risk of immunological rejection** Whilst allogeneic mesenchymal stem cells are shown to modulate immune responses (Aggarwal, 2005), other cell types may require more elaborate (and complex) genetic modification techniques to lower chance of rejection (Yang et al., 2015).	**Efficacy related to the quality of source material** (Palmer and Sagonowsky, 2018) **Better clinical trial designs** (Corbett et al., n.d.)

Technological	Cell expansion	**Lot-size challenges** Traditional planar cultures are labour intensive and the process is not robust, hence the requirement of better cell culture technologies and methods (Rowley et al., 2012).	**Expanding to adequate cell numbers and viability** Dependent on patient cell quality as mentioned above.
	Scale-up/out	**Centralised facility** Traditional pharma scale-up model (Medcalf, 2016)	**Decentralised model** Complex supply logistics, small lot sizes, short shelf lives of products, limited time available for transport of cells from patients and therapy to patient are drivers for decentralised small facilities. However, establishing product comparability between sites requires expensive validation and clinical qualification tests (Hourd et al., 2012, 2014; Harrison et al., 2018).
	Raw and ancillary material	**Media supply (serum or serum-free)** Changes in serum type impact cell expansion and final product quality (Smith and Brindley, 2017). **Genome-editing materials** The main ways of genome editing include transcription activator-like effector nucleases, zinc finger nucleases, CRISPR/Cas system and viral vectors (Maeder and Gersbach, 2016). Viral vector shortages anticipated by industrial experts due to the increase of cell and gene therapies (Michael MacRae, 2018).	
	Technology options	**Large-scale cell culture** Control of oxygen, nutrients, fluid flow, mass transfer and shear becomes more difficult as scale increases, and these in turn impact the cell quality (Abbasalizadeh et al., 2017). **Limited downstream technology options for larger scale** (Abbasalizadeh et al., 2017)	**Small-scale cell culture** Require more automation and process integration to reduce manual labour and errors to achieve better process robustness (Harrison et al., 2016; Mock et al., 2016).
	Facility design	**Similar to biopharma large-scale facilities**	**Cross-contamination risks for parallel production** Facility designs should prevent cross-contamination so that multiple patients' cells are handled at the same time. Other risk mitigation strategies, e.g., time segregation, can also be employed (Chen et al., 2017).

continued

Table 22.2 Challenges of Commercialisation of Autologous and Allogeneic Therapies.—cont'd

	Challenge	Allogeneic	Autologous
	Quality control (QC) and characterisation	**Product characterisation** Development of appropriate potency assays (Bravery et al., 2013)	**Batch-to-batch variability** Development of appropriate potency assays (Bravery et al., 2013) **QC tests for each batch** Time and cost of QC tests for each batch (for each patient) (Brandenberger et al., 2011)
	COGs	**Relatively lower** (Malik, 2012)	**Higher COGs for personalised treatment** Does not benefit from economies of scale, and QC tests have to be conducted for each batch (Malik, 2012)
	Product storage and distribution	**High cost of inventory** Because of cryogenic storage requirement. For products that are not cryopreserved, the shelf life is short (discussed in next section) (Abbasalizadeh et al., 2017). **Challenging cold and ultracold chain distribution** (Donnell et al., n.d.)	**Challenging cold and ultracold chain distribution both for cell collection and delivery** (Donnell et al., n.d.)
Commercialisation	Partnering opportunities	**Less incentive to outsource/ partner**	**Outsourcing to contract manufacturing organisations** Complex logistics and cost considerations drive outsource decisions **Partner/outsource to regional companies** The service model and potential risks of the therapies drive partnering decisions with companies in foreign markets as more training is required at the point of delivery (Kite Pharma, n.d.; Wuxi AppTec, 2016).
	Business model	**Off-the-shelf business model** (Abbasalizadeh et al., 2017)	**Service-based business model** (Abbasalizadeh et al., 2017)

PARTNERING AND CAPACITY PLANNING DECISIONS

A common strategy for companies is to lease or build facilities where the technology was spun out (from universities) or invented and to subsequently seek contract manufacturing capacity in alternative locations. Because of geographical and supply chain constraints, as well as capital expenditure (CAPEX) considerations, companies are unlikely to build many facilities but rather will tend to choose to rely on local CDMOs to perform certain manufacturing functions, at least until the regenerative medicine arena matures sufficiently to decrease technology and market risk to the point where large CAPEX for manufacturing facility is justified. Strategic advantages, including not only building of internal know-how but also capacity access and control of reputational risk, are enabled in this construct through close monitoring of product quality and demand realisation. Novartis, for example, opted to build their own facility to cater for the US demand for their autologous CAR-T therapy (estimated to be around 600 patients annually) (Ferreira, 2018) and use contract manufacturers to serve the European and Chinese demands (Nawrat, 2018; Anon, 2017). Bellicum Pharmaceuticals (Houston, United States) also plans to implement similar approaches. In their 2016 annual report, Bellicum reported to have leased an additional 30,400 square feet of manufacturing suite space in Houston and undergoing construction for in-house manufacturing to meet US clinical and early commercial demands. Furthermore, to serve the predicted European demands, they stated that they should be relying mostly on contract manufacturers (Bellicum Pharmaceuticals, 2016).

Similarly, Bluebird Bio (Cambridge MA, United States) purchased a partially completed 125,000 square feet facility for viral vectors production in Durham in November 2017, with multi-year agreements signed with viral vector manufacturers such as Brammer Bio, LLC (Cambridge MA, United States), Novasep Inc. (Charleroi, Belgium) and EMD Millipore Sigma (Darmstadt, Germany) to ensure robust supply for clinical trials. However, manufacturing space had not been allocated for cell processing but rather Bluebird Bio committed to multi-year agreements with Lonza Houston, Inc. in the United States and apceth Biopharma in Germany to serve its regional demands there (Bluebird Bio, 2016).

CAR-T, as one of the newest and, at the time of this writing, the most hyped therapies in the regenerative medicine field with curative efficacies for life-threatening diseases, has an uncertain commercial future ahead. As Chabannon et al. (2017) aptly commented, the path between hope and bankruptcy is narrow and plenty of obstacles remain. The autologous cell-based therapy Kymriah, as the first commercially approved CAR-T therapy in August 2017, has already ran into production issues (Palmer and Sagonowsky, 2018) and the sales as approval has been reported to be disappointing (Pagliarulo, 2018). Whilst these challenges are unsurprising, given the relative infancy of the industry, learning from other industries and past experience of translating novel therapeutic modalities could enable stronger engineering management and thus better enable successful commercialisation to serve more patients.

Decisional Tools

Decisional tools or decision-support tools are tools that can be used to facilitate complex decision-making and problem solving. Since their advent in the 1970s (Keen, 1987), these tools have been used to support evidence-based decision-making in various industries, including healthcare (Lucidi et al., 2016), agriculture (Rose et al., 2016) and environment (Sullivan, 2002). In the biopharmaceutical industry, decisional tools have been applied on monoclonal antibodies and vaccine manufacturing decisions for over 20 years and have proven to be useful for understanding cost structures and risks to inform decisions in various areas including CAPEX, technology evaluation, facility fit and capacity planning (Farid et al., 2005b; Lim et al., 2006; Mustafa et al., 2004; Rajapakse et al., 2005). Decision-support tools such as cost of goods (COGs) modelling have demonstrated effectiveness in informing the industry about economic drivers in switching to new technologies. One such example is the shift from stainless steel to single-use production strategies for biologics over the last 15 years across the biopharmaceutical industry that allowed faster campaign turnover, lower initial capital costs and manufacturing cost savings (Farid et al., 2005a,b; Langer and Rader, 2014). Through better understanding the cost levers for change, decisional tools were instrumental in assisting building a valid commercial case to influence decision-makers in making important business and bioprocess decisions from technology choice and process change to supply chain, capacity planning decisions and investment project portfolio management (Rajapakse et al., 2005; Chhatre et al., 2007; Nie, 2015; Pollock et al., 2013; Tsang, 2005).

Decision Objectives

The first step towards constructing a methodology to decision-making is to establish the decision objective(s) or goal(s) of the decision-maker. There are usually three types of decisions: (1) strategic, (2) tactical and (3) operational (Anon, 2015). Strategic decisions are typically made by senior management to plan and support the long-term strategy of the company. For cell and gene therapy, these could be investment decisions, such as the composition of the company product portfolio or merger and acquisition (M&A) decisions. Tactical decisions are made by managers to plan and execute midterm tactics to implement long-term decisions. These can be planning decisions such as capacity planning (in-house manufacturing vs. outsourcing), partnerships and collaborations, or when and how to implement process changes to meet anticipated demands. With the recent approvals of therapies and an increase in M&A activities, these tactical decisions are more vital than ever to set up the architecture for the manufacture, delivery and successful adoption of these lifesaving therapies. Operational decisions are generally made by low-level management looking into short-term or day-to-day decisions. These include decisions including and not limited to: choice of technology to lower the COGs, scheduling decisions to meet demand and supplier selection.

Table 22.3 Decision Objectives in the Cell and Gene Therapy Industry Studied in Existing Literature.

Decision Type	Examples of Decisions	References
Strategic	Minimisation of developmental and investment risks of cell therapy project portfolio	McCall and Williams, 2013
Tactical	Timing of upstream process change for scale-up production	Hassan et al., 2016
	Risk-adjusted net present value	
Operational	Optimisation of operational yield of cell expansion process for mesenchymal stem cells	Ungrin et al., 2012
	Cost of goods (COGs) optimisation of upstream process	Simaria et al., 2014
	COGs optimisation of downstream process	Hassan et al., 2015
	Overall manufacturing process for COGs optimisation	Weil et al., 2017; Harrison et al., 2018; Jenkins and Farid, 2018

Table 22.3 represents examples of decision objectives in the cell and gene therapy industry studied previously. As shown, most existing models focus on operational decisions for optimisation of the costs for manufacturing or product development. Manufacturing COGs were further broken down to show subcategories such as raw material, labour, consumables, and capital equipment. Product development costs relate to the investments that are required to bring the product from bench to bedside, including particularly clinical trial costs. Optimising these costs is critical in the sustainable development of companies and to enable operational efficiency. Project net present value (NPV) is a commonly used method in project evaluation (Remer and Nieto, 1995). Through evaluating the NPV as an impact of process change in the development timeline, Hassan et al. (2016), were able to reflect the riskiness and benefits of making a process change from one technology to another.

An important gap currently unfilled is capacity planning decision-making. As suggested by Rader et al., capacity planning in the advanced therapies of today can be likened to the mAbs sector in the early 1990s when the first mAbs showed good therapeutic potential, but the industry was hesitant to invest in manufacturing facilities causing a serious capacity crunch and failure to meet global demand (Rader, 2017a,b). For monoclonal antibodies, Siganporia et al. looked into capacity planning across multiple facilities and the ratio of in-house to contract manufacturer for different demand and production titres (Siganporia et al., 2014). However, capacity planning tools are currently unavailable for autologous therapies such as CAR-T. For these therapies, both manufacturing and treatment sites capacity and availability planning to meet anticipated demands should be considered. Unlike monoclonal antibodies, these therapies have to be manufactured on

demand. Rather than centralised manufacturing, autologous therapies developers may consider a more distributed approach whereby smaller facilities are scattered in the country (Medcalf, 2016; Harrison et al., 2017; Kaiser et al., 2015).

SYSTEMS

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

System Boundary

As defined by Parnell et al. (Parnell et al., 2010), a system boundary is a physical or conceptual boundary that contains all the essential elements, subsystems and interactions necessary to address a systems decision problem. Different decision objectives motivate different definitions of systems boundaries.

The systems in the eligible publications can be generalised into two types: (1) product development systems and (2) manufacturing and supply chain systems.

Product Development Systems

For high-level decisions, such as investment and process changes, corresponding system boundaries are more abstract. For example, McCall and Williams (2013) defined its systems boundary as being between preclinical trials and Phase III clinical trials to look into the costs of developing a cell therapy whilst Hassan et al. (2016) defined its systems boundaries as being between Phase 1 clinical trials and regulatory approval to study the impact of process changes along the development phases on NPV of the project.

Manufacturing and Supply Chain Systems

Fig 22.2 conveys system boundaries mapped against the needle-to-needle/ patient-to-patient (i.e., from patient tissue procurement to therapy administration) COGs road map proposed by Lipsitz et al. (2017).

Whilst Ungrin et al. (2012) and Lambrechts et al. (2016) addressed optimisation of the cell expansion process upstream through experiments, bioprocess modelling and visualisation, Hassan et al. (2016) focused on process change impacts along the product development pathway using the change of upstream processing technology. Particularly, the impact of process change and the timing for CAPEX investment in automated and scaled-up technologies for allogeneic MSCs were studied. However, autologous cell therapies would require innovative manufacturing models allowing scale-out manufacturing whilst ensuring reproducibility. Hence, the impact of process changes and the timing for automation will have to be studied in future models, as the previous experience gained with the practice of allogeneic MSCs cannot be translated for these more service-oriented pharmaceutical modalities.

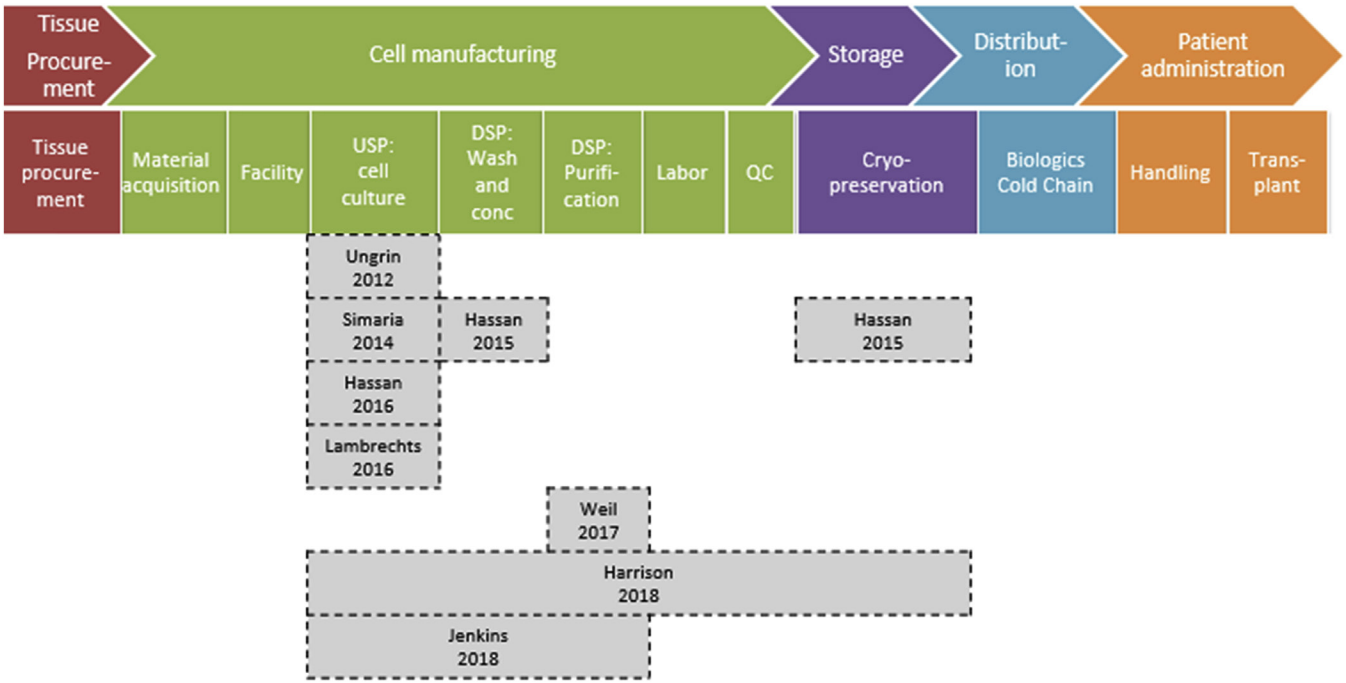

Figure 22.2 Coverage of existing decisional tools (Lam et al., 2018).

Product type Cell type/ Transplant type	MSC	CAR-T	hPSC/iPSC	Not specified	Not applicable
Allogeneic	Hassan 2015 Hassan 2016 Lambrechts 2016 Harrison 2018	Jenkins 2018		Simaria 2014	
Autologous			Weil 2017		
Not specified			Ungrin 2012		
Not applicable					McCall 2013

Figure 22.3 Cell types and type of transplant (Lam et al., 2018).

To bridge this gap, Simaria et al. (2014), Hassan et al. (2015), Weil et al. (2017), Harrison et al. (2018) and Jenkins (2018) among others evaluated different technology options for the studied steps within their defined system boundaries to better understand the advantages, disadvantages and bottlenecks in adopting different technology options and their implications on manufacturing COGs.

Product Type

As shown in Fig. 22.3, current studies focus on allogeneic therapies. However, as discussed in Table 22.2, autologous cell therapies face unique challenges. As a result, unique constraints in the manufacturing of autologous cell therapies will have to be identified and modelled to inform decisions in these novel therapies.

DECISION VARIABLES, PARAMETERS AND ASSUMPTIONS

The choice of decision variables represent decisions to be made early with the view to enable optimal decision objectives. The determination of a decision variable is typically affected by internal and external settings or characteristics, which are referred to as decision parameters. In other words, decision parameters, together with other assumptions taken for internal or external settings, form the input to a decision process, while the determined values for the decision variables are its output (Ragsdale, 2014).

Decision Variables

Decision variables are variables under the direct control of the decision-makers. Such variables are dependent on the decision objectives and the problems that are sought to be answered.

For product development systems, the models seek to answer objectives such as minimising development duration, risks and investment costs. The timing for technology

change is addressed by the decision variable modelled in Hassan et al. (2016) to study the impact of process change in product development on the project NPV. McCall and Williams (2013) studied the impacts of product development risks and uncertainties as well as rework probability on the investment costs, and as there was no optimisation module in this study, no decision variable was identified.

For manufacturing and supply chain systems, models seek to provide answers to objectives such as process yield (Ungrin et al., 2012) and manufacturing cost minimisation (Simaria et al., 2014; Hassan et al., 2015; Weil et al., 2017; Harrison et al., 2018; Jenkins, 2018). In these systems, the choice of unit operations in the manufacturing process sequence, chosen equipment and their capacities are critical decision variables. In Fig. 22.4, the upstream and downstream unit operation options considered in the publications are shown. Together with process parameters, process flow sheet and requirements, the processes were modelled to understand the associated COGs. Conclusions on the relative advantages of various technology options under different demand scenarios were drawn for bottleneck analysis and decision recommendations.

Input Parameters

Input parameters are defined as 'a constant element or factor, especially serving as a limit or boundary' (Burchfield, 1998). These are inputs defined as prerequisites of the objective function, in other words, constants of the objective function and not the values to be optimised. These can include scale, throughput, demand goal and technical process parameters.

Scale, Throughput and Demand Goal

For nonorphan products, the demand was estimated to be around the monoclonal antibodies ballpark (1000–500,000 doses of allogeneic MSCs per year (Simaria et al., 2014)). For orphan products, the demand was estimated to be around 2500 doses per year for a regional centre for allogeneic MSCs (Harrison et al., 2017) and 500–5000 doses per year for CAR-T (Jenkins and Farid, 2018).

The demand scenario was chosen according to the cell type and the therapeutic target. For non–orphan-type products, the scale of demand is more likely to be similar to monoclonal antibodies.

As more and more real-world commercial cases emerge, recent analyses were given a lot more consideration to the clinical applications and their specific demands, hence resulting in more realistic demand scenario being proposed.

Upstream and Downstream Operations Process Parameters

For upstream operations, comparisons were drawn from a range of equipment scale, cell culture modes and extent of automation. Process parameters previously considered and explicitly mentioned in their respective publications are summarised in Table 22.4.

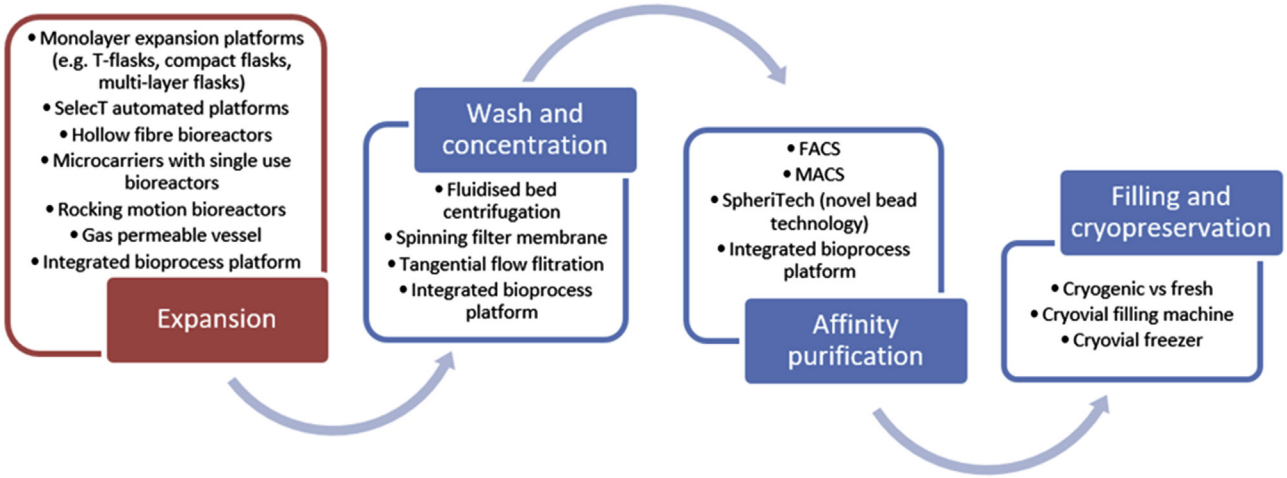

Figure 22.4 Upstream and downstream operations considered in various literature (Lam et al., 2018).

Table 22.4 Input Process Parameters for Upstream Processing.

Input Process Parameters	Ungrin et al. (2012)	Simaria et al. (2014)	Harrison et al. (2018)	Jenkins (2018)
Studied technologies	Microwell	• T-flasks • Multilayers • Compact flasks and multilayer bioreactors • Automated multilayers • Single-use bioreactors with microcarriers	• T-175 flasks • SelecT automated platform	• Planar culture flasks • Rocking motion bioreactor • Gas-permeable vessel • Integrated bioprocess platform
Cell Culture Process Parameters				
Population doublings	√			
Inoculation cell count			√	
Seeding density		√	√	
Harvest density		√		√
Technology Process Parameters				
Surface area	√	√		
Equipment size and volume range		√	√	√
Number of expansion stages		√		
Perfusion rate				√
Max units		√		
Biosafety cabinet requirement		√		
Incubator capacity requirement		√	√	
Time Duration Assumptions				
Seed time		√		
Feed time		√		
Harvest time		√		
Cell culture duration			√	
Material Use and Cost Assumptions				
Media requirements		√	√	√
Labour requirements		√	√	√
Consumable unit price		√	√	√
Capital charge		√	√	√

Planar culture flasks (e.g., T-flasks and multilayer flasks) are consistently found to be the most expensive out of all evaluated technologies for allogeneic therapies and infeasible for higher cell number per lot. The number of cells harvest per surface area was found to be the most important cost driver as it dictates the number of expansion units required and hence the raw materials and consumables requirements (Simaria et al., 2014; Jenkins and Farid, 2018). Using technology S-curves, Simaria et al. illustrated the introduction, growth and maturation of various upstream adherent cell manufacturing technologies (Simaria et al., 2014). A first learning is expectedly that the sweet spot for switching to a more sophisticated manufacturing system is highly dependent on the cell dose. Therefore, the higher the number of cells required per dose, the sooner it is to make the switch to more efficient systems such as single-use bioreactors with microcarriers. An interesting insight is that for typical dose sizes of 10^7–10^8 cells/dose (Jenkins and Farid, 2018), unless the demand is above 100,000 doses (10^8 cells/dose) annually, there seems to be very little reason to make the switch to a more capital-intensive single-use bioreactor with microcarrier system. Given the demand estimates of products launched in recent years, less capital-intensive smaller systems may be the preferred technology option for upstream systems.

Table 22.5 shows the process parameters for downstream processing discussed previously (Lam et al., 2018).

The downstream process starts with the wash and concentration step, and common wash concentration unit operations were discussed in detail in Hassan et al. (2015) and Jenkins and Farid (2018). In Hassan et al., wash and concentration downstream steps were shown to be a bottleneck for high cell dose lots at high demand. As the demand estimate was lowered in Jenkins et al., wash and concentration was no longer shown to be a bottleneck, except in integrated bioprocess platforms such as in the CliniMACS Prodigy (Miltenyi Biotec, Bergisch Gladbach, Germany), which has a smaller volume-reduction capacity.

Following wash and concentration, affinity purification has also been a target for modelling and optimisation. Weil (2017) and Jenkins (2018), looked into affinity purification for autologous induced pluripotent stem cells and allogeneic CAR-T cells, respectively (Weil et al., 2017; Jenkins and Farid, 2018). Weil et al. compared fluorescent-activated cell sorting (FACS) with magnetic-activated cell sorting (MACS) and evaluated a novel technology that does not require cell labelling. MACS was determined to be more cost-effective for dose sizes with a higher cell count ($>7.0 \times 10^7$ cells per dose) as FACS is limited by its process scale. In the model of Jenkins (2018), for affinity purification, only MACS and integrated bioprocess platform (INT) were considered.

Assumptions and Constraints

Apart from technology-related assumptions and constraints, other assumptions have been made.

For scheduling-related problems where one task follows another, the task precedence constraint methodology has been used. For example, in McCall and Williams (2013), task

Table 22.5 Input Process Parameters for Downstream Processing.

Input Process Parameters	Hassan (2015)	Weil (2017)	Jenkins (2018)
Wash and concentration Studied technologies	• Tangential flow filtration • Fluidised bed centrifugation	N/A	• Fluidised bed centrifugation • Spinning filter membrane • Integrated bio-process platform
Purification Studied technologies	NA	• Fluorescent-activated cell sorting • MACS (magnetic-activated cell sorting) • Novel bead	• MACS • Integrated bio-process platform
Technology process parameters			
Number of washes/cycles	√	√	
Equipment size and volume range	√	√	√
Maximum cell processing capacity	√	√	√
Step yield	√	√	√
Time duration assumptions			
Maximum time	√		
Material use and cost assumptions			
Raw material requirements	√	√	√
Labour requirements	√	√	√
Consumable unit price	√	√	√
Capital charge	√	√	√

precedence constraint was used for dictating the start and end of a task, which is useful for setting up of the scheduling problem. Iteration loops were built in the development pathway with assumption of learning. In Hassan et al. (2016), a linear project development pathway was assumed with failure probability. Importantly, a database with information on clinical trial development times and failure rates of all 592 commercial cell therapy projects from 1981 to 2011 was constructed to estimate the duration and failure rate of similar products. This approach allows more industrially relevant benchmark assumptions to be made and hence gives rise to high-quality results.

For resource utilisation, McCall and Williams (2013) assumed a fixed and steady-rate consumption of resources and a renewable resource pool throughout the project duration. Similar assumptions were adopted in all the other cost models to better understand the impact of resource utilisation on the overall COG. For example, in Simaria et al. (2014), it was shown

that an efficient use of equipment and facility can lower the depreciation costs shared across doses. Harrison et al. (2018) looked into the impact of human resource turnover in detail to understand the impact of increased operators on the relative cost of labour in overall COGs.

Having reasonable cost assumptions is one of the most important factors determining the validity of the model.

In Harrison et al. (2018), quality control (QC) assumptions were based on QC test panels in accordance to Good Manufacturing Practices (GMP) requirements of the specific product and listed in detail in the supplementary material and based on industry information from Athersys, Inc. (Cleveland, United States). However, the basis of cost assumptions for the other papers reviewed here was not provided. Depending on product characteristics, each product requires different QC tests and assay requirements and hence the ultimate costs can be quite different. For example, genetically modified cells would require assays on transformed cell populations to demonstrate appropriate and reproducible expression of newly acquired characteristics (Committee for Medicinal Product For Human Use, 2008).

Labour costs differ widely depending on geographical location and purchasing power parity. In an interview with the chief executive of Nanjing Legend (Nanjing, China), this executive estimated that the manufacturing costs for CAR-T in China can be one-sixth of that in the United States because of cheaper overheads (Crow, 2018). Furthermore, Simaria et al. (2014) suggested in their sensitivity analysis that labour rate is one of the most important cost drivers for less automated processes. This comes as no surprise, given the relatively manual manufacturing strategies and high requirement on personnel skill level for cell and gene therapy manufacturing.

The two main methods for accounting for facility costs are equipment-factored estimates (e.g., Lang Factor) and cost per m^2 estimates. The facility costs are averaged over the period of depreciation and shared amongst all doses. Lang Factor is a commonly used method in project cost estimates in the engineering industry and recommended by the American Association of Cost Engineers. Lang Factor takes into account pipework and installation, process control, instrumentation, electrical power, building works, detail engineering, construction and site management, commissioning and contingency factor (Borowicz et al, 2013). To use the cost per m^2 method for cleanroom space fixed and running cost estimation, it is important to understand the manufacturing process and associated GMP requirements in order to propose a fit-for-purpose cleanroom grade (Harrison et al., 2018).

SOLUTION METHOD

A solution method is required to relate the decision variables to the decision objective to eventually determine the former according to the latter. Process models were built and proposed in all the identified literature; those solution methods employed are discussed in this section (Table 22.6). The two main approaches are process economics modelling in the form of 'what-if' studies and multi-attribute decision-making.

Table 22.6 Techniques and Algorithm Used (Lam et al., 2018).

	Ungrin (2012)	McCall (2013)	Simaria (2014)	Hassan (2015)	Hassan (2016)	Weil (2017)	Harrison (2018)	Jenkins (2018)
Process economics modelling			√	√	√	√	√	√
Value systems modelling		√						
Design structure matrix		√						
What-if scenario analysis			√	√	√	√	√	√
Multi-attribute decision-making								√
Database evaluation		√			√			
Latin hypercube		√						
Monte Carlo simulation					√			√
Sensitivity analysis			√			√		√
Deterministic process evaluation	√		√	√		√	√	√
Stochastic model		√			√			√
Data visualization								

Process Economics and Value Systems Modelling

To ensure that all relevant costs are identified, typically models simulating the actual manufacturing or product development process are constructed, and costs associated with each step are summed. Cost analyses were performed by Simaria et al. (2014), Hassan et al. (2015, 2016), Weil et al. (2017), Harrison et al. (2018) and Jenkins and Farid (2018). This method allows process-centric costing that in turn supports cost analyses based on different technology options.

Value system modelling is a way of modelling a firm by sets of activities that it uses to create value and competitive advantages (Hergert and Morris, 1989). McCall et al. modelled the set of activities in product development and accounted for development process characteristics such as interdependency, iteration, activity cost and duration uncertainties. Through this model, McCall et al. was able to highlight the critical processes, resources and risks in product development. The importance of early stage investment, clinical trials rework and regulatory requirements were highlighted in their report (McCall and Williams, 2013).

Design Structure Matrix

Design structure matrix (DSM) is a method developed by Steward (1981) for planning and communicating engineering works. DSM can represent the events, their sequence and the interdependencies between events to reduce uncertainty and ambiguity in product development, project planning and management (Danilovic and Browning, 2007). In the context of product development for cell and gene therapies, the industry is highly regulated, and oftentimes activities are interdependent. For example, a clinical trial failure may require the project team to return to the design phase. The sequence of events and their dependencies can be clearly illustrated using DSM. McCall and Williams (2013) used a DSM to clearly represent the precedence constraints whilst considering iteration circuits inherent to product development, and in doing so, they developed an early stage assessment tool for development cost prediction for cell therapy products.

'What-If' Scenario Analysis

'What-if' scenario analysis is a method used to explore different alternatives based on changing conditions and assumptions (Peltier, 2017; Røberg, 2017). For example, where the anticipated demands of products are different, the optimal scale of production will differ. Different scenarios where dose sizes, lot sizes and demand for products, clinical adoption rate, etc. are varied, can be studied through models and simulations to allow the decision-maker to make more informed and risk-adjusted decisions.

Single-Objective Versus Multi-Attribute Decision-Making

Whilst looking into single objectives such as manufacturing and investment costs is a useful approach in optimising single objectives, to successfully translate cell and gene

therapies from benchtop to clinic, many different parameters must be considered. Some of these include operational performance (e.g., yield, processing time, resource utilisation), economic (e.g., capital investment, COGs), QC and regulatory compliance (e.g., automation vs. manual processing, process robustness), safety (e.g., cross-contamination, cell or tissue handling) and flexibility (e.g., process change) (Jenkins and Farid, 2015). To assess all these objectives at the same time, multicriteria decision-making can be used.

Notably, the weighted sum technique provides a simple way to account for both quantitative and qualitative attributes of a solution, and by assigning weights, considered the perceived relative importance of different attributes.

Jenkins and Farid (2018) assessed different technology options for cell culture, concentration and purification technologies for allogeneic CAR-T based on preferences and priorities gathered through a survey completed by industry experts. Through assigning different weights to attributes including COG per dose, fixed capital investment, ease of operation, process control, validation effort, ease of scale-up and process containment, the flow sheets were ranked according to preference. Interestingly, according to their findings, for allogeneic CAR-T, the flow sheet using rocking motion bioreactor (RMB) for cell culture, spinning filter member for cell concentration and MACS for purification performed better than RMB combined with a self-contained, integrated bioprocess platform–based approach (e.g., MACS platform) for both concentration and purification. Although the process containment attribute scores higher in the latter process, the lower capital investment for spin filter and MACS still makes the former flow sheet a more attractive option (Jenkins and Farid, 2018).

The weighted sum method, however, is just one of many methods of multi-attribute decision-making. For example, Velasquez and Hester (Hester et al., 2013) conducted a comprehensive review and comparison of the various methods commonly used. Particularly, analytic hierarchy process allows pairwise comparisons to compare alternatives that are less data-intensive and more suitable for qualitative performance-type problems and resource management applications.

HANDLING OF RISKS AND UNCERTAINTIES

Common themes incorporated into these manufacturing and development cost models are the risks and uncertainties lurking the industry. The major methods of capturing risks and uncertainties in the studied models are stochastic modelling, Latin hypercube sampling, Monte Carlo analyses and sensitivity analyses (Helton and Davis, 2003; Schmitt and Singh, 2009; Wallace, 2000).

Deterministic Versus Stochastic Modelling

Deterministic models use discrete values. This means that for a certain input, the output will always be the same; whereas stochastic models have at least one quantity with random values, thereby leading to an ensemble of different outputs (Parnell et al., 2010).

To account for the uncertain and variable nature of stochastic systems, probability distributions can be applied to parameters. With regard to cell and gene therapies, the product development duration (McCall and Williams, 2013; Hassan et al., 2016), the variable preference of quality attributes (Jenkins, 2018), the variability of source materials and manufacturing process are all uncertainties that should be accounted for.

Latin Hypercube Sampling and Monte Carlo Simulation

McCall and Williams (2013) categorised the risks into product risk factors and enterprise risk factors. Product risks were defined as risks that can harm the patient, namely the choice of cell type, manufacturing processes and delivery mechanism. Enterprise risks were defined as risks that affect the commercialisation of the product and the business developing the product, namely technical risks and market risks. The Latin hypercube sampling method was utilised to take into account the probability of failure and duration for each task along the product development pathway and the interdependencies. It is worthwhile to note that in this model, iterations caused by failures and impact of failures during each phase were taken into account using three matrices – design structure, rework probability and rework impact.

Hassan et al. simulated the risks and uncertainties of process change along the product development pathway through Monte Carlo analyses. To adjust the project NPV according to risk, a discount rate based on the riskiness and expected development time is employed (Hassan et al., 2016).

Sensitivity Analysis

'Sensitivity analysis is the study of how the uncertainty in the output of a model (numerical or otherwise) can be apportioned to different sources of uncertainty in the model input' (Saltelli, 2002). In other words, it is a methodology that can be used to understand the relative impact and importance of input parameters on the final outcome. This is a very common strategy to account for uncertainties and identify key cost drivers (Simaria et al., 2014; Weil et al., 2017; Jenkins and Farid, 2015). As an example, for the upstream steps of production processes for MSCs, the main cost drivers were found to be microcarrier area, harvest density, media price and downstream yield (Simaria et al., 2014). While for processes requiring differentiation or gene modification, the key cost drivers were consistently cited to be the efficiency of differentiation and gene modification for both autologous and allogeneic processes of different cell types (Weil et al., 2017; Jenkins and Farid, 2018). These findings can subsequently allow R&D efforts to be focused on optimising the manufacturing processes.

Hypothetical Case Studies

Hypothetical case studies are useful in filling the gaps where real data are not available. Different demand and dose size scenarios and the potential impact of these scenarios can

be studied through these case studies for evaluating process bottlenecks while scaling up production and technology-switch sweet spot analysis. If higher demand for the product is anticipated, there is a greater tendency to switch to a more scalable system earlier on (Simaria et al., 2014; Hassan et al., 2015; Weil et al., 2017; Jenkins and Farid, 2018).

IMPLEMENTATION

System implementation is the process of defining how the system should be built, ensuring that the system is operational and that the quality of the system is sufficient to deliver its purpose (Lee-Post, 2002). While it is challenging to validate some of these models in a real-world scenario, there are other strategies that can be adopted to ensure credibility and validity of assumptions. We discuss in this section several ways of model validation and the simulation platforms that can be used for building decisional tools.

Model Validation

Data Mining

Previous successes and failures statistics are very useful not only for benchmarking purposes but also for model validation. McCall et al. collected data from development programmes surrounding orphan and nonorphan cell therapies, while Hassan et al. collected information on clinical trial development times and failure rates of all 592 commercial cell therapy projects that entered development from 1981 to end of 2011. Such data from real commercial case studies are useful for informing assumptions and subsequently increase the validity of assumptions such as the development duration. (McCall and Williams, 2013; Hassan et al., 2016).

Laboratory Experiments

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

Simulation Platforms

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

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

For models with larger databases, it is worth examining relational database management software (RDBMS). RDBMS provides better scalability if the amount of data is very large; moreover links can be built in more robust ways compared with spreadsheets. Visualisation software tools such as Google Charts allow information to be easily updated and visualised, and hence these are very useful for presenting a lot of data in a meaningful way (Lambrechts et al., 2016).

PERSPECTIVES

In this chapter, we have reviewed the decisional tool landscape available for optimising the implementation of cell and gene therapies. Current research has largely addressed the manufacturing challenges and cost reduction drivers for allogeneic cell therapies manufacturing, but the diversity of decisions that has been modelled in the cell and gene therapy area is still to this date very limited compared with the current practice for monoclonal antibodies and small molecule pharmaceuticals. Some areas that are currently unpopulated include scheduling (Jain and Grossmann, 1999), facility fit (Yang et al., 2014), capacity planning (Levis and Papageorgiou, 2004; Sundaramoorthy et al., 2012; Timpe and Kallrath, 2000), supply chain optimisation (Papageorgiou, 2009; Sousa et al., 2011) and portfolio management (Rajapakse et al., 2005).

Many of the challenges that are currently faced by the cell and gene therapy industry have been faced by the biologics industry over the past 50 years. Galambos et al. studied the transition to biotechnology in the 1990s in great detail in their 1998 report on strategic innovation (Galambos and Sturchio, 1998). In the late 1960s, when the recombinant DNA technology first became possible (Lenzi et al., 2014), small biotechnology companies paved the way to this new modality of medicine, transitioning the industry from synthetic organic chemistry–focused to biologics. Many large pharmaceutical companies did not invest in molecular genetics and rDNA technologies until the early 1980s, when many large pharmaceuticals began to make investments into biotechnology and building their own biotechnology capabilities and pipelines. An estimated loss of $3–$4 billion in total revenue might have been forgone due to the late realisation of the importance of new scientific and technological paradigm (Galambos and Sturchio, 1998). In the 1990s, very similar challenges were faced by the mAb industry when serious capacity crunches were experienced and the global available capacity was insufficient to support the demand for the products (Rader, 2017b). Contract manufacturers and developers stepped in to build the required capacity that supported the exponential growth

of the industry. Building GMP-compliant facilities, however, takes a long time. For a greenfield project, according to Levine et al., building a conventional GMP-biomanufacturing facility takes approximately 4.5 years, whilst a modular facility where construction can happen off-site and subsequently assembled on site offer a 1 year time saving. Bearing in mind a typical patent provides market exclusivity for only 20 years from the date the application was filed, and the fact that premarket clinical trials and regulatory approval procedures can take years to complete (Tam, 2010), and for a company to maximise its economic payout on innovation investment, there is a clear incentive to ensure that appropriate manufacturing capacity is available through building or contracting out as soon as the product receives regulatory approval, and even before.

Another example of the importance of informed decision-making on cost of production is the shift observed in the mAb production industry from stainless steel to single use. Various decisional tools and case studies have illustrated capital cost reduction of around 50%, COGs reduction of around 33% and a 25% reduction of facility set-up time (Farid et al., 2000; Lopes, 2015). These benefits encouraged the industry to adopt the technologies, and between 2006 and 2013, there was a 57% increase in single-use bioreactor usage (Langer and Rader, 2014).

Today's cell and gene therapy industry is very much like that of biologics back in the 1970s. As previously, a few early large pharmaceutical adopters moved in the new technology segment, as illustrated by Novartis, which were quick to invest and partner with biotechnology firms in the nascent field. Many major regulatory authorities such as Japan's Pharmaceuticals and Medical Devices Agency, Europe's EMA, and the US Food and Drug Administration are supportive in the commercialisation of these products with various fast-track initiatives in place to encourage faster commercialisation of regenerative medicines for serious life-threatening diseases. Some of these early access initiatives include breakthrough therapy designation in the United States (Corrigan-Curay et al., 2018), PRIME in the EU and SAKIGAKE in Japan (Smith and Brindley, 2017; Corrigan-Curay et al., 2018; Elsanhoury et al., 2017; Kondo et al., 2017; Raggio, 2015). Some examples of cell and gene therapy products that have been granted regulatory pathways or designations that allow an acceleration of the commercialisation process are shown in Table 22.7. For the first-approved CAR-T product, Kymriah, the first clinical trial was sponsored by the University of Pennsylvania in 2009 for leukaemia and lymphoma. Notably, breakthrough therapy designation was approved around 1 month after initial submission, and Biologics License Application (BLA) data were submitted as they were accumulated. Besides breakthrough therapy, Kymriah was also granted orphan designation, rare paediatric disease designation and fast-track designation. Because of the priority review status given, the approval process was expedited, and Kymriah was approved in the United States in August 2017 by a unanimous decision of the review panel (FDA/CBER, 2017; Novartis, 2017). This is around 40% faster than the conventional regulatory pathway that averages a 10-month turnover from the date of initial BLA submission.

Table 22.7 Examples of Cell and Gene Therapy Products That Have Been Granted Early Access Designations (Lam et al., 2018).

	Regulatory Pathway	Example of Cell/Gene Therapy Products
US Food and Drug Administration	Priority review (1992)	Novartis: Kymriah
	Accelerated approval (1992)	Pfizer: bosutinib
	Fast track (1998)	Renova: RT-100 AC6 gene transfer (Ad5.hAC6); DNAtrix therapeutics: DNX-2401; AveXis: AVXS-101
	Breakthrough therapy (2012)	Enzyvant: RVT-802; Juno and Celgene: JCAR017; Adaptimmune and GSK: NY-ESO-1c259T; bluebird and Celgene: bb2121
	Expedited access pathway (2015)	Avita: Recell (Avita Medical, 2015)
	Orphan drug designation (1983)	uniQure: AMT-130 (UniQure, 2017)
	Rare Pediatric Disease Priority Review (2014)	Spark Therapeutics: Luxturna (Morrison, 2018)
	RMAT designation (2017)	Abeona Therapeutics: ABO-102 (Abeona Therapeutics, 2018); Mesoblast: MPC therapy (Globesnewswire, 2018)
EU European Medicines Agency	Accelerated assessment (2004) (McBlane, 2015)	bluebird: LentiGlobin (Stanton, 2016)
	Orphan drug designation (2000) (McBlane, 2015)	uniQure: AMT-130; Orchard Therapeutics: Strimvelis
	Marketing authorisation under exceptional circumstances (2005) (McBlane, 2015)	uniQure: Glybera (YlÃ, 2012)
	Conditional marketing authorisation (2006) (McBlane, 2015)	Chiesi Farmaceutici: Holoclar (Elsanhoury et al., 2017); MolMed: Zalmoxis (Mullard, 2017)
	Adaptive pathway (2015) (McBlane, 2015)	Atara Bio: ATA129
	PRIME(2016) (McBlane, 2015)	uniQure: AMT-060, AMT-061; Juno and Celgene: JCAR017; bluebird: LentiGlobin (Stanton, 2016); Adaptimmune and GSK: NY-ESO-1c259T; bluebird and Celgene: bb2121 (European Medicines Agency, 2018a,b)
JAPAN Pharmaceuticals and Medical Devices Agency	Priority review (Jokura et al., 2017)	Glecaprevir/pibrentasvir (G/P), AbbVie
	Orphan designation (1993) (Jokura et al., 2017)	Edison Pharmaceuticals: EPI-743
	Conditional and time-limited approval (2014) (Jokura et al., 2017)	
	SAKIGAKE forerunner review assignment (2015) (MHLW, 2014)	Nippon Shinyaku: NS-065/NCNP-01 (Nakamura, 2018)
CHINA	Accelerated and conditional approval (draft issued in 2017) (CFDA, 2017)	Not yet in practice

As more products are granted these designations, to facilitate decision-making, the implications of these pathways should be taken into account. For example, breakthrough therapy designation allows New Drug Application/BLA data to be submitted as they are accumulated, and orphan drug designation allows approval of medicinal products within 6 months. These accelerated regulatory mechanisms constitute powerful levers to usher products into market; however, the infrastructure for providing these therapies to the marketplace remains the obvious next challenge.

The 'Servitisation' of Therapies

For personalised therapies such as autologous CAR-T, the manufacturing model is shifted from the 'make-to-stock' model to the 'make-to-order' model. In the make-to-order model, manufacturers are required to be more 'hands-on', from the training of medical staff to deliver the products to patients in a reproducible manner and to cope with potential adverse events to coordinating with the hospital for shipment. Very local interactions between manufacturing facility and hospital are required for scheduling purposes, as patients' disease management also has to be considered during the manufacturing. Preconditioning regimens and treatment plans, such as lymphodepleting chemotherapy, have to be conducted before the delivery of the cell-based treatment (Mcguirk et al., 2017), which further complicates the manufacturing and delivery workflow. This is particularly challenging when it comes to multinational delivery because this bespoke nature of work does not lend itself to scale. Whilst the increasing digitisation of manufacturing and healthcare are providing a great platform for facilitating these deliveries, it is critical that the service component is dissociated from the off-the-shelf component and then distributed to parties that are most suitable for scaling up/out.

Outlook: What are the Critical Decisions That Will Drive the Industry Forward?

Current available models provide good guidance for technology evaluation at various scales for large-scale allogeneic process unit operations. However, autologous products make up more than half of the clinical trial pipeline, and with their unique challenges, innovative business and manufacturing models have to be proposed, backed up by trade-off analyses conducted through modelling studies (Medcalf, 2016).

As more products come to maturity, the industry must be prepared to dramatically increase its manufacturing capacity. The United Kingdom has been leading in this regard, accounting for 48% of the 52 current registered cell therapy contract manufacturing organisation facilities (GlobalData Healthcare, 2018). Having an efficient regulatory framework and an efficient hospital infrastructure is also vital to successfully deliver these lifesaving therapies. Streamlining communication between parties whilst protecting patient data is yet another challenge to be addressed in the process.

In terms of manufacturing technologies, there is a general drive towards closed and automated processes. M&A activities for larger companies to acquire smaller companies specialising in technologies for automated closed systems in cell therapy production have been noted (Lonza, 2018; Pomerantz, 2016).

Whilst the field of cell and gene therapy is still looming with uncertainty, these therapies have the potential to offer a truly life-changing treatment paradigm. It is through learning, not only from the past experience of introducing the use of biologics and mAbs in clinical use, but also by event analysis of the introduction of a first wave of regenerative medicine products, that the time for the cell and gene therapy industry to establish itself as the fourth pillar of medicine (Fischbach et al., 2013) can be brought about sooner, for the ultimate benefit of patients who need them (Eric Palmer, 2012).

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