

# Impact of fast-track regulatory designations on strategic commercialization decisions for autologous cell therapies

Ching Lam<sup>1</sup> , Edward Meinert<sup>2,3,4</sup> , Aidong Yang<sup>5</sup>  & Zhanfeng Cui<sup>\*,1</sup> 

<sup>1</sup>Department of Engineering Science, Institute of Biomedical Engineering, University of Oxford, Oxford, OX3 7DQ, UK

<sup>2</sup>Centre for Health Technology, University of Plymouth, Plymouth, UK

<sup>3</sup>Department of Primary Care and Public Health, Imperial College London, London, UK

<sup>4</sup>Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

<sup>5</sup>Department of Engineering Science, University of Oxford, Oxford, OX1 3PJ, UK

\*Author for correspondence: [zhanfeng.cui@eng.ox.ac.uk](mailto:zhanfeng.cui@eng.ox.ac.uk)

**Background:** Regulatory authorities around the world have introduced incentives to improve the speed-to-market of innovative therapies. **Aim & methods:** To better understand the capacity and portfolio planning decisions of autologous cell therapies and particularly the impact of fast-tracking designations, this paper describes a mixed-integer linear programming approach for the optimization of capacity investment and portfolio selection decisions to maximize the net present value of a candidate portfolio of therapies under different regulatory programs. **Results:** The illustrative example shows that fast-track designations allow a 25% earlier breakeven, 42–86% higher net present value over a 20-year horizon with earlier upfront capital and reduce the portfolio's sensitivity to uncertainties. **Conclusion:** Fast-track designations are effective in providing commercialization incentives, but high capital risks given the compressed timeline should be better considered.

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**Keywords:** autologous cell therapies • capacity planning • decisional tool • drug development • optimization • regulatory

Autologous cell therapies are a unique class of products where tissues/cell originate from the patient and are returned to the patient for therapeutic purposes. A previously published study examined three autologous interventions (Epice<sup>®</sup>, Provenge<sup>®</sup> and Cartice<sup>™</sup>) and summarized the premarket and postmarket challenges of commercializing cell therapies, citing unclear regulatory environment and long developmental timelines as the main premarket challenges and manufacturing and supply chain challenges as two key postmarket challenges [1]. More specifically, these challenges are manifested in three aspects.

First, as the products are living cells, they are very sensitive to environmental changes and therefore to ensure safety and quality of the product, cold or ultracold supply chain has to be considered. Distribution logistics can have a massive impact on the formulation of the product and has to be considered early in the product development cycle [2]. The unique requirement for autologous cell therapy products to be produced on-demand with cell material originating from patients presents new capacity and supply chain complications that have proven to be commercially challenging [3]. Specific to autologous therapies, the geographical constraint and sometimes, trade-off for quality, has led to more interest in decentralized manufacturing [4].

Second, managing the cost of goods and marketing cost is a key contributing factor to commercial success. Lipsitz *et al.* have outlined the cost of good (COG) planning roadmap for manufacturing of cell therapies from cell sourcing to patient administration [5]. An interesting challenge faced in the commercialization of Dendreon, one of the first immunotherapy products for prostate cancer, was the financial implications of substantial upfront investment in specialized good manufacturing process (GMP) production facilities. The lag in treatment adoption and the expensive underutilized facilities caused massive amounts of debts and eventual market failure [1]. Given the requirement for GMP-compliant facilities to be in place and listed for market authorization, the lead strategy

toward capacity planning (i.e., capacity added in anticipated of increase in demand) can become a huge burden for resource-constrained companies seeking to commercialize cell therapies.

Third, autologous cell therapies are specific to the patient, which means manufacturing cannot be scaled up using larger-scale equipment and has to be scaled out to produce a single batch of therapy per patient. This not only diminishes the effect of traditional economies of scale but also presents risks in mix-ups and cross-contamination [6].

For pharmaceutical product development, process development for manufacturing scale-up and production planning take place alongside clinical trials to prepare for mass production and market roll-out. In drug development, the critical path for new medicinal products proposed by the US FDA, manufacturing scale-up and production planning are often only considered in later phases of clinical trials [7]. When applying for market authorization, the proposed manufacturing sites should be listed and must be GMP compliant. Setting up GMP-compliant facilities is time-consuming and capital-intensive [8], but for the product to attain maximal economic returns during the market exclusivity period (only 20 years from the filing date of the patent), the GMP-compliant manufacturing capacity has to be available when the product is market-ready, whether through contracting out or building own facilities.

The capacity planning problem has been a long-standing one in the pharmaceutical industry due to the uncertainties around product development, high upfront investment costs and highly regulated industry landscape. These challenges make the optimization of capacity planning for pharmaceuticals different from other industries such as agrochemicals. Ineffective capacity planning can lead to serious capacity crunches such as that faced by the monoclonal antibody (mAb) industry in the 1990s, which were estimated to have caused around US\$3–4 billion in total revenue loss due to insufficient supply of products [9,10]. Papageorgiou *et al.* studied the optimization of investment strategies for product development and introduction of active pharmaceutical ingredient [11] and others have looked into similar problems under uncertain clinical trial outcomes, market pressures and regulations [12]. Liu and Papageorgiou used a mixed-integer linear programming (MILP) approach to simultaneously optimize the global supply chain for pharmaceuticals considering costs, responsiveness and customer service levels [13]. For biopharmaceutical facility planning, Sigantoria *et al.* have formulated a discrete-time MILP model to optimize in-house and contract manufacturing decisions and to study the adoption of fed-batch and continuous perfusion culture processes [14]. More recently, Wang *et al.* studied the chimeric antigen receptor T-cell therapy (CAR-T) supply chain to maximize the overall net present value (NPV) and minimize average response time of patients under demand distribution uncertainties [15]. Simulation studies looking into demand resilience and reagent supplies conducted by Lam *et al.* and Wang *et al.* [16,17] have discussed the operational challenges for autologous cell therapies. Optimization studies have also been proposed to look at the use of mobile medical units for delivering therapies from manufacturing centers to local treatment facilities for autologous cell therapies [18]. However, these existing models have not addressed the impact of unique regulatory pathways for autologous cell therapies on strategic commercialization decisions such as timing for capital investment and portfolio considerations.

With the maturation of advanced therapeutic medicinal products (ATMPs) as a drug modality and more and more products moving from bench to market, regulatory authorities around the world have evolved to address to put forward clearer regulatory guidelines and strategies to reduce the developmental timelines. Regulatory authorities around the world have introduced frameworks to allow faster access to these treatments for life-threatening diseases such as blood cancers and genetic disorders [19–21]. These policies have been shown to accelerate the commercialization of ATMPs and have been generally well-accepted and well-adopted (Supplementary Material 1).

With the introduction of accelerated approval processes, the clinical development duration can reduce from 6–7 years (full-fledged phase I, phase II and phase III clinical trial) to 2–3 years (small-scale clinical trials with surrogate end points) [22], which requires the industrialization timeline for process development and capacity planning to be managed accordingly. Therefore, the industry needs to re-evaluate the outsourcing and investment strategies for securing manufacturing capacities to benefit fully from accelerated approval. This is a highly relevant decision to consider as the number of clinical trials in the cell and gene therapy domain has been increasing exponentially over the last few years. Just for the cancer cell therapy pipeline, the number of active agents increased by 46.7% [23].

Therefore, this study aims to develop a mathematical model for investigating capacity planning decisions to maximize the NPV of an autologous cell therapy portfolio to illustrate the impact of ‘fast-track’ approval processes. An illustrative example comparing ‘fast-track’ and standard approval processes is conducted to assess the implications of the former on the timing for capital investment in cell therapy manufacturing facilities, the scale and location of facilities of different scales (smaller-decentralized facilities vs larger-centralized facilities) and product portfolio.

## Methods

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

### Problem statement

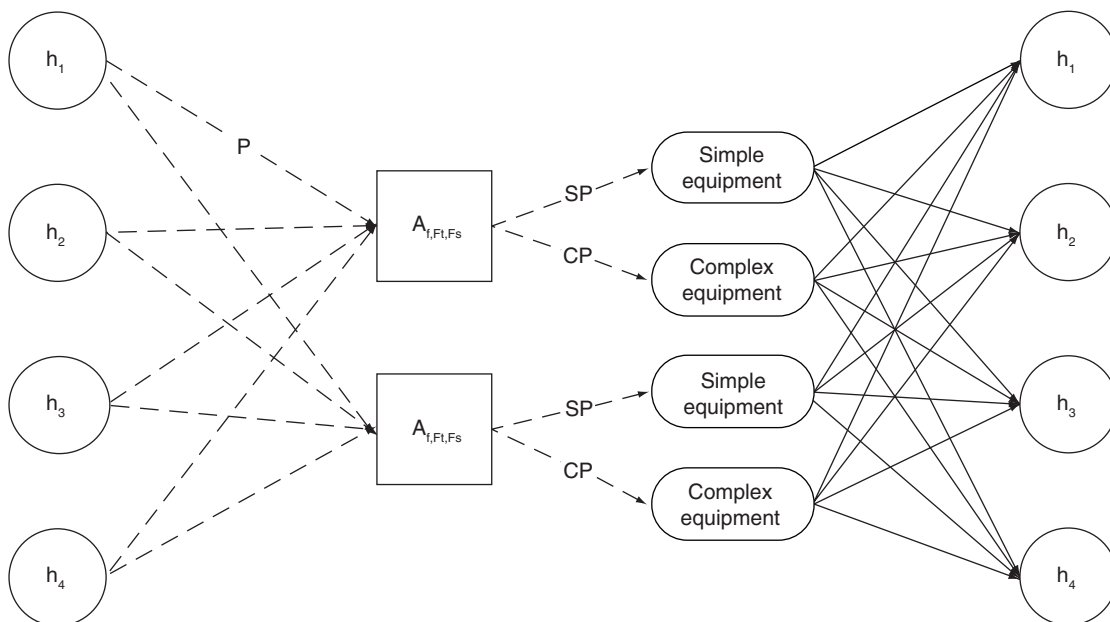
A holistic approach that simultaneously considers product portfolio, capacity planning and equipment procurement is needed to address the challenges facing the commercial development of autologous cell therapies. The problem is summarized as follows:

Given:

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

Determine:

- Set of products selected;
- Facility investment schedule;
- Optimal facility location;
- Optimal facility scale;
- Optimal engagement of facility type over the time horizon;
- Equipment procurement schedule for each built facility over the time horizon.



**Figure 1.** The general algebraic modeling system network diagram.

CP: Complex product; P: Product; SP: Simple product.

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

### Model formulation

A uniform time discretization MILP problem is formulated. Specific to the nature of autologous cell therapies, some key features include parallel closed automated processing (scale-out manufacturing); total product consumption (product generated from patients return to patients at the same location); location, facility scale (pilot, small, medium, large) and type (contract or newbuild) specific considerations. Previous published models have considered the treatment delivery response time [15], which is an important operational level decision for autologous cell therapies, but this model focuses on strategic decisions on portfolio, capacity planning and investment, paying particular attention on the impacts of regulatory programs.

The formulation is presented in detail as follows and the overall supply chain network structure diagram is presented in Figure 1.

### Notations

#### Indices

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

#### Sets

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

#### Parameters

$Dd_{m,t}^{P,h}$	Annual Demand of product $P$ at hospital $h$ requiring process $m$ at year $t$
$CD_t^P$	Annual demand for all complex products
$SD_t^P$	Annual demand for all simple products
$Price_t^P$	Price of product $P$ in year $t$ (thousand US\$), $t \in Mkt$
$\varphi$	Funding available (thousand US\$)
Facility	
$\sigma_{Fs}$	Facility footprint for facility scale $Fs$ (m <sup>2</sup> )
$Inv_{Fs}^f$	Investment cost of facility at location $f$ and scale $Fs$ (thousand US\$)
$\tau_{Ft,Fs}^f$	Set-up time of facility at location $f$ , type $Ft$ , scale $Fs$ (thousand US\$)
$Ctc_f$	Contract cost of engaging contract facility at $f$ (thousand US\$)
$FC_{Fs,Ft}^f$	Annual facility fixed cost for facility at location $f$ , type $Ft$ , scale $Fs$ (thousand US\$)
$\sigma_{support,Fs}$	Footprint of utilities and support equipment (m <sup>2</sup> )
$C_{support,Fs}$	Capital Cost of utility equipment (thousand US\$)
$\sigma_{core,Fs}$	Footprint of core equipment for facility scale $Fs$ (m <sup>2</sup> )
$C_{core,Fs}$	Capital cost of Core equipment for facility scale $Fs$ (thousand US\$)
$\sigma_{QC,Fs}$	Footprint of quality control (QC) equipment space for facility scale $Fs$ (m <sup>2</sup> )
$C_{QC,Fs}$	Capital cost of QC equipment for facility scale $Fs$ (thousand US\$)

$\sigma_{eq,m,Fs}$	Production equipment floor space for process $m$ (m <sup>2</sup> )
$C_{eq,m,Fs}$	Capital cost of production equipment for process $m$ (thousand US\$)
$maxps_{Fs}$	Max production space for facility of scale $Fs$
$m$	Maximum operating days in each time period
$Op_{cost}$	Facility operating cost per square meter per year (thousand US\$)
$Inv_{Fs}^f$	Investment cost of a facility at location $f$ and scale $Fs$
Cost of goods	
$VCCOG^P$	Manufacturing variable cost of goods of product $P$ (thousand US\$)
$Out_{Ft}$	Outsource penalty of facility type $Ft$
$Sp_{Fs}$	Scale penalty of facility scale $Fs$
$Lp_f$	Location penalty of facility location $f$
$COG_{Fs,Ft}^{P,f}$	Cost of goods of product $P$ at facility location $f$ , type $Ft$ , scale (thousand US\$)
$d_h^f$	Distance between facility at $f$ and hospital at $h$ (in miles)
$tc$	Transport cost per mile (US\$)
$tr_h^f$	Transport cost per treatment (US\$)
$Pt^P$	Process turnaround time for product $P$ (days)
$\delta_t$	Discount factor at year $t$

## Variables

$FI_t$	Investment cost at year $t$
$Ctrt_t$	Contract cost at year $t$
$EqInvCost_t$	Production equipment investment cost at year $t$
$FEqInvCost_t$	Fixed equipment (support, core and QC) investment cost at year $t$
$EqP_{f,Ft,Fs,t}^m$	Number of equipment for process $m$ purchased for facility at $f$ of scale $Fs$ at year $t$
$EqNo_{f,Ft,Fs,t}^m$	Number of equipment available for process $m$ at facility location $f$ , type $Ft$ , scale $Fs$ at year $t$
$EqCapacity_{f,Ft,Fs,t}^{Complex}$	Annual maximum operational days of available complex equipment for producing complex products
$EqCapacity_{f,Ft,Fs,t}^{Simple}$	Maximum operational days of available simple equipment for producing simple products
$Fixop_t$	Fixed operating costs at year $t$
$Trt_{f,Ft,Fs,t}^{Complex}$	Complex treatments produced at facility location $f$ , type $Ft$ , scale $Fs$ at year $t$
$Trt_{f,Ft,Fs,t}^{Simple}$	Simple treatments produced at facility location $f$ , type $Ft$ , scale $Fs$ at year $t$
$TrTH_{h,t}^P$	Product $P$ delivered at hospital $h$ in year $t$
$TTH_t^P$	Total treatment $P$ delivered in all hospitals at year $t$
$TTP_t^P$	Total treatment $P$ produced in all facilities at year $t$
$\varepsilon_{f,Ft,Fs,h,t}^P$	Total treatment $P$ delivered at hospital $h$ from facility location $f$ , type $Ft$ , scale $Fs$ at year $t$
$Sales_t^P$	Total sales of product $P$ at year $t$ (in US\$)
$Transport_t$	Total transportation cost at year $t$ (US\$)
$TCOG_t$	Total COG at year $t$ (US\$)
$TRev_t$	Total revenue at year $t$ (US\$)
$cflow_t$	Total cashflow at year $t$ (US\$)
$NPV$	Net present value over time horizon (US\$)

## Binary variables

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

### Mathematical descriptions

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

#### Facility-level constraints & costing

##### Facility availability constraint

##### Contract manufacturing facilities

It is assumed that at every location, a pilot-scale contract manufacturing facility (CMO) is available to be engaged at the start of the time horizon for planning. Contracting out manufacturing to CMOs requires no upfront capital investment, but it involves contract negotiations for the price, intellectual property ownership and exclusivity that require significant technical and legal expertise [24]. Hence, an upfront cost for contract negotiation ( $Ctc_f$ ) is required, as well as a contract negotiation period ( $\tau_{contract,pilot}^f$ ). The contract facilities are assumed to have a fixed number of equipment for complex and simple processes ( $EqNo_{f,contract,pilot,t}^{Ppt}$ ).

##### Newbuild facilities

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

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

$$A_{Ft,Fs,t}^f \leq A_{Ft,Fs,t-1}^f + Fac_{Ft,Fs,t-\tau_{Ft,Fs}^f}^f \quad (\text{Equation 1})$$

##### Contract facility upfront cost

As explained in Equation 1, if a contract facility is engaged at year  $t$ , the binary variable  $Fac_{contract,pilot,t}^f$  is assigned to be 1. An upfront cost of engaging a contract facility will be incurred (once the negotiation is concluded) to account for contract negotiation costs or retainer contract costs (upfront contract cost even if nothing is produced; Equation 2).

$$Ctct_t = \sum_f Fac_{contract,Fs,pilot,t-\tau_{contract,pilot}^f}^f * Ctc_f \quad (\text{Equation 2})$$

##### Newbuild facility investment cost

The investment cost of a facility at location  $f$  and scale  $Fs$  is given by  $Inv_{Fs}^f$ , which includes design and construction costs, basic cleanroom hardware (cleanroom panels), land costs and qualification and validation costs. If the decision of building a facility is made at year  $t$  (i.e.,  $Fac_{newbuild,Fs,t}^f = 1$ ), the facility investment cost ( $FI_t$ ) is given by Equation 3.

$$FI_t = \sum_f \sum_{Ft} \sum_{Fs} Fac_{Ft,Fs,t}^f * Inv_{Fs}^f \quad (\text{Equation 3})$$

##### Fixed facility costs & fixed operating costs

Fixed facility costs include the rental and land cost of the facility ( $FC_{Ft,Fs}^f$ ) and the fixed operating costs ( $Fixop_t$ ) are the fixed operating costs of running the heat, ventilation and air-conditioning (HVAC) of the facility (Equation 4). The fixed operating costs are given by the cost of air changes per m<sup>2</sup> ( $Opcost$ ) multiplied by the footprint of facility ( $\sigma_{Fs}$ ), which is scale-dependent.

$$Fixop_t = \sum_f \sum_{Ft} \sum_{Fs} (A_{Ft,Fs,t}^f * (\sigma_{Fs} * Opcost + FC_{Ft,Fs}^f)) \quad (\text{Equation 4})$$

#### Equipment-level constraints & costing

##### Equipment availability constraint

Closed processes are assumed for each facility to allow parallel production of treatments for different patients within the same cleanroom with a grade C/D background and reduced risks of cross-contamination. Shared space and

equipment are assumed within a facility to account for equipment common for all types of processes. A facility is divided into four main spaces as shown in the illustrative facility schematic shown in [Supplementary Material 2](#).

The support footprint ( $\sigma_{support, F_s}$ ) accounts for airlocks between cleanrooms and corridors, changing rooms, waste management, utilities and HVAC areas. QC footprint ( $\sigma_{QC, F_s}$ ) accounts for the area required for quality control (QC) equipment. Core equipment footprint ( $\sigma_{core, F_s}$ ) accounts for the area required for core equipment such as filling lines, incubators and cold storage facilities. These spaces are dependent on the scale of the facility, in other words, the bigger the facility the more support space is required. The remaining space in the facility is given by Equation 5A and can be used to accommodate production equipment.

Production equipment footprint ( $\sigma_{eq, m, F_s}$ ) is dependent on the number of equipment to support the quantity of products P produced using process m. The number of production equipment that can be accommodated in an available facility is constrained by Equation 5B.

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

$$\max ps_{F_s} = \sigma_{F_s} - \sigma_{support, F_s} - \sigma_{core, F_s} - \sigma_{QC, F_s} \quad (\text{Equation 5A})$$

$$\max ps_{F_s} * A_{F_t, F_s, t}^f \geq \sum_m (EqNo_{f, F_t, F_s, t}^m * \sigma_{eq, m, F_s}) \quad (\text{Equation 5B})$$

Equipment available at given year  $t$  ( $EqNo_{f, F_t, F_s, t}^m$ ) is the number of equipment available in the previous year plus the equipment purchased during the period ( $EqP_{f, F_s, t}^m$ ). It is assumed that the equipment purchased the year before will stay in the facility for the lifetime of the facility (Equation 6) and therefore the equipment purchased must be a positive integer (Equation 7).

$$EqNo_{f, newbuild, F_s, t}^m = EqNo_{f, newbuild, F_s, t-1}^m + EqP_{f, newbuild, F_s, t}^m \quad (\text{Equation 6})$$

$$EqP_{f, newbuild, F_s, t}^m \geq 0 \quad (\text{Equation 7})$$

#### Equipment investment cost

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

Support equipment refers to HVAC, utilities and environmental monitoring system-related equipment, and the capital cost is dependent on facility scale ( $C_{support, F_s}$ ). Core equipment costs ( $C_{core, F_s}$ ) refer to costs of equipment core to all processes such as filling lines, incubators and cold storage facilities ([Supplementary Material 7 \[1\]](#)). QC equipment costs ( $C_{QC, F_s}$ ) refer to costs of equipment for product quality control, the list of commonly used are listed in [Supplementary Material 7 \(2; Equation 8\)](#).

Production equipment can be purchased at any point after the completion of the facility and as demand arises. Therefore, the equipment investment cost at a certain year is given by the number of equipment purchased that year multiplied by the capital cost of the production equipment (Equation 9).

$$FEqInvCost_t = \sum_f \sum_{F_s} Fac_{newbuild, F_s, t}^f * (C_{support, F_s} + C_{core, F_s} + C_{QC, F_s}) \quad (\text{Equation 8})$$

$$EqInvCost_t = \sum_f \sum_{F_s} \sum_m C_{eq, m, F_s} * EqP_{f, newbuild, F_s, t}^m \quad (\text{Equation 9})$$

#### Product-level constraints

##### Product type & demand

The types of cell therapy products can be generalized into simple and complex, where simple products require a simple process to produce (i.e., expansion process without genetic modifications) and complex products require a complex process to produce (i.e., require genetic modifications through viral transduction). The annual product demand at each hospital ( $Dd_{m, t}^{P, h}$ ) is assumed to be a known parameter. Only products authorized for market use are allowed to be sold at the expected price ( $Price_t^P$ ); products in clinical trials are not reimbursed and are costed as developmental costs.



Equations 10 and 11 aggregate, respectively, the total demand for each complex ( $CD_{te}^P$ ) and simple product ( $SD_{te}^P$ ) across all hospitals at location  $h$ .

$$CD_t^P = \sum_h Dd_{Complex,t}^{P,h} \quad (\text{Equation 10})$$

$$SD_t^P = \sum_h Dd_{Simple,t}^{P,h} \quad (\text{Equation 11})$$

### Product production & cost of goods

#### Equipment capacity constraint

The number of products produced cannot exceed the maximum capacity of the facility and its available equipment. Complex products can only be produced using complex equipment (Equation 12) and simple products can only be produced using simple equipment (Equation 13).

$$\sum_P TrtF_{f,Ft,Fs,t}^{Complex} * Pt_p \leq EqNo_{f,Ft,Fs,t}^{Complex} * M \forall P \in CP \quad (\text{Equation 12})$$

$$\sum_P TrtF_{f,Ft,Fs,t}^{Simple} * Pt_p \leq EqNo_{f,Ft,Fs,t}^{Simple} * M \forall P \in SP \quad (\text{Equation 13})$$

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

While scale-out manufacturing is a more common approach for autologous cell therapies, better utilization of human resources and equipment allows a certain degree of economies of scale [6]. Therefore, a scale penalty ( $Sp_{Fs}$ ) is used to account for scale-related cost savings.

For outsourcing, successful contract manufacturers generally operate at 20–30% profit margins [25], hence, an outsource penalty cost multiplier ( $Out_{Ft}$ ) is used to simulate the additional costs incurred. A location penalty multiplier ( $Lp_f$ ) is used to account for areas where the costs of lab our is more expensive, for example, London.

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

$$COG_{Fs,Ft}^{P,f} = VCCOG^P * Out_{Ft} * Sp_{Fs} * Lp_f \quad (\text{Equation 14})$$

#### Complete product consumption constraint

As a feature of autologous cell therapy, all products manufactured must be used at the hospitals where the initial demand arose, therefore the total number of treatments delivered at hospitals equals to the total number of the treatments produced at the facilities (Equation 15). The total number of treatments delivered at hospital  $h$  equals the total number of treatments produced that are delivered to the hospital (Equation 16). The total number of treatments produced at a certain facility equals the total number of treatments demanded at all hospitals produced at the facility (Equation 17).

$$TTP_t^P = TTH_t^P = \sum_h TrtH_{h,t}^P = \sum_f \sum_{F_t} \sum_{F_s} TrtF_{f,Ft,Fs,t}^P \quad (\text{Equation 15})$$

$$TrtH_{h,t}^P = \sum_f \sum_{F_t} \sum_{F_s} \varepsilon_{f,Ft,Fs,h,t}^P \quad (\text{Equation 16})$$

$$TrtF_{f,Ft,Fs,h,t}^P = \sum_h \varepsilon_{f,Ft,Fs,h,t}^P \quad (\text{Equation 17})$$

#### Transportation costs

For autologous therapies, transportation between facilities and hospitals is an important cost to consider as the raw material originates from patients and must finally be delivered to the same patient at the same hospital. Transportation cost per treatment from the hospital at  $h$  to the facility at  $f$  and back ( $tr_b^f$ ) is given by the transportation cost



per mile ( $tc$ ) multiplied by the return distance between the hospital and facility ( $d_h^f * 2$ ; Equation 18).

$$tr_h^f = tc * d_h^f * 2 \quad (\text{Equation 18})$$

The total transportation cost ( $Transport_t$ ) incurred in year  $t$  is given by the total number of treatments delivered from hospital at  $h$  to facility at  $lf$  at year  $t$  ( $\epsilon_{f,Ft,Fs,h,t}^P$ ; Equation 19).

$$Transport_t = \sum_P \sum_f \sum_{Ft} \sum_{Fs} \sum_h \epsilon_{f,Ft,Fs,h,t}^P * tr_h^f \quad (\text{Equation 19})$$

#### Clinical trial & sales constraint

For the optimization model to decide which product to invest in and produce, a binary variable ( $V_p$ ) is used, where  $V_p$  equals 1 if the product is selected.

Since the planning objective to maximize overall NPV, it may decide not to produce products to its maximum demand. However, to ensure that products are produced for clinical trial phases, product demand during clinical trial phases must be met despite the products not fetching any reimbursements (Equation 20).

$$TrtH_{h,t}^P = \sum_m Dd_{m,t}^{P,h} * V_p \quad \forall t \in CT \quad (\text{Equation 20})$$

The number of treatments of product  $P$  delivered at the hospital at location  $h$  cannot exceed the demand of the product at the same hospital when the product is on market (Equation 21).

$$TrtH_{h,t}^P \leq \sum_m Dd_{m,t}^{P,h} * V_p \quad \forall t \in Mkt \quad (\text{Equation 21})$$

#### Product sales & revenue

The annual sales of each product at year  $t$  is given by the total treatments multiplied by the price of the product ( $Price_{te}^P$ ; Equation 22). The product can only be sold when it receives its market authorization; before then, the selling price equals zero (Equation 23).

$$Sales_{Mkt}^P = \sum_P \sum_f \sum_{Ft} \sum_{Fs} \sum_h \epsilon_{f,Ft,Fs,h,t}^P * Price_t^P \quad \forall t \in Mkt \quad (\text{Equation 22})$$

$$Sales_t^P = 0 \quad \forall t \in CT \quad (\text{Equation 23})$$

The total revenue is given by the summation of all sales of developed products (Equation 24).

$$TRev_t = \sum_P Sales_t^P \quad (\text{Equation 24})$$

#### Objective function & overall capital constraint

During the development phase, the total amount of capital is limited by the investment capital raised. Therefore, the summation of the cash flows during the development phase is limited by the funding available ( $\phi$ ; Equation 25).

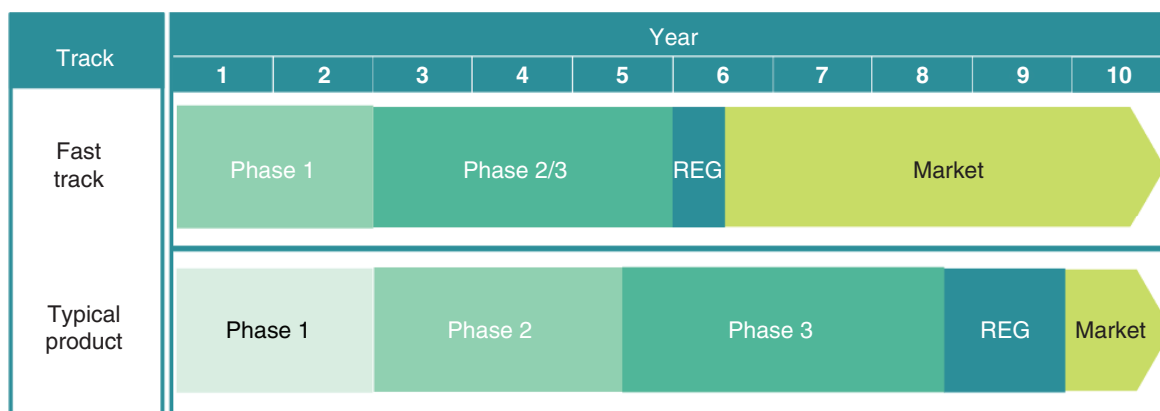
$$\phi \leq \sum_t cflow_{CT} \quad \forall t \in Mkt \quad (\text{Equation 25})$$

Discount factors are used for discounting future investments or cash flows into current values using the interest rate ( $r$ ). It is a weighing factor that is commonly used to reflect the present value of future cash flows (Equation 26).

$$\delta_t = \frac{1}{(1+r)^t} \quad (\text{Equation 26})$$

Over the time horizon, it is assumed that the objective of the company is to maximize its financial returns through optimizing its capacity investment strategies based on the product development portfolio, for example, prioritizing products that will bring the most financial returns while minimizing capital expenses.

The cash flow in a certain year is given by the incomes minus the costs incurred in the year (Equation 27). Cash flow ( $cflow_t$ ) is the total revenue ( $TRev_t$ ) minus the facility investment ( $FI_t$ ), contract set-up ( $Ctrl_t$ ), equipment procurement (Fixed,  $FEqInvCost_t$  and production equipment  $EqInvCost_t$ ), fixed operating costs ( $Fixop_t$ ), total



**Figure 2.** Product development timeline of unmet medical need product.

variable cost of goods ( $TCOG_t$ ) and transportation costs ( $Transport_t$ ; Equation 27).

$$cflow_t = \begin{aligned} &TRev_t - FI_t - Ctrt_t - FEqInvCost_t - EqInvCost_t \\ &- Fixop_t - TCOG_t - Transport_t \end{aligned} \quad (\text{Equation 27})$$

The overall objective of this model is to maximize the NPV of the product portfolio. The summation of discounted cashflows at each year gives the expected NPV over the time horizon (Equation 28).

$$NPV = \sum_t cflow_t * \delta_t \quad (\text{Equation 28})$$

#### Model application on an illustrative case study

The mathematical model was implemented within the general algebraic modeling system (GAMS) 26.2 and the problem was solved using the CPLEX solver. The optimization was performed on an Intel Core i5–2500K 3.3 GHz processor, with 12 GB random access memory. All optimizations were completed to optimality. Two scenarios of a UK-based case study, with fast-track (FT) and without fast-track designations (NFT), are solved to validate the proposed mathematical model. The main advantages of fast-track regulatory schemes (detailed in [Supplementary Material 1](#)) are shorter review times, quicker approvals and conditional market authorizations. In this study, this is reflected by the shorter product development timeline and the early ‘takeoff’ of the product demand levels ([Supplementary Material 4](#)).

The time horizon for this study is taken to be 20 years, reflecting the typical patent exclusivity period before the entrance of generic products [26]. In this model, a discrete-time formulation is used, in other words, time horizon is discretized into 1-year time intervals. As single-use closed automated systems are assumed to be used at scale, the changeover time is assumed to be negligible in the time horizon of 20 years. [Figure 2](#) shows the product development timeline of orphan/unmet medical need products versus the typical drug development timeline.

The number of products and manufacturing capacity investment is limited by the availability of funding ( $\varphi$ ). The model optimizes the product portfolio based on the amount of funding available. Benchmarking against typical series A–C funding rounds, available funding ranges from US\$10 to 200 million [27].

#### Product portfolio & demand scenario

A hypothetical product portfolio can be found in [Table 1](#). The demand level of cell therapy products are categorized into niche and mass, where niche products are targeted at orphan diseases with a small patient population (e.g., late-stage rare blood cancers such as acute lymphoblastic leukemia) and mass products are targeted at a larger patient population (e.g., solid tumours, cartilage). A list of products, their estimated demand and price base on NICE and NHS estimates for five indications are shown in [Table 1](#). It is assumed that only products authorized for market use are allowed to be sold and products in clinical trials are not reimbursed.

In this study, four geographical locations are assumed for hospital and facility locations for illustrative purposes, namely London, Bristol, Newcastle and Edinburgh. All hospital locations are assumed to be capable of delivering

**Table 1. Hypothetical product data.**

Product, $P$	Clinical indication	Annual UK demand	Selling price $Price_t^P$ (\$)	Process type, $m$	Cost per treatment, $COG_{Fs, Ft}^{P, f}$ (US\$)	Process duration, $Pt^P$ (days)	Ref.
P1	Cartilage transplantation	500	20,000	Simple	3000	20	[28]
P2	Limbal stem cell deficiency	100	100,000	Simple	10,000	14	[29]
P3	Refractory large B-cell lymphoma	200	475,000	Complex	60,000	20	[30]
P4	Multiple myeloma	2100	276,000	Complex	40,000	14	[31]
P5	Stage IV breast cancer	5500	200,000	Complex	45,000	14	[32,33]

both complex and simple products. The distance between the locations ( $d_b^f$ ) can be found in [Supplementary Material 3](#), and the location influences the cost of manufacturing (Equation 14) and the transportation costs (Equation 18).

The national product demand for both scenarios, with fast-track designations and without fast-track designations, are distributed among the four locations at a ratio of 4:2:2:2. After market approval, a ‘ramp-up’ period is assumed to simulate the time needed for a mature sales level to be reached [34], [Supplementary Material 4](#) shows the forecasted demand level for each product.

The problem is defined such that the capacity planning decision will be made at the initial year under the assumption that products will be successful in clinical trials. The exact product demand for each product in various hospital location in each year within the time horizon is given in [Supplementary Material 5](#).

#### Facility & equipment assumptions

The facility assumptions are shown in [Supplementary Material 6](#). According to Airgate Engineering (Hong Kong), a cleanroom design and construction company based in Hong Kong, support space accounts for around 40% of the whole facility for small facilities and 20% for larger ones. Floor space occupied by core, QC and production equipment is calculated by summation of individual equipment footprint that is estimated by the equipment size specified in manufacturer manuals plus 1 meter of working space allowed around each equipment. [Supplementary Material 7](#) shows the list of equipment included and their size and floorspace requirement.

Other model parameters are provided in [Supplementary Material 8](#).

#### Sensitivity analysis

The main barriers to cell therapy commercial adoption identified by Davies *et al.* are reimbursement, manufacturing and cost–effectiveness [35] and distribution logistics is another important challenge mentioned by Dodson *et al.* [1]. To better analyze the effect of commercialization challenge-related parameters on the NPV and the robustness of the investment plan, a sensitivity analysis of the following parameters is conducted:

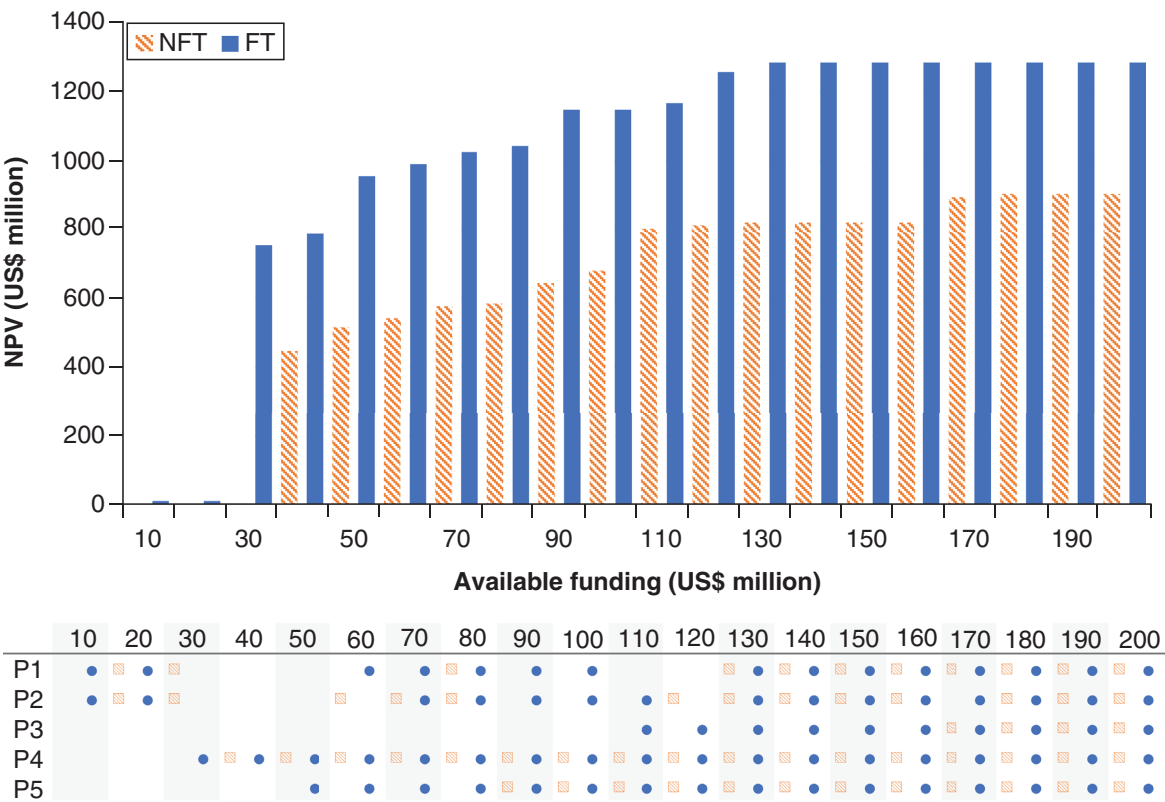
- Funding availability: funding available ( $\phi$ );
- Reimbursement: product selling price ( $Price_t^P$ ), product demand uptake ( $Dd_{m,t}^{P,b}$ );
- Manufacturing: variable COG of product ( $VCCOG^P$ ), process turnaround time ( $Pt(P)$ );
- Logistics: transport cost per mile ( $tc$ ).

## Results

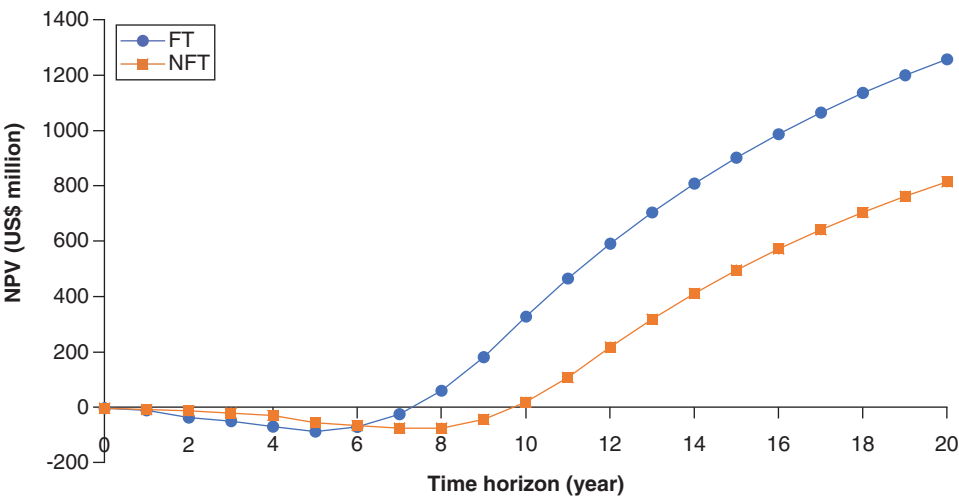
### Product selection decision

The set of five candidate products represents the characteristics of a variety of currently commercialized autologous products. P1 represents a moderate demand product with an indication with a relatively low reimbursement price. P2 illustrates the case of a niche demand product with a higher reimbursement price. P3 represents a niche product for a high-value indication. P4 and P5 finally represent high demand products for high-value indications. Two scenarios are compared, FT and NFT designations.

Figure 3A shows the changes in NPV and product portfolio selected with increasing available funding (Figure 3B). For both scenarios, with a limited amount of funding, P1 and P2 are selected. P1 and P2 require cheaper upfront equipment investments and lower variable cost of goods but fetches a lower selling price. With a higher amount of investment funds, complex products with higher annual demands (P4, P5) are preferred. Although the selling price of these products is relatively lower compared with P3, the market size is much greater and delivers a greater

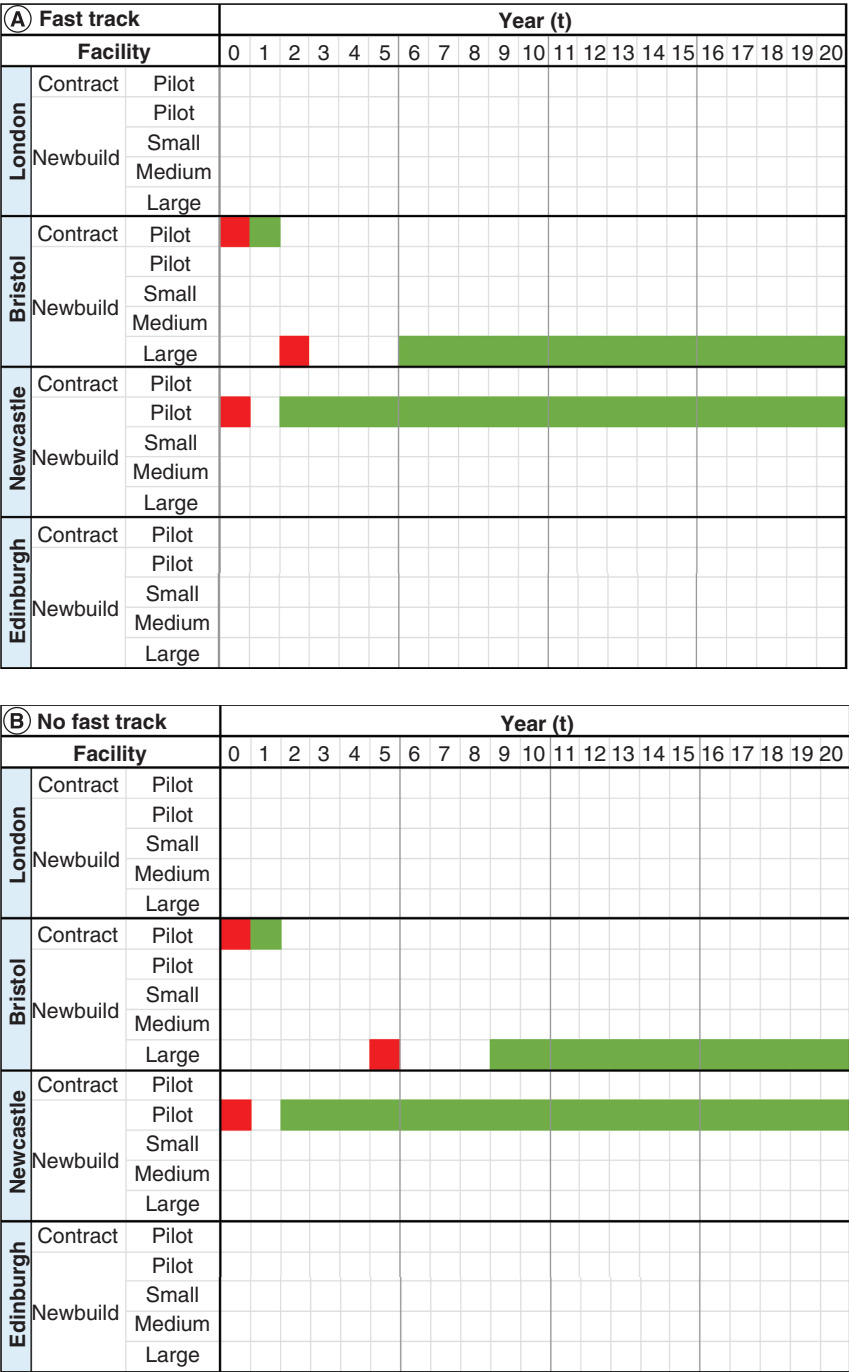


**Figure 3. Changes in net present value and product portfolio selected with increasing available funding. (A)** NPV of the product portfolio with increasing funding available for the scenario with fast-track designations and without. **(B)** Table showing the products selected for development and scale-up manufacturing, where orange represents scenario NFT and blue represents scenario FT. FT: With fast-track; NFT: Without fast-track; NPV: Net present value; P: Product.



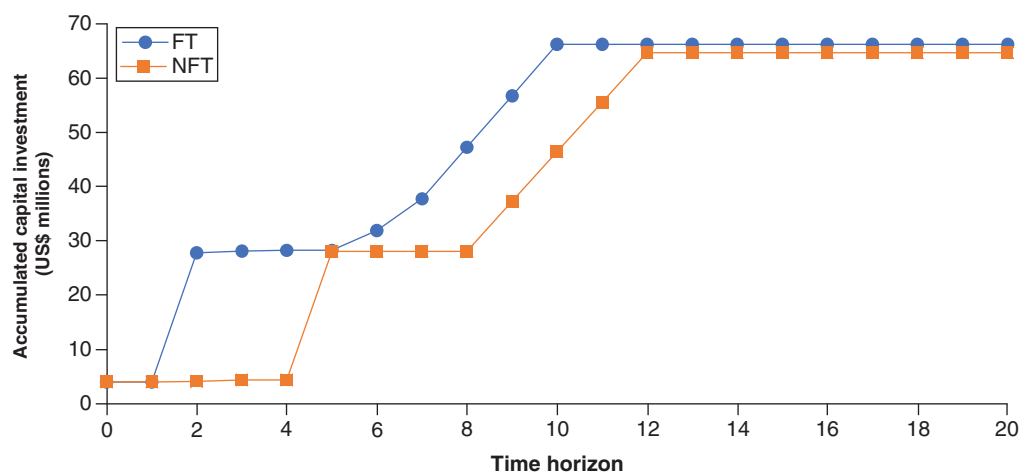
**Figure 4. Net present value over time horizon for investment funding constraint of US\$120 million.** FT: With fast-track; NFT: Without fast-track; NPV: Net present value.

overall return. With funding above US\$40 million, the NPV for scenario FT is consistently higher than that of scenario NFT, by a range from 40% ( $\phi = \$180\text{--}200$  million) to 86% ( $\phi = \$50$  million).



**Figure 5. Facility investment schedule over time horizon. (A) Fast track scenario. (B) No fast track scenario.** Red blocks show the decision to build/engage, green blocks show period when the facility is available. t: Time.

A more in-depth analysis of the discounted NPV over 20 years for an investment funding constraint of US\$120 million shows that the breakeven for scenario FT occurs at year 7.5, approximately 2.5 years earlier than the scenario NFT schemes. This represents a 25% reduction in the time to achieve breakeven of investments (Figure 5).



**Figure 6. Facility and equipment capital investment for scenario with fast-track and without fast-track over 20 years.**

FT: With fast-track; NFT: Without fast-track.

### Facility investment decision schedule

Further analysis with  $\phi = \text{US\$120 million}$  is considered, where for both scenarios four products are selected to be developed and manufactured.

The facility investment and equipment purchase decision schedule are shown in Figure 5. For both scenarios, CMO are engaged at base year to produce clinical trial materials and disengaged once the newbuild pilot facility is available. As the clinical trial demand for all chosen products is forced to be completely satisfied, both scenarios invested in newbuild facilities early in the time horizon. Once newbuild facilities are available, contract facilities are no longer engaged.

Comparing the two scenarios, the decision to invest in a larger-centralized facility (built at Bristol, Figure 5) came in earlier at year 2 on in the FT scenario rather than year 5 in the NFT scenario, and correspondingly larger upfront investment is incurred earlier (Figure 6). In terms of the total facility and equipment capital investment costs, those of scenario FT are 2% higher than scenario NFT. Due to the long construction and validation lead-times of facilities, it is noted that for the fast-track option, the investment decisions to build a large newbuild facility is made at year 2, which is 3 years earlier for the NFT scenario, highlighting the high capital risk nature of commercialization of autologous cell therapies, especially with the crunched timeline.

### Product distribution

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

### Sensitivity analysis

To understand the sensitivity of the NPV to market and manufacturing uncertainties and the robustness of the product selection robustness, the input parameters were varied  $\pm 20\%$ . A sensitivity analysis was conducted for capital funding investment of US\$120 million.

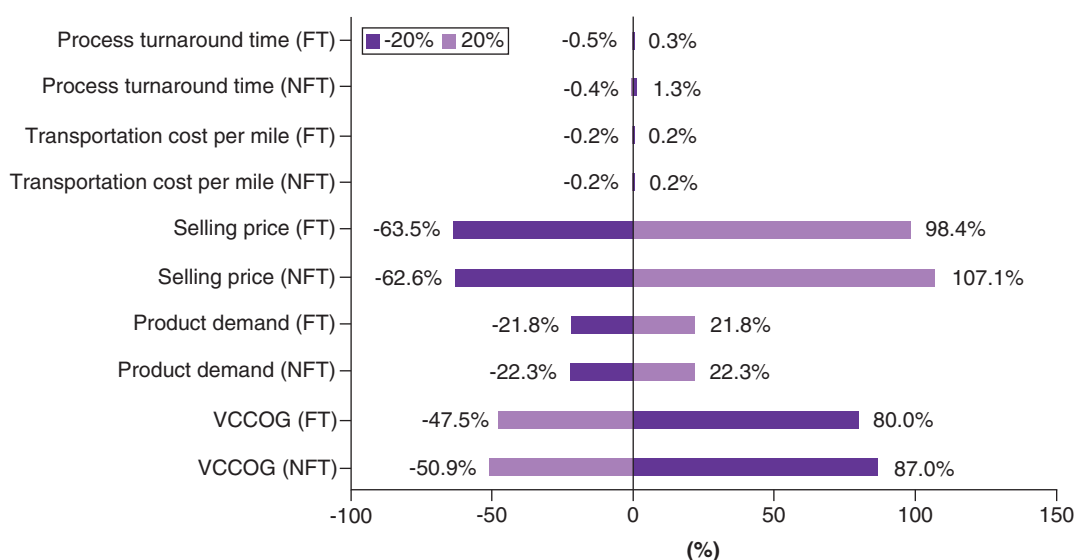
As the model allows for simultaneous optimization of product selection and capacity planning, changes in the input parameters have an impact on both product selection and facility investment decisions and in turn the NPV over the time horizon (Table 2). The product selection decision is more robust in scenario FT with fewer changes in the product portfolio. This, in turn, impacts facility investment and equipment investment decisions.

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

**Table 2. Product selection portfolio with changes in input parameters (A) without fast-track and (B) fast-track.**

A	Product characteristic			Without fast track														
	Demand	Indication value	Process type	VCCOG			Product demand			Selling price			Transportation cost			Process turnaround time		
				-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%
P1	Moderate	Low	Simple	✓		✓				✓						✓		
P2	Niche	Moderate	Simple	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
P3	Niche	Very High	Complex							✓								
P4	High	High	Complex	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
P5	Very high	High	Complex	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
B	Product characteristic			With fast track														
	Demand	Indication value	Process type	VCCOG			Product demand			Selling price			Transportation cost			Process turnaround time		
				-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%	-20%	0	+20%
P1	Moderate	Low	Simple	✓		✓				✓								
P2	Niche	Moderate	Simple	✓		✓				✓								
P3	Niche	Very high	Complex	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
P4	High	High	Complex	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
P5	Very high	High	Complex	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

P: Product; VCCOG: Variable cost of good.

**Figure 7. Sensitivity of net present value to parameter changes.**

FT: With fast-track; NFT: Without fast-track; VCCOG: Variable cost of good.

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

For both scenarios, the overall NPV is most sensitive to the selling price, followed by the manufacturing variable cost of goods and finally the product demand; the sensitivity to the transportation cost and the process turnaround time is minimal (Figure 7). Transportation only accounts for around 0.1–0.2% of the total cost and hence its changes have very little impact on the overall cost and NPV. Scenario NFT is more sensitive to negative changes in both price and manufacturing variable costs than scenario FT.

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



Table 3. Model statistics for various numbers of products, hospital and facility locations at $\Phi = \$120m$ .					
Case	Equations (n)	Variables (n)	Nonzero elements (n)	Discrete variables (n)	CPU solution time (s)
5P, 4lh, 4lf (base case)	15,081	21,499	91,900	20,973	9.86
10 P, 10lh, 10lf	47,622	197,115	781,421	196,274	19.47
20 P, 20lh, 20lf	137,032	1,439,815	5,520,531	1,438,344	62.05
CPU: Central processing unit; lf: Facility location; lh: hospital; P: Product.					

decrease in manufacturing variable costs, for both scenarios, P1 is selected. Although the profit margin for P1 is smaller, the barrier of commercialization P1 is also the lowest as shown by the low required funding as shown in Figure 3.

Computational statistics

The case study presented in detail here is relatively small, comprising five products, four hospital locations and four facility locations. However, the formulation can be applied to larger-scale problems. As summarized in Table 3, the numbers of equations and variables increase substantially with the size of the problem, making the numerical solution computationally more demanding yet still handleable.

Discussion

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

Specific to the unique challenges of commercializing autologous cell therapies, this model addressed scale-out, geographical constraints, long-term capacity investment decisions and the unique regulatory routes of these therapies. A relatively small system is evaluated to illustrate the impact of these fast-track designations on the commercialization pathways. With a small number of hospital locations considered, the model favored a centralized facility, which is closer to the hub-and-spoke model which is currently favored for advanced therapies instead of the decentralized single-center colocated manufacturing approach [36].

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

Fast-track regulatory designations can allow companies to achieve breakeven years earlier and higher NPV over the time horizon (Figure 4). This is consistent with the observations by Capital Cell, an online investment platform for healthcare and biotechnology in Europe, which concluded that fast-track therapeutics provide lower exit times and higher valuations [37]. A review of the value of companies holding Breakthrough Therapy Designations also shows that such designations add significant value to the company [38].

However, with the crunched development timeline, large upfront investments for manufacturing would be incurred earlier. This can have great risk implications, especially for small–medium enterprises seeking to commercialize clinical-stage autologous cell therapy products. Second, with a small amount of clinical data, the risk of the marketed product may be higher. A review on fast-tracked products withdrawn cited lack of efficacy, adverse events and safety issues as the main reasons for withdrawal [39]. Further analysis looking into the trade-off between developmental risks and speed-to-approval can be critical in instilling patient and commercial confidence in such therapies.

Strengths & limitations of the model

This model considers common product-market characteristics, manufacturing scale-out instead of scale-up to simultaneously optimize strategic commercialization decisions such as product portfolio selection, facility and equipment selection for autologous cell therapies. The impact of the introduction of fast-track schemes for therapies targeting unmet medical need is considered in a comparative scenario analysis exercise. Using sensitivity analysis, we identified the critical input parameters that the system is most sensitive to.

For illustrate the impact of regulatory incentives, the MILP model is applied to a UK-specific example to demonstrate the applicability of the model. With further extensions including tax and trading structures, the model can be applied for simultaneous facility planning and product portfolio selection for a wider region. Also, cross-

national regulation harmonization is a challenge faced by the regenerative medicine industry [40]. A limitation of the model is that the costs of patents and intellectual property rights are not considered. IP licensing is a cost that can be significant in the product development process [41]. However, this is considered out of scope for analyzing the impact of fast-track regulatory schemes on product portfolio selection and overall project NPV. Another limitation is that clinical trial failure is not accounted for. However, it is unrealistic to assume that each product will be successful in clinical trials, the model can serve as a decision aid for companies that need to produce capacity investment plans for internal planning and capital raising purposes. In addition, the reduced timeline for clinical trial phases also leads to crunched timelines for process development for scaling up/out operations, which may in turn require significant adjustment in manufacturing strategy and supply chain management later in the development incurring time delay and additional costs [42]. Future extensions to the model will consider stochasticity in product demand and probabilities of failures in clinical trials.

The model proposed is a deterministic model and a sensitivity analysis was conducted to address the parametric uncertainties. The main intention of this work is to better understand the impact of fast-track approval processes on commercialization decisions. However, the approach is limited in addressing issues such as time-varying uncertainty. Future work could explore more sophisticated approaches such as stochastic programming.

## Conclusion

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

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

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

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

## Future perspective

Given the increasing number of clinical trials of innovative therapies for unmet medical needs, it is important to consider the implications of specific regulatory incentives on the process development and commercial development timelines to optimize the commercialization pathway of autologous cell therapies.

This study highlighted the high capital risks associated with these therapies under crunched timelines and the need to better understand the associated uncertainties and market conditions for successful commercialization of these therapies. In addition, further research into the more iterative approach to process development where failures in trials provide learnings for future successes would be important, especially for rare diseases with unique disease pathways.

## Summary points

**Specific regulatory incentives for innovative therapies for unmet medical needs**

- Regulatory authorities around the world have introduced various incentives to improve the speed-to-market of innovative therapies.
- These fast-track designations have an impact on the process development and capital investment timelines for autologous cell therapies.

**Mixed-integer linear programming model**

- Concurrently optimizes facility investment timing, scale, location and product portfolio of autologous cell therapies.
- Assessed the impact of fast-track designations on commercialization of autologous therapies in terms of breakeven time and net present value (NPV).

**Illustrative example**

- Sensitivity analysis showed a reduction of the portfolio's sensitivity to selling price, manufacturing costs and demand fluctuations with fast-track designations.
- Variable manufacturing costs showed a higher than proportionate impact on the overall NPV for both scenarios.

**Conclusion**

- Fast-track designations are effective in helping drug developers achieve faster breakeven and higher NPV.

## Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/rme-2021-0061](http://www.futuremedicine.com/doi/suppl/10.2217/rme-2021-0061)

## Author contributions

C Lam conceptualized and carried out the modeling work and wrote the manuscript. A Yang and ZF Cui provided supervision to model construction, data analysis and simulation studies. E Meinert, A Yang and ZF Cui provided comments to the manuscript for better relevance and clarity. All the authors approved the final manuscript.

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