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

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Abstract

Background: Regulatory authorities around the world have introduced incentives to improve the speed-to-market of innovative therapies.

Aim and 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 optimisation of capacity investment and portfolio selection decisions to maximise 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 NPV 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 commercialisation incentives, but high capital risks given the compressed timeline should be better considered.

Keywords: autologous cell therapies, capacity planning, optimisation, regulatory, drug development, decisional tool

Introduction

Autologous cell therapies are a unique class of products where tissues/cell originate from the patient and are returned to the patient for therapeutic purposes. A previously published study examined three autologous interventions (Epicel, Provenge and Carticel) and summarised the premarket and post-market challenges of commercialising cell therapies, citing unclear regulatory environment and long developmental timelines as the main premarket challenges and manufacturing and supply chain challenges as two key post-market challenges [1]. More specifically, these challenges are manifested in three aspects.

Firstly, as the products are living cells, they are very sensitive to environmental changes and therefore to ensure safety and quality of the product, cold or ultra-cold supply chain has to be considered. Distribution logistics can have a massive impact on the formulation of the product and has to be considered early in the product development cycle [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 decentralised manufacturing [4].

Secondly, managing the cost of goods and marketing cost is a key contributing factor to commercial success. Lipsitz et al have outlined the cost of good (COG) planning roadmap for manufacturing of cell therapies from cell sourcing to patient administration [5]. An interesting challenge faced in the commercialisation of Dendreon, one of the first immunotherapy products for prostate cancer, was the financial implications of substantial upfront investment in specialised GMP production facilities. The lag in treatment adoption and the expensive underutilised facilities caused massive amounts of debts and eventual market failure [1]. Given the requirement for GMP-compliant facilities to be in place and listed for market authorisation, the lead strategy towards capacity planning (i.e. capacity added in anticipated of increase in demand) can become a huge burden for resource-constrained companies seeking to commercialise cell therapies.

Thirdly, autologous cell therapies are specific to the patient, which means manufacturing cannot be scaled up using larger-scale equipment and has to be scaled out to produce a single batch of therapy per patient. This not only diminishes the effect of traditional economies of scale but also presents risks in mix-ups and cross-contamination [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 FDA, manufacturing scale-up and production planning are often only considered in later phases of clinical trials [7]. When applying for market authorisation, the proposed manufacturing sites should be listed and must be GMP-compliant. Setting up GMP-compliant facilities is time-consuming and capital-intensive [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 optimisation of capacity planning for pharmaceuticals different from other industries such as agrochemicals. Ineffective capacity planning can lead to serious capacity crunches such as that faced by the monoclonal antibody (mAb) industry in the 1990s, which were estimated to have caused around $3-$4 billion in total revenue loss due to insufficient supply of products [9,10]. Papageorgiou et al studied the optimisation of investment strategies for product development and introduction of active pharmaceutical ingredient (API) [11] and others have looked into similar problems under uncertain clinical trial outcomes, market pressures and regulations [12]. Liu used a MILP approach to simultaneously optimise the global supply chain for pharmaceuticals considering costs, responsiveness and customer service levels [13]. For biopharmaceutical facility planning, Siganporia et al have formulated a discrete-time MILP model to optimise in-house and contract manufacturing decisions and to study the adoption of fed-batch and continuous perfusion culture processes [14]. More recently, Wang et al studied the CAR-T supply chain to maximise the overall net present value and minimise average response time of patients under demand distribution uncertainties [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. Optimisation studies have also been proposed to look at the use of mobile medical units for delivering therapies from manufacturing centres 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 commercialisation decisions such as timing for capital investment and portfolio considerations.

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

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to accelerate the commercialisation 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 1, phase 2, phase 3 clinical trial) to 2-3 years (small scale clinical trials with surrogate end-points) [22], which requires the industrialisation timeline for process development and capacity planning to be managed accordingly. Therefore, the industry needs to re-evaluate the outsourcing and investment strategies for securing manufacturing capacities to benefit fully from accelerated approval. This 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 maximise the net present value (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 decentralised facilities vs larger centralised facilities) and product portfolio.

Method

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

I.   Problem statement

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

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

II.   Model formulation

A uniform time discretisation mixed-integer linear programming (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 focusses on strategic decisions on portfolio, capacity planning and investment, paying particular attention on the impacts of regulatory programmes.

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

(1) Notations

Indices

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

Sets

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

Parameters

$Dd_{m,t}^{P,h}$	Annual Demand of product P at hospital h requiring process m at year t
CD_t^P	Annual demand for all complex products
SD_t^P	Annual demand for all simple products
$Price_t^P$	Price of product P in year t (thousand USD), $t \in Mkt$
φ	Funding available (thousand USD)
Facility	
σ_{Fs}	Facility footprint for facility scale Fs (m^2)
Inv_{Fs}^f	Investment cost of facility at location f and scale Fs (thousand USD)
$\tau f_{Ft,Fs}^f$	Set-up time of facility at location f, type Ft, scale Fs (thousand USD)
Ctc_f	Contract cost of engaging contract facility at f (thousand USD)

$FC_{Fs,Ft}^{f}$	Annual facility fixed cost for facility at location f, type Ft, scale Fs (thousand USD)
$\sigma_{support,Fs}$	Footprint of utilities and support equipment (m^2)
$C_{support,Fs}$	Capital Cost of utility equipment (thousand USD)
$\sigma_{core,Fs}$	Footprint of core equipment for facility scale Fs (m^2)
$C_{core,Fs}$	Capital cost of Core equipment for facility scale Fs (thousand USD)
$\sigma_{QC,Fs}$	Footprint of QC equipment space for facility scale Fs (m^2)
$C_{QC,Fs}$	Capital cost of QC equipment for facility scale Fs (thousand USD)
$\sigma_{eq,m,Fs}$	Production equipment floor space for process m (m^2)
$C_{eq,m,Fs}$	Capital cost of production equipment for process m (thousand USD)
$maxps_{Fs}$	Max production space for facility of scale Fs
M	Maximum operating days in each time period
$Opcost$	Facility operating cost per square meter per year (thousand USD)
Inv_{Fs}^{f}	Investment cost of a facility at location f and scale Fs
Cost of goods	
$VCCOG^{P}$	Manufacturing variable cost of goods of product P (thousand USD)
Out_{Ft}	Outsource penalty of facility type Ft
Sp_{Fs}	Scale penalty of facility scale Fs
Lp_{f}	Location penalty of facility location f
$COG_{Fs,Ft}^{P,f}$	Cost of goods of product P at facility location f, type Ft, scale (thousand USD)
d_{h}^{f}	Distance between facility at f and hospital at h (in miles)
tc	Transport cost per mile (USD)
tr_{h}^{f}	Transport cost per treatment (USD)
Pt^{P}	Process turnaround time for product P (days)
δ_{t}	Discount factor at year t

Variables

FI_{t}	Investment cost at year t

$Ctrt_t$	Contract cost at year t
$EqInvCost_t$	Production equipment investment cost at year t
$FEqInvCost_t$	Fixed equipment (support, core and QC) investment cost at year t
$EqP^m_{f,Ft,Fs,t}$	Number of equipment for process m purchased for facility at f of scale Fs at year t
$EqNo^m_{f,Ft,Fs,t}$	Number of equipment available for process m at facility location f, type Ft, scale Fs at year t
$EqCapacity^{Complex}_{f,Ft,Fs,t}$	Annual maximum operational days of available complex equipment for producing complex products
$EqCapacity^{Simple}_{f,Ft,Fs,t}$	Maximum operational days of available simple equipment for producing simple products
$Fixop_t$	Fixed operating costs at year t
$TrtF^{Complex}_{f,Ft,Fs,t}$	Complex treatments produced at facility location f, type Ft, scale Fs at year t
$TrTF^{Simple}_{f,Ft,Fs,t}$	Simple treatments produced at facility location f, type Ft, scale Fs at year t
$TrTH^P_{h,t}$	Product P delivered at hospital h in year t
TTH^P_t	Total treatment P delivered in all hospitals at year t
TTP^P_t	Total treatment P produced in all facilities at year t
$\varepsilon^P_{f,Ft,Fs,h,t}$	Total treatment P delivered at hospital h from facility location f, type Ft, scale Fs at year t
$Sales^P_t$	Total sales of product P at year t (in USD)
$Transport_t$	Total transportation cost at year t (USD)
$TCOG_t$	Total COG at year t (USD)
$TRev_t$	Total revenue at year t (USD)
$cflow_t$	Total cashflow at year t (USD)
NPV	Net present value over time horizon (USD)

Binary Variables

$Fac^f_{Ft,Fs,t}$	Facility investment decision of facility at location f, type Ft, scale Fs at year t

$A^f_{Ft,Fs,t}$	Facility availability at year t
V^P	Product selection decision

(2) Mathematical descriptions

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

Facility-level constraints and costing

Facility availability constraint

Contract manufacturing facilities (CMO)

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

Newbuild facilities

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

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

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

Contract facility upfront cost

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

$$Ctrt_t = \sum_f Fac^f_{contract,Fspilot,t-\tau f^f_{contract,pilot}} * Ctc_f \qquad \text{Eq 2}$$

Newbuild facility investment cost

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

$$FI_t = \sum_f \sum_{Ft} \sum_{Fs} Fac^f_{Ft,Fs,t} * Inv^f_{Fs} \qquad \text{Eq 3}$$

Fixed facility costs and fixed operating costs

Fixed facility costs include the rental and land cost of the facility ($FC^f_{Ft,Fs}$) and the fixed operating costs ($Fixop_t$) are the fixed operating costs of running the heat, ventilation and air-conditioning (HVAC) of the facility (*Eq 4*). The fixed operating costs is given by the cost of air changes per m² ($Opcost$) multiplied by the footprint of facility (σ_{Fs}) which is scale dependent.

$$Fixop_t = \sum_f \sum_{Ft} \sum_{Fs} (A^f_{Ft,Fs,t} * (\sigma_{Fs} * Opcost + FC^f_{Ft,Fs})) \qquad \text{Eq 4}$$

Equipment-level constraints and costing

Equipment availability constraint

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

A facility is divided into 4 main spaces as shown in the illustrative facility schematic shown in Supplementary Material 2.

The support footprint ($\sigma_{support,Fs}$) accounts for airlocks between cleanrooms and corridors, changing rooms, waste management, utilities and HVAC areas (heat, ventilation and air conditioning). QC footprint ($\sigma_{QC,Fs}$) accounts for the area required for QC equipment. Core equipment footprint ($\sigma_{core,Fs}$) accounts for the area required for core equipment such as filling lines, incubators and cold storage facilities. These spaces are dependent on the scale of the facility, i.e. the bigger the facility the more support space is required. The remaining space in the facility is given by *Eq 5*a and can be used to accommodate production equipment.

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

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

$$maxps_{Fs} = \sigma_{Fs} - \sigma_{support,Fs} - \sigma_{core,Fs} - \sigma_{QC,Fs} \qquad \text{Eq 5a}$$

$$maxps_{Fs} * A^{f}_{Ft,Fs,t} \geq \sum_{m}(EqNo^{m}_{f,Ft,Fs,t} * \sigma_{eq,m,Fs}) \qquad \text{Eq 5b}$$

Equipment available at given year t ($EqNo^{m}_{f,Ft,Fs,t}$) is the number of equipment available in the previous year plus the equipment purchased during the period ($EqP^{m}_{f,Fs,t}$). It is assumed that the equipment purchased the year before will stay in the facility for the lifetime of the facility (*Eq 6*) and therefore the equipment purchased must be a positive integer (*Eq 7*).

$$EqNo^{m}_{f,newbuild,Fs,t} = EqNo^{m}_{f,newbuild,Fs,t-1} + EqP^{m}_{f,newbuild,Fs,t} \qquad \text{Eq 6}$$

$$EqP^{m}_{f,newbuild,Fs,t} \geq 0 \qquad \text{Eq 7}$$

Equipment investment cost

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

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

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.

$$FEqInvCost_t = \sum_f \sum_{Fs} Fac^f_{newbuild,Fs,t} * (C_{support,Fs} + C_{core,Fs} + C_{QC,Fs}) \qquad \text{Eq 8}$$

$$EqInvCost_t = \sum_f \sum_{Fs} \sum_m C_{eq,m,Fs} * EqP^m_{f,newbuild,Fs,t} \qquad \text{Eq 9}$$

Product-level constraints

Product type and demand

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

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

$$CD_t^P = \sum_h Dd_{Complex,t}^{P,h} \qquad \text{Eq 10}$$

$$SD_t^P = \sum_h Dd_{Simple,t}^{P,h} \qquad \text{Eq 11}$$

Product production and cost of goods

Equipment capacity constraint

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

$$\sum_P TrtF_{f,Ft,Fs,t}^{Complex} * Pt_P \leq EqNo_{f,Ft,Fs,t}^{Complex} * M \qquad \forall\, P \in CP \qquad \text{Eq 12}$$

$$\sum_P TrtF_{f,Ft,Fs,t}^{Simple} * Pt_P \leq EqNo_{f,Ft,Fs,t}^{Simple} * M \qquad \forall\, P \in SP \qquad \text{Eq 13}$$

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

Whilst scale-out manufacturing is a more common approach for autologous cell therapies, better utilization of human resources and equipment allows a certain degree of economies of scale [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 labour is more expensive, e.g. London.

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

$$COG_{Fs,Ft}^{P,f} = VCCOG^P * Out_{Ft} * Sp_{Fs} * Lp_f \qquad \text{Eq 14}$$

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 (*Eq 15*). The total number of treatments delivered at hospital *h* equals the total number of treatments produced that are delivered to the hospital (*Eq 16*). The total number of treatments produced at a certain facility equals the total number of treatments demanded at all hospitals produced at the facility (*Eq 17*).

$$TTP_t^P = TTH_t^P = \sum_h TrtH_{h,t}^P = \sum_f \sum_{Ft} \sum_{Fs} TrtF_{f,Ft,Fs,t}^P \qquad \text{Eq 15}$$

$$TrtH_{h,t}^P = \sum_f \sum_{Ft} \sum_{Fs} \varepsilon_{f,Ft,Fs,h,t}^P \qquad \text{Eq 16}$$

$$TrtF_{f,Ft,Fs,t}^P = \sum_h \varepsilon_{f,Ft,Fs,h,t}^P \qquad \text{Eq 17}$$

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_h^f) is given by the transportation cost per mile (tc) multiplied by the return distance between the hospital and facility $(d_h^f * 2)$ (*Eq 18*).

$$tr_h^f = tc * d_h^f * 2 \qquad \text{Eq 18}$$

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 $(\varepsilon_{f,Ft,Fs,h,t}^P)$ (*Eq 19*).

$$Transport_t = \sum_P \sum_f \sum_{Ft} \sum_{Fs} \sum_h \varepsilon_{f,Ft,Fs,h,t}^P * tr_h^f \qquad \text{Eq 19}$$

Clinical trial and sales constraint

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

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

$$TrtH_{h,t}^P = \sum_m Dd_{m,t}^{P,h} * V_p \qquad \forall\, t \in CT \qquad \text{Eq 20}$$

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

$$TrtH_{h,t}^P \leq \sum_m Dd_{m,t}^{P,h} * V_p \qquad \forall\, t \in Mkt \qquad \text{Eq 21}$$

Product Sales and Revenue

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

$$Sales_{Mkt}^P = \sum_P \sum_f \sum_{Ft} \sum_{Fs} \sum_h \varepsilon_{f,Ft,Fs,h,t}^P * Price_t^P \qquad \forall t \in Mkt \qquad \text{Eq 22}$$

$$Sales_t^P = 0 \qquad \forall t \in CT \qquad \text{Eq 23}$$

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

$$TRev_t = \sum_P Sales_t^P \qquad \text{Eq 24}$$

Objective function and overall capital constraint

During the development phase, the total amount of capital is limited by the investment capital raised. Therefore, the summation of the cash flows during the development phase is limited by the funding available (φ) (*Eq 25*).

$$\varphi \leq \sum_t cflow_{CT} \qquad \forall\, t \in Mkt \qquad \text{Eq 25}$$

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

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

Over the time horizon, it is assumed that the objective of the company is to maximise its financial returns through optimising its capacity investment strategies based on the product development portfolio, e.g. prioritizing products that will bring the most financial returns whilst minimizing capital expenses.

The cash flow in a certain year is given by the incomes minus the costs incurred in the year (*Eq 27*).

Cash flow ($cflow_t$) is the total revenue ($TRev_t$) minus the facility investment (FI_t), contract set-up ($Ctrt_t$), equipment procurement (Fixed, $FEqInvCost_t$ and production equipment $EqInvCost_t$), fixed operating costs ($Fixop_t$), total variable cost of goods ($TCOG_t$) and transportation costs ($Transport_t$) (*Eq 27*).

$$cflow_t = TRev_t - FI_t - Ctrt_t - FEqInvCost_t - EqInvCost_t - Fixop_t \qquad \text{Eq 27}$$
$$- TCOG_t - Transport_t$$

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

$$NPV = \sum_t cflow_t * \delta_t \qquad \text{Eq 28}$$

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(3) Model application on an illustrative case study

The mathematical model was implemented within the General Algebraic Modelling System (GAMS) 26.2 and the problem was solved using the CPLEX solver. The optimisation was performed on an Intel Core i5-2500K 3.3GHz processor, with 12 GB random access memory (RAM). All optimisations 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 authorisations. 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, i.e. time horizon is discretised into 1-year time intervals. As single-use closed automated systems are assumed to be used at scale, the changeover time is assumed to be negligible in the time horizon of 20 years. Figure 2 shows the product development timeline of orphan/unmet medical need products versus the typical drug development timeline.

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

Product portfolio and demand scenario

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

In this study, four geographical locations are assumed for hospital and facility locations for illustrative purposes, namely London, Bristol, Newcastle and Edinburgh. All hospital locations are assumed to be capable of delivering both complex and simple products. The distance between the locations (d_h^f) can be found in Supplementary Material 3, and the location influences the cost of manufacturing (*Eq 14*) and the transportation costs (*Eq 18*).

The national product demand for both scenarios, with fast-track designations and without fast-track designations, are distributed amongst the four locations at a ratio of 4:2:2:2. After market approval, a 'ramp-up' period is assumed to simulate the time needed for a mature sales level to be reached [28], 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 and 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 which 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 [29] and distribution logistics is another important challenge mentioned by Dodson et al [1]. To better analyse the effect of commercialization challenge-related parameters on the NPV and the robustness of the investment plan, a sensitivity analysis of the following parameters is conducted:

- Funding availability: Funding available (ϕ)

- Reimbursement: Product selling price ($Price_t^P$), Product demand uptake ($Dd_{m,t}^{P,h}$)

- Manufacturing: Variable COG of product ($VCCOG^P$), Process turnaround time ($Pt(P)$)

- Logistics: Transport cost per mile (tc)

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Results

I.   Product selection decision

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

Figure 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 to P3, the market size is much greater and delivers a greater overall return. With funding above $40m, the NPV for scenario FT is consistently higher than that of scenario NFT, by a range from 40% (φ = $180-200m) to 86% ($\varphi$ = $50m).

A more in-depth analysis of the discounted NPV over 20 years for an investment funding constraint of $120m shows that the breakeven for scenario FT occurs at year 7.5, approximately 2.5 years earlier than the scenario without fast-track schemes. This represents a 25% reduction in the time to achieve breakeven of investments (Figure 5).

II.   Facility investment decision schedule

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

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

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.

III.   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).

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

As the model allows for simultaneous optimization of product selection and capacity planning, changes in the input parameters have an impact on both product selection and facility investment decisions and in turn the NPV over the time horizon (Table 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, whilst for scenario FT, product P3 and P4 are selected for all cases. Fast-track designations make the decision to develop and produce niche, high-value products (P3, P4) more resistant to uncertainties and without FT designations, niche, very high-valued products (P3) are not chosen.

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

For both scenarios, the overall NPV is most sensitive to the selling price, followed by the manufacturing variable cost of goods and finally the product demand; the sensitivity to the transportation cost and the process turnaround time is minimal (Figure 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 which has a greater product demand but has a lower profit margin. This shows the importance of maintaining profit margins for high demand products. With the decrease in selling price and either increase or decrease in manufacturing variable costs, for both scenarios, P1 is selected. Although the profit margin for P1 is smaller, the barrier of commercialisation P1 is also lowest as shown by the low required funding as shown in Figure 3.

V. Computational statistics

The case study presented in detail here is relatively small, comprising 5 products, 4 hospital locations and 4 facility locations. However, the formulation can be applied to larger scale problems. As summarised 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 commercialise autologous cell therapies considering the recent introduction of fast-track regulatory schemes and the autologous nature of these therapies. Using the United Kingdom as an illustrative example, we have shown the impact of fast-track regulatory designations on capacity planning and investment decisions.

Specific to the unique challenges of commercialising autologous cell therapies, this model addressed scale-out, geographical constraints, long-term capacity investment decisions and the unique regulatory routes of these therapies. A relatively small system is evaluated to illustrate the impact of these fast-track designations on the commercialisation pathways. With a small number of hospital locations considered, the model favoured a centralised facility, which is closer to the hub-and-spoke model which is currently favoured for advanced therapies instead of the decentralised single-centre co-located manufacturing approach [30].

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

Fast-track regulatory designations can allow companies to achieve breakeven years earlier and higher NPV over the time horizon (Figure 4). 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 [31]. A review of the value of companies holding Breakthrough Therapy Designations also shows that such designations add significant value to the company [32].

However, with the crunched development timeline, large upfront investments for manufacturing would be incurred earlier. This can have great risk implications especially for small-medium enterprises seeking to commercialise clinical-stage autologous cell therapy products. Secondly, with a small amount of clinical data, the risk of the marketed product may be higher. A review on fast-tracked products withdrawn cited lack of efficacy, adverse events and safety issues as the main reasons for withdrawal [33]. 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 and Limitations of the model

This model considers common product-market characteristics, manufacturing scale-out instead of scale-up to simultaneously optimise strategic commercialisation decisions such as product portfolio selection, facility and equipment selection for autologous cell therapies. The impact of the introduction of fast-track schemes for therapies targeting unmet medical need is considered in a comparative scenario analysis exercise. 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 harmonisation is a challenge faced by the regenerative medicine industry [34]. 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 [35]. However, this is considered out of scope for analysing the impact of fast-track regulatory schemes on product portfolio selection and overall project NPV. Another limitation is that clinical trial failure is not accounted for. However, whilst it is unrealistic to assume that each product will be successful in clinical trials, the model can serve as a decision aid for companies that need to produce capacity investment plans for internal planning and capital raising purposes. 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 [36]. 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 commercialistion 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 modelled the unique challenges and opportunities for capacity planning and investment strategies for autologous cell therapies in a mixed-integer linear programming model. An illustrative example comparing fast-track regulatory schemes and typical developmental timelines in the United Kingdom with a hypothetical set of products was used to demonstrate the applicability of the model. The results were validated against real-world observations in relevant investments.

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

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

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

Translational 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 optimise the commercialisation 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 commercialisation 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 (MILP)

- Concurrently optimises facility investment timing, scale, location and product portfolio of autologous cell therapies
- Assessed the impact of fast-track designations on commercialisation of autologous therapies in terms of breakeven time and 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

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