Cytotherapy, 2017; 19: 1383–1391

International Society for Cellular Therapy
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A roadmap for cost-of-goods planning to guide economic production of cell therapy products

YONATAN Y. LIPSITZ[1], WILLIAM D. MILLIGAN[2], IAN FITZPATRICK[3], EVELIEN STALMEIJER[4], SUZANNE S. FARID[5], KAH YONG TAN[6], DAVID SMITH[7], ROBERT PERRY[8], JESSICA CARMEN[9], ALLEN CHEN[6], CHARLES MOONEY[10] & JOHN FINK[11]

*[1]Institute for Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Canada, [2]Steminent Biotherapeutics, Taipei, Taiwan, [3]Scinogy Pty Ltd, Melbourne, Australia, [4]eXmoor Pharma Concepts, Berkshire, United Kingdom, [5]University College London, London, United Kingdom, [6]Bioprocessing Technology Institute, A*STAR, Singapore, [7]PCT, a Caladrius Company, Allendale, New Jersey, USA, [8]Atara Biotherapeutics, San Francisco, California, USA, [9]MaxCyte, Gaithersburg, Maryland, USA, [10]Oklahoma Blood Institute, Oklahoma City, USA, and [11]Brooks Automation, Chelmsford, Massachusetts, USA*

Abstract

Cell therapy products are frequently developed and produced without incorporating cost considerations into process development, contributing to prohibitively costly products. Herein we contextualize individual process development decisions within a broad framework for cost-efficient therapeutic manufacturing. This roadmap guides the analysis of cost of goods (COG) arising from tissue procurement, material acquisition, facility operation, production, and storage. We present the specific COG considerations related to each of these elements as identified through a 2013 International Society for Cellular Therapy COG survey, highlighting the differences between autologous and allogeneic products. Planning and accounting for COG at each step in the production process could reduce costs, allowing for more affordable market pricing to improve the long-term viability of the cell therapy product and facilitate broader patient access to novel and transformative cell therapies.

Key Words: *cell therapy, cost of goods, COG, autologous cell products, allogeneic cell products, tissue procurement, material costs, facility costs, production costs, storage*

Introduction

Current and expected pricing for approved and late-stage cellular therapy products reflect the high cost of goods (COG) used today to produce most therapies (Figure 1). Optimizing COG will promote the development and commercialization of more affordable cell therapy products, which in turn are more likely to achieve reimbursement from payers and gain broader adoption for patient treatment [6]. Ideally, the economic aspects of a product will be addressed from the very beginning of development to enable a viable, profitable product life cycle because process changes become more difficult as development progresses. A robust cell therapy business model cannot be fully realized without addressing every cost-relevant "needle-to-needle" consideration. Starting from cell sourcing through to manufacturing, distribution, and finally clinical application, COG optimization aims to minimize the cost per unit of cells and ultimately the cost per dose while maintaining product quality.

In June 2013, a survey was distributed to the International Society for Cellular Therapy (ISCT) membership asking about the COG breakdown in therapies under development by member organizations (see supplemental Figure S1 for survey overview). The survey results indicated that commonalities can be drawn between process components of similar cell products. The two main cell therapy modalities, allogeneic (donor to patient) and autologous (patient

Correspondence: **Yonatan Y. Lipsitz**, PhD, Institute for Biomaterials and Biomedical Engineering, University of Toronto, 164 College Street, Toronto, Ontario, Canada M5S 3G9. E-mail: yonatan.lipsitz@mail.utoronto.ca

(Received 13 June 2017; accepted 29 June 2017)

ISSN 1465-3249
https://doi.org/10.1016/j.jcyt.2017.06.009

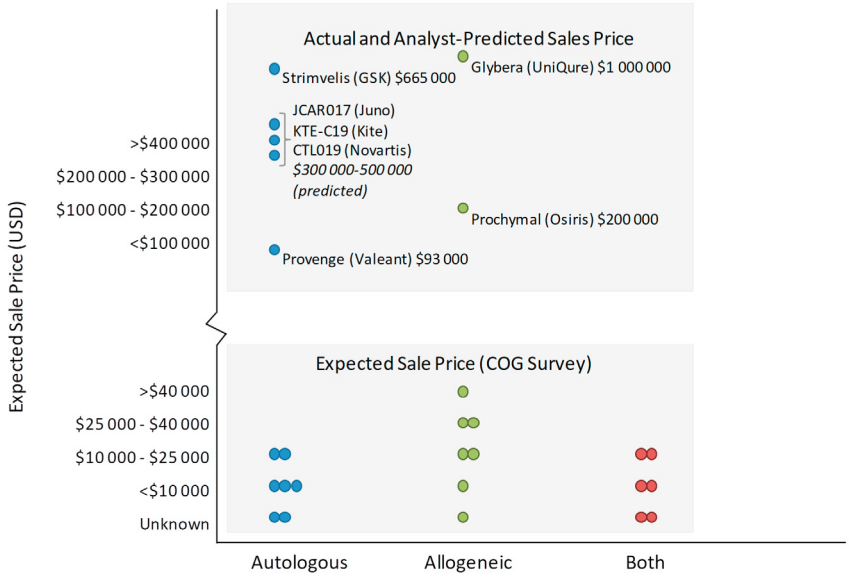

Figure 1. Sales price of autologous and allogeneic cell therapies. Expected sales prices from the COG survey in 2013 are compared with published and anticipated costs for therapies approved or in trials. Prices for Glybera, Strimvelis, Prochymal and Provenge are based on published prices from each company. Analyst reports of expected chimeric antigen receptor T-Cell prices range from $300 000 to 500 000 [1–4]. While these prices have not been confirmed by the companies developing these therapies, the $800 000 cost of stem cell transplants has been seen as a benchmark for these therapies [5].

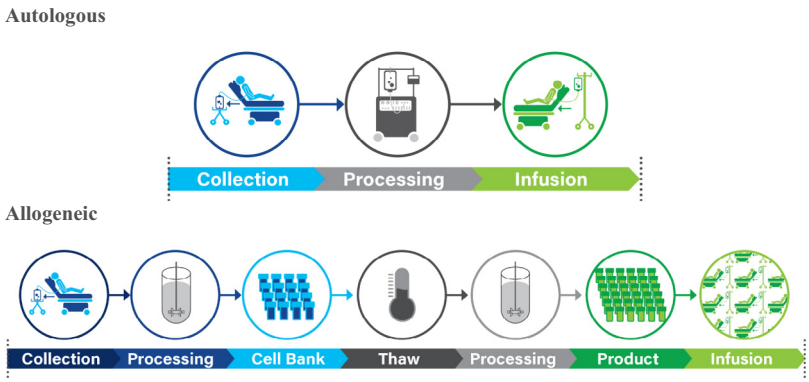

Figure 2. Allogeneic versus autologous manufacturing models. In allogeneic therapies, a single sample is saved in a master cell bank from which a working cell bank is used for manufacturing. These therapies are then distributed to large patient populations. In autologous therapies, each single patient sample is manufactured into a product that is used to treat a single patient.

to self), necessitate different "needle-to-needle" pathways (Figure 2). The production process differences between manufacturing strategies used for allogeneic products and the patient-specific manufacturing strategies used for autologous products result in distinct COG optimization decisions. Notably, allogeneic products benefit highly from economies of scale in a similar manner to traditional pharmaceuticals, whereas costs are relatively consistent as autologous products are scaled out.

In this article, we outline a COG roadmap of key considerations and objectives for each step in cell manufacturing to plan for reduced COG, enable lower product pricing, and improve patient access. Designed to inform early process development of the connection between each development decision and the eventual cost-efficiency of the final therapy, this roadmap augments the ISCT COG survey results with relevant published references on how to address the challenges encountered with each manufacturing step (Figure 3).

COG impact analysis for cell therapy products

When beginning translation of a preclinical process to clinical production, the various manufacturing methods available can significantly influence the final COG at commercial scale. Impact analysis is a valuable tool to understand the sensitivity of the final COG in response to different manufacturing strategies and

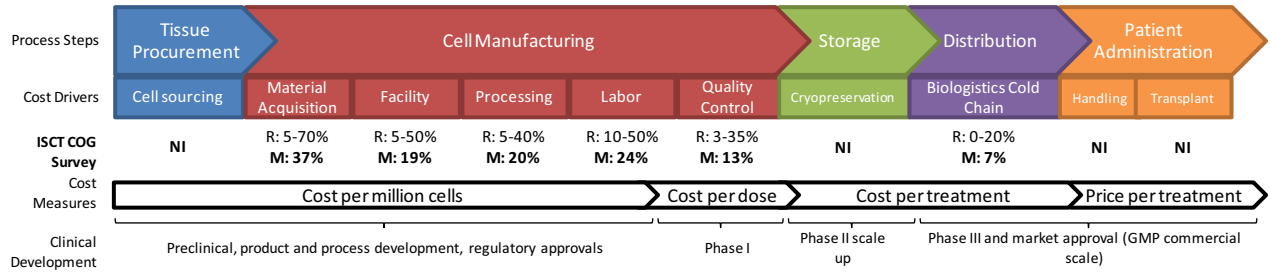

Figure 3. Needle-to-needle cost center roadmap. COG survey respondents indicated the expected cost of each stage of the production process, identifying key cost drivers. Each stage and associated cost drivers can be aligned with a guiding cost measure and a stage of clinical development. M, mean response; NI, not included in survey questions; R, range of responses.

product demand scenarios forecast at the end of the expected decade of development of a cell therapy [7–10]. By comparing future manufacturing scenarios to the current manufacturing process, this analysis will identify elements of both manufacturing strategy and development to prioritize COG reduction. Common development priorities can include development of new technologies, distribution systems, shelf-life enhancement, and closed system solutions and automation. Manufacturing strategy priorities often include CMO usage, number of manufacturing sites, central or decentralized manufacturing and intermediate demand transition facility usage. Importantly, a quantitative understanding of the influence of process changes on the key factors that ensure product quality using frameworks, such as Quality by Design, should guide the decision to incorporate these COG reduction steps (described by Lipsitz *et al.* [11]).

Analysis of the COG roadmap early in development can help determine the impact of different scenarios on achieving a future cost-optimal process. These scenarios should consider variations such as differences in future demand, process automation, shorter versus longer shelf life of final product and point-of-care needs. Comparison of different scenarios will show which considerations have the highest impact on the overall COG and on quality risk, specific for each cell product. To analyze manufacturing COG, processes and outcomes for each manufacturing step should be carefully described. These steps include tissue procurement, material acquisition, facility operation, production and storage (Table I). As clinical development progresses, the model predicting the impact of these decisions on final COG can be updated for relevance and accuracy. The following sections provide insights from the ISCT COG survey and relevant literature into the cost considerations associated with each of these steps.

Table I. Cell therapy manufacturing processes steps considered in this document and relevant cost considerations that are discussed.

Process step	Relevant cost considerations
Tissue procurement	Screening, clinical acquisition, scheduling, variability in quality, transport, regulatory compliance
Material acquisition	Medium, supplements, cell cultures, commercial demand, consistency, bioequivalence
Facility operation	Forecast demand, production scale required, outsourcing or building, central or multi-center, clean-room environment for GMP manufacturing, comparability between sites
Production	Personnel, cell culture, aseptic processing, automation, and quality control selection
Storage	Packaging, cryopreservation agents, storage temperature and storage time

Tissue procurement

Tissue stability during transport from the site of origin to processing can have high COG consequences. In many cases, cadaveric tissue must be processed when it becomes available, requiring a processing facility to operate continuously. Fresh material drawn from clinical sites will be shipped Monday through Friday. Patients prefer that procedures such as apheresis or bone marrow recoveries are performed late in the week, allowing them the weekend to recover before returning to work. These concerns affect COG through facility utilization and labor-demand profiles, and the supply chain logistic must be optimized to minimize this impact.

Tissue procurement considerations differ greatly between allogeneic and autologous therapies (highlighted in Table II). In allogeneic therapies, cells for routine manufacturing are sourced from specially recruited donors. The cost to recruit and incentivize each donation is directly related to the size of the qualifying donor pool. Donors must be willing and able to undergo stringent screening procedures to protect both the donor and the product recipient. Additionally, it is critical that tissue and donor screening adheres to regulatory agency donor and procurement guidelines for all markets where the cells may ultimately be used. Failure to do so can result in therapies that are unsuitable for use in certain markets. As well, one must determine the need for and frequency of primary cell culture qualification, which exerts a significant cost on production.

Table II. Considerations in tissue procurement for allogeneic and autologous therapies.

Topic	Key considerations
General considerations	Develop/acquire technology for clear traceability of tissues and cells
	Ensure aseptic handling from the initial collection to the initiation of manufacturing processing
	Efficiently schedule processing to match time of tissue arrival
Allogeneic	Screen tissue/donors, adhering to regulatory agency donor and procurement guidelines of all markets where the cells may be ultimately used
	Determine need and/or frequency of primary cell culture qualification
Autologous	Establish and control consistent acquisition processes for multiple patients at multiple clinics
	Use GMP-compliant and sterile procurement, handling, preservation and storage of the starting materials
	Drugs required for procurement of tissue

In autologous therapies, consistent acquisition processes for multiple patients at multiple clinics must be established and controlled because common techniques such as bone marrow acquisition and apheresis can be highly operator dependent [12–15]. Variability in acquisition is compounded by variability in donor samples [16–18], both of which must be understood in a manufacturing context to ensure consistent cell therapy product quality. Notably, development is often conducted on healthy samples, without indication of how diseased samples will perform until phase I trials, introducing manufacturing risk that may affect timelines and development costs. The regulatory requirements of ensuring Good Manufacturing Practice (GMP) compliance, sterile procurement, handling, preservation, and storage of the starting materials also add significant costs to tissue acquisition. In certain cases, the drugs required to procure the desired tissue (e.g., mobilization of stem cells to peripheral blood) may represent an important cost consideration.

Material acquisition

Overall, 40% of ISCT COG survey participants estimated that more than 20% of their COG are due to media (12% of respondents estimated the COG to be between 20% and 30%, 24% estimated between 30% and 50%, and 4% estimated a COG more than 50%). On average, the estimated materials costs accounted for 36% of overall manufacturing COG. In addition, 92% of survey participants have considered using serum-free or xeno-free media; however, more than 50% of participants did not understand the cost impact of switching to serum-free or xeno-free media.

Cell growth media components can be divided into two functions: maintaining basic functions required for cell survival and maintaining advanced functions required for cell state and differentiation. Basal media that allow for cell survival and growth are well established, and the growth factors, cytokines and signaling molecules required for cell state and differentiation account for the major media costs. Although many cells (notably human mesenchymal stem cells [hMSCs]) have been generated through conventional static adherent cultures in the presence of fetal bovine serum (FBS) for clinical applications [19], these methods are not appropriate to meet the expected future demand for safe, quality-assured hMSCs for global human therapeutic use. FBS is a complex and undefined mixture of proteins, signaling molecules, and other bioactive factors that vary in concentration and activity between batches. Furthermore, a significant supply chain challenge exists for sourcing sufficient FBS to meet demand as these products approach commercial scale production. Sustainability of the supply chain can often be a critical risk and cost driver. Single-use disposables incur a significant cost per patient in patient-specific therapies. For example, CD34 microbeads and a single-use cell sorting tube-set for hematopoietic therapies can cost more than $7000 simply to purify the starting cells for further processing (see Table III for more examples).

Facility operation and labor

Of ISCT COG survey respondents, 94% used fresh starting material and planned to deliver fresh product, which can be challenging to manufacture due to stability and contamination issues. Sixty-eight percent of respondents planned to manufacture internally in their own facility, although 33% of respondents did not know what this would cost.

Facility costs are strongly affected by the choice between a "fresh" (non-cryopreserved) product and a cryopreserved product amenable to longer storage and transport times. A fresh product component restricts a facility's market reach and ties manufacturing to the patient and clinic schedules, possibly necessitating a multicenter approach. In contrast, cryopreserved products can be manufactured at a single centralized site that meets the regulatory requirements in each primary market to be considered (Table IV).

This choice between centralized and multicenter manufacturing affects several cost considerations, such as the logistics of future capacity increases and the potential hurdle of technology transfer from one facility to another [20,21] (Table IV). This choice can be made by first determining the demand forecast for the marketed product, which dictates the scale of manufacturing

Table III. Considerations in material costs in manufacturing.

Topic	Key considerations
Tissue procurement	Secure required quantities by selecting supplements and other consumables that will be readily available in large quantities to meet production scale requirements for commercial demand Start with materials that are deemed by regulatory authorities in key target markets to be safe ancillary materials to avoid any required changes in manufacturing process downstream Consistently use the same materials, from the same sources, to reduce the risk of variance resulting from changes in materials used in the cells produced When possible, replace complex, animal-sourced materials from media formulations with well-defined components Create and test strategies for "bioequivalence" as part of the chemistry, manufacturing, and controls for those reagents at risk of supply disruption Minimize the amount of consumable and disposable waste materials to manage costs and minimize environmental considerations Anticipate the systematic costs driven by process decisions (e.g., antibody-based cell selection is likely to be a high cost)

required. This informs whether manufacturing will be outsourced to a contract manufacturing organization (CMO), done internally, or divided between the two options. Importantly, if multiple sites will be required, analytical tools will be needed to ensure comparability in manufactured product between sites.

In addition to distinguishing between fresh and frozen products, the level of cell manipulation influences facility costs. Autologous, minimally manipulated products do not require costly GMP processing, whereas more than minimally manipulated products would incur these costs [22]. Allogeneic therapies are all manipulated cell products for which facility costs can be reduced on a per unit basis as the process is scaled up. Strategies for cost-effective progressive batch-size increases should be implemented when moving toward commercial production scales.

Table V. Labor considerations in clean-room operations.

Topic	Key considerations
Training	Qualification and regular revalidation of operator aseptic technique [23]
Staffing	Independent protocol verification of batch record for manual protocols (dedicated staff required to monitor active operator) [24]. Reduced productive hours of personnel working in clean rooms due to gowning times and restricted movement Additional personnel required to supply and remove materials from clean spaces

Labor is a dominant cost factor: 47% of ISCT COG survey respondents reported more than 30% of COG were due to labor costs, with processes comprising between 2 and 15 steps. Respondents indicated the need for automated processing to increase productivity and reduce labor costs.

Allogeneic products benefit from the ability to share labor costs in a batch across many patient doses. Autologous therapies often include complex manipulations requiring skilled labor and long production times, increasing cost per dose. Increasing demand for autologous products can only be met by increasing the number of batches. Autologous products with a large manual component can also struggle with scale-out from the lack of access to skilled labor either due to geographic issues or, when establishing new manufacturing sites, due to disruption of the core manufacturing team to enable technology transfer. Thus, automation of autologous processes has emerged as a tactic to alleviate the high COG associated with manual methods requiring a skilled workforce.

A related key cost driver is the development of functionally closed systems. By closing manufacturing systems, non-classified spaces can be used instead of more costly class 10 000 (Grade C, ISO 7) facilities. Gowning and training costs are also reduced, and decentralized manufacturing systems can more readily be incorporated (Table IV). Key considerations for labor costs are outlined in Table V.

Production: scaling up cell expansion

Sixty percent of respondents planned to use fewer than 3×10^6 cells/kg dose. Sixty-four percent planned to launch

Table IV. Considerations for centralized or multicenter facility approach.

Facility design	Product	Capacity	Capacity increase	Change implementation	Logistics
Centralized	Frozen	Dependent on market demand	Expansion of existing facility or conversion to multicenter	Centralized to one facility	Potentially more flexible, depending on existing infrastructure
Multicenter	Fresh, frozen	Dependent on local demand	Establishment of new centers	Complex (technology transfer to each site, and inter-site comparability)	Dependent on local infrastructure

Table VI. Considerations for cell expansion technology selection.

Topic	Key COG considerations
Demand	Where possible, design the manufacturing process to be suitable for commercial demands from the start
Operational performance and lot size	Use estimates of expansion yields or harvest densities and downstream yields to determine if number of expansion units per lot is practical for each technology choice
Quality control and regulatory compliance	Automated or manual processing and open or closed processing are key decisions. Currently, most processes involve manual handling. Automated and closed processing may reduce costs and improve cell quality
	Costs of developing process understanding to implement Quality by Design process development [11]
Scalability	Multi-layer vessels can reach production limitations at higher cell production numbers
	Determine by using the S-curve method [8] if the desired lot sizes over a product life cycle can be met by planar technologies or whether a switch to bioreactor technologies is required
Process development effort	If switches in technology are planned later in the development pathway, then the economic consequences of process changes need to be considered [10]
Upstream vs. downstream processing costs (USP:DSP)	Consider the ratio of USP to DSP costs and potential bottlenecks to prioritize R&D efforts
	Typical contributions of DSP are 10–20% in planar processes employing multi-layer vessels and 50–80% in bioreactor-based processes [9]

with fewer than 50 000 doses per year as their commercial target, and 43% planned launch with fewer than 10 000 doses per year as their commercial target. Thirty-eight percent of the ISCT COG survey respondents indicated that cell processing is the rate-limiting factor in manufacturing, contributing substantially to manufacturing costs.

To provide commercial quantities of allogeneic, clinical-grade cell therapy products as well as many patient-specific, expansion-dependent therapy products, an efficient cell expansion method that reliably produces high quality product at acceptable cost is required [25]. Trade-offs will occur between the cost of developing process knowledge to ensure product quality in manufacturing and scale-up versus the costs of discarding batches that do not meet specifications. Quality by Design is a risk-based framework that can guide cell therapy process development and scale-up to identify and control the parameters most likely to influence product safety and efficacy [11]. By overlaying a quantitative understanding of how process parameters affect cell quality with the costs of gaining that knowledge and the costs associated with not having this knowledge, Quality by Design process development closely complements COG reduction strategies.

Key considerations for technology selection when scaling up cell expansion are highlighted in Table VI. The anticipated demand for large numbers of cells will necessitate bioreactor production methods, an alternative to traditional planar culture. Different bioreactor types and scales can be tailored to different operating sizes and target doses [26]. Simaria *et al.* [8] present a detailed process economics analysis for allogeneic cell expansion that predicts dose–demand combinations when planar technologies would cease to be cost-effective, as well as target performance capabilities of microcarrier-based systems for the industry to be sustainable for high-demand, high-dose (10^9 cells/dose) scenarios [8]. Technology S-curves are used to describe the development of new technologies in several industries by depicting the introduction, adoption and maturation of the new technology [27]. An S-curve can be used to visualize the performance trajectory of various cell expansion technology in terms of billion cells achieved per lot against R&D effort. Published S-curve analyses [8] highlight that each progressive technology covers approximately 10-fold greater performance (billion cells per lot) before being replaced by a newer technology.

Storage

Liquid nitrogen storage will be required for the majority of products in development (identified by 55% of ISCT COG survey respondents), with cold chain distribution being an integral part of cell therapy delivery (52% of products shipped frozen). The majority of the respondents indicated anticipated storage time requirements of less than 2 years.

The cold chain for cell therapy begins as early as tissue acquisition, storage before and after processing, and transport and handling upon receipt to end users. A wide range of biopreservation solutions, methods and storage options are available for users to choose based on their specific requirements [28]. Factors influencing the associated cost include storage time, cell bank size and concentration, temperature and stability (Table VII).

A balance among storage time, cell bank size (i.e., lot size), clinical pre-treatment preparation and stability must be established to reduce the cost and minimize the impact on cell functionality. Extended storage time can incur additional running costs and may raise uncertainty regarding cell stability. Lower temperatures (below −150°C) can improve stability but may be more costly. Several reviews addressing the technical aspects, such as selection of cryopreservative, cooling protocols,

Table VII. Considerations for cryopreservation of cell therapies.

Topic	Key Considerations
Cryopreservation	DMSO (dimethyl sulfoxide), a common cryopreservative may cause dose-related side effects [29–31]; costly proprietary agents can be substituted [32]
Storage temperature,	Four methods are available for cryogenic temperature storage: 1. Electrical mechanical freezer (–130°C): high running cost, warm temperature 2. Liquid nitrogen, liquid phase (–196°C): medium running cost, very steady temperature, risk of cross contamination, higher user safety risks 3. Liquid nitrogen, vapor phase, low efficiency (>–150°C): medium running cost, temperature fluctuation and no risk of cross-contamination 4. Liquid nitrogen, vapor phase, high efficiency (–190°C): low running cost, steady temperature, no risk of cross contamination Additional cryopreservation equipment should be used to control cryovial transfers between storage containers during transport to avoid temperature variance [33]
Cell concentration	Reduced cell viability after thawing might necessitate larger or more complex-to-harvest source tissue [34,35]
Storage duration	Production should closely match demand to minimize storage costs

storage container system, temperature, period and the effect on cell functionalities are listed in supplementary Table S1. Development of new technologies for cell preservation at ambient temperatures has emerged as a potential area technology innovation (e.g., the Prestige Lyotechnology system from Osiris Therapeutics).

Cost structure illustration

Examining the cost structure of a cell therapy product illustrates the systematic cost components and can highlight opportunities to minimize costs through early process development planning. Figure 4 presents an example of a manually implemented protocol completed in Grade B suites, optimized as far as possible to minimize cost. This example is an anonymized cell therapy process derived from analysis of three autologous therapies. These data align with the COG survey results where respondents highlighted labor costs around 30% of the total product cost.

By applying automated processing within functionally closed disposables many commercial and quality attributes of the manufacturing process are improved while dramatically reducing the dependence on skilled labor (Figure 4). Of particular interest is the change in cost structure, where the systematic facility and labor costs are replaced with disposable and process specific capital costs that are responsive to the economies of scale, as previously mentioned. In this example, automation led to more than 30% savings in COG. Although automation can significantly reduce COG, indirect costs associated with developing automation strategies must be considered.

Conclusions

A strong cell therapy business model cannot be realized without taking into consideration every relevant aspect of a product life cycle and how it can influence product cost (Figure 5). Through strategic process

	Suite Processing Manual	Automated Closed Consumables	Cost profile of Automated process
Facilities Amortized	15%	3%	4%
Equipment Amortized	3%	3%	4%
Gowning	3%	0%	0%
Cleaning	5%	1%	1%
Disposables	8%	18%	28%
Reagents	29%	29%	45%
QC	5%	5%	8%
Direct Labor	25%	3%	4%
Indirect Labor	8%	3%	5%
Savings	0%	**37%**	
Total	100%	100%	100%

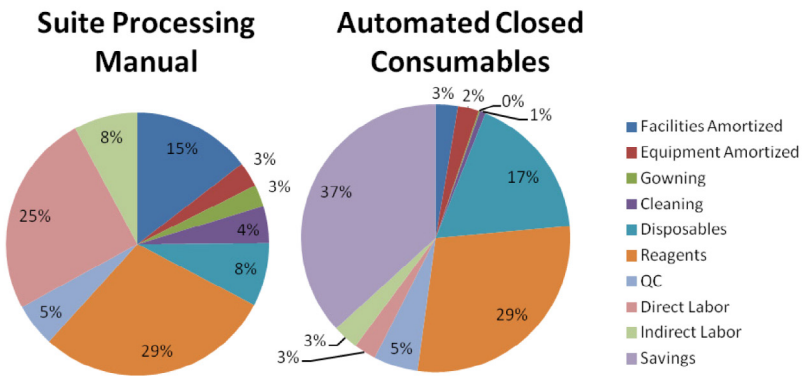

Figure 4. COG reduction through automation. This anonymized case study of three autologous processes indicates a significant savings from process automation using closed consumables of more than 30%.

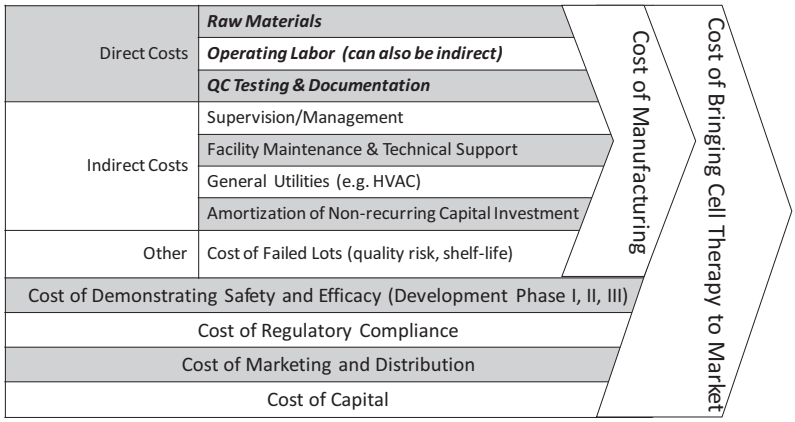

Figure 5. Costs related to cellular therapy business model. Many costs can be influenced through careful process design. These influences can be realized at the time the application for a new drug is being written, highlighting the importance of commercial strategy (in addition to therapeutic strategy) when investing in a cell therapy product. Consideration of COG as discussed in this article (see terms in the figure in Bold) are an important component in identifying and managing the cost of manufacturing. Other costs not discussed here must also be taken into consideration when identifying the overall cost of bringing a cell therapy to market.

design, one can influence multiple costs: capital (i.e., production facility and equipment), supply chain (consumables, cold chain), compliance (GMP production area costs), regulatory (strategic selection of quality assurance/quality control testing, automation where justified), manufacturing, quality deviations and licensing. Success is built not only on therapeutic efficacy but also on well-defined strategies for pricing, reimbursement, and commercialization. Regulatory approval and marketing licenses are not the ultimate key to commercial success, as health care and reimbursement agencies are increasingly looking for cost-effective solutions. Understanding and planning the economic aspects of a new cellular therapeutic from the early phases of development will enable a viable life cycle. The gross profit margin between the selling price of the product and all its associated costs is the only source of revenue to pay for all costs related to development, approval and sustained marketing of an innovative new therapy. Although we have discussed only COG-related concerns here, other important costs warrant future discussion (as outlined in Figure 5).

It is critical to align the initial process to the preferred long-term production methods as soon as possible in clinical development. Changes to processes place the entire clinical history at risk because the product is defined by the production process itself. Product COG issues described in this article are a tool for designing the clinical scale manufacturing process to ensure all costs are well analyzed and considered. Value emerges from a seamless translation from clinical trials into successful and profitable commercial manufacture.

Ultimately, developing rigorous understanding and modeling all costs is ideal for the theoretical cell therapy company with unlimited capital resources. In the capital-constrained environment in which most cell therapy companies operate, a trade-off must be made between allocating resources toward understanding cost drivers and allocating resources toward product, process and business development. By implementing impact analysis during process development guided by the key cost drivers outlined here, such capital-constrained companies can prioritize studying the highest cost and highest risk aspects of their process development. Cost-conscious product development will make cell therapy products affordable and available to broad populations of patients in need.

Acknowledgments

We acknowledge the contributions made by Knut Niss in the early stages of this project. YYL is supported as an NSERC Canada graduate scholar.

All authors belong to the International Society for Cellular Therapy Business Models and Cost of Goods Subcommittee of the ISCT Commercialization Committee

Disclosure of interest: The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcyt.2017.06.009.