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CELL THERAPY ECONOMICS

Putting a price tag on novel autologous cellular therapies

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Abstract

Cell therapies, especially autologous therapies, pose significant challenges to researchers who wish to move from small, probably academic, methods of manufacture to full commercial scale. There is a dearth of reliable information about the costs of operation, and this makes it difficult to predict with confidence the investment needed to translate the innovations to the clinic, other than as small-scale, clinician-led prescriptions. Here, we provide an example of the results of a cost model that takes into account the fixed and variable costs of manufacture of one such therapy. We also highlight the different factors that influence the product final pricing strategy. Our findings illustrate the need for cooperative and collective action by the research community in pre-competitive research to generate the operational models that are much needed to increase confidence in process development for these advanced products.

Key Words: *adoptive T-cell therapy, commercialization, cost of goods, good manufacturing practice, immunotherapy, market adoption, price, regulation, reimbursement, scale-up*

Introduction

In the past decade, there has been a rapid increase in the development of autologous cell therapies, with several investigational products demonstrating encouraging clinical outcomes, especially in immunotherapies. It has been recognized, for instance, that adoptive transfer of *in vitro* expanded virus-specific T cells can prevent and also effectively treat viral infectious complications in immunocompromised patients after solid organ transplantation (SOT) or hematopoietic stem-cell transplantation (HSCT) [1–4]. Infectious complications that arise due to immunosuppression, which organ recipients need for the lifetime of the transplanted organ to prevent rejection, are mainly caused by the cytomegalovirus (CMV), BK virus, and the Epstein-Barr virus (EBV) [5]. Although the adoption of universal antiviral prophylactic strategies has significantly reduced the incidence of CMV infection and disease, the development of drug-resistant and late-onset CMV disease after discontinuation of these prophylactic antivirals is prone to high risk of malignancy, graft loss and mortality [6], and associated with a significant increase in treatment costs [7]. Additionally, other serious adverse events such as nephrotoxicity and neutropenia can also result from the administration of anti-viral agents [8]. Thus, adoptive immunotherapies associated with lower toxicities for the prevention and treatment of CMV infection and disease are highly needed and may also produce overall cost savings in post-transplantation patient care. Indeed, a recent study has suggested that even if the prevention capabilities of anti-viral donor-derived cytotoxic T lymphocytes (CTL) in HSCT, which cost $10,000 to manufacture, would only be 50% effective at avoiding the need for antiviral treatment, it is still considered the less expensive option compared with the cost of anti-viral treatment and associated hospital care of more than $50,000 per patient [9]. Researchers working in this field anticipate that

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such therapies could replace conventional treatments, possibly allowing this novel therapeutic category to be accepted as standard practice [10]. However, if these products are to find their way into routine clinical practice, obvious hurdles associated with their lengthy development timelines, pricing, reimbursement and commercialization need to be addressed and overcome. We sought to identify and describe some of these challenges from the perspective of academic institutions developing these advanced therapies. We are also providing a relevant case study to illustrate a detailed measure of manufacturing costs of a CMV-specific T-cell immunotherapy.

Developing a tailored business model for cell therapies

Autologous cell therapies are patient-specific products that require a considerable degree of flexibility in their manufacturing process, while following the principles of Good Manufacturing Practice (GMP), as mandated by regulations [11] and guidelines [12]. Any business models developed for the commercialization of autologous therapies, therefore, differ substantially from those used for small molecule drugs or other biologics. To compete with small molecule pharmaceuticals on the market, which are normally cheaper to manufacture, autologous cell therapies need to demonstrate superior safety and at least equivalent, if not better, efficacy as compared with the available standard of care, or should be applicable in diseases with no available therapeutic treatments. Interestingly, setting a market price for autologous cellular therapies is very ambitious where complex supply logistics, need to scale out, rather than scale up, production and lack of transparency of the production costs, due to the large variety of manufacturing operations, are characteristic of the sector. A significant cost contribution also arises from the fixed manufacturing overhead costs and these can be difficult to quantify without detailed studies. Therefore, new and tailored prospective economic models are required for autologous cell therapy products that focus rather on optimizing the operational efficiency while reducing risks associated with the manufacturing process [13,14]. By reducing the manufacturing costs of these products, which are typically driven by sophisticated manufacturing facilities, highly trained labor, expensive materials and high overheads for assurance of quality, the final price tag of autologous cell therapies can reach a more affordable level [15].

Several authors of this article reported in 2013 a novel cost model (Clean Technology Assessment Technique [CTAT]) that integrates manufacturing economics and optimization approaches to accurately assess the optimal cost of producing a clinical-grade cell therapy product [13]. The possible strength of this proposed model lies in the vigorous approach to splitting the interdependence between costs resulting from operating a GMP facility and those resulting from manufacturing a specific cellular product. Although annual direct and indirect operating costs represented in personnel, utilities, maintenance, quality management system, materials and supplies are already covered by the model, additional costs that can result from expanding the infrastructure and purchasing new equipment to accommodate increased demand for production need to be included in a sequential application of the model. CTAT is also dependent on local and regional cost variations for materials and services, limited to the manufacturing costs of the therapy and does not account for costs of research and development (R&D). Nevertheless, the model may still help to provide a snapshot of the commercial viability of cell and gene therapies by accurately estimating the cost of goods (CoG). Without any doubt, if such products are to be introduced into the pharmaceutical market, their price will be several-fold higher than the CoG to cover R&D costs, expenses incurred in translational research and marketing plus generating a profit, which is essential for the developer's survival and growth. To make the cost assumptions in such a tailored business model robust enough to support ongoing sustainability and to increase the applicability of its results, the key cost drivers in the manufacturing of cell therapy products should be examined and understood.

Identifying the key cost drivers in manufacturing cell therapies

The relevant manufacturing costs of cellular products can be broken down into direct (variable) and indirect (fixed) costs. Material, personnel costs and process validation costs are examples of direct costs that have a variable cost share, depending on the manufacturing volume. Preventive maintenance, amortization of facility and equipment capital purchases and environmental monitoring are examples of indirect costs and have a fixed cost share, independent of actual GMP facility use times for product manufacturing. For the total variable costs, the cost driver is the number of manufacturing runs carried out in the facility. For the total fixed costs, cost drivers are GMP facility size, personnel wages (including support services such as finance, marketing, maintenance and legal services) and degree of optimization of the manufacturing process, including the failure and wastage rate of batch production. For most cellular therapies, the major cost driver for the unit fixed cost (the cost of a single therapeutic cellular product) is the duration of the manufacturing process. An increase in product manufacturing time results in a linear increase in fixed costs. For products that need only little manufacturing time,

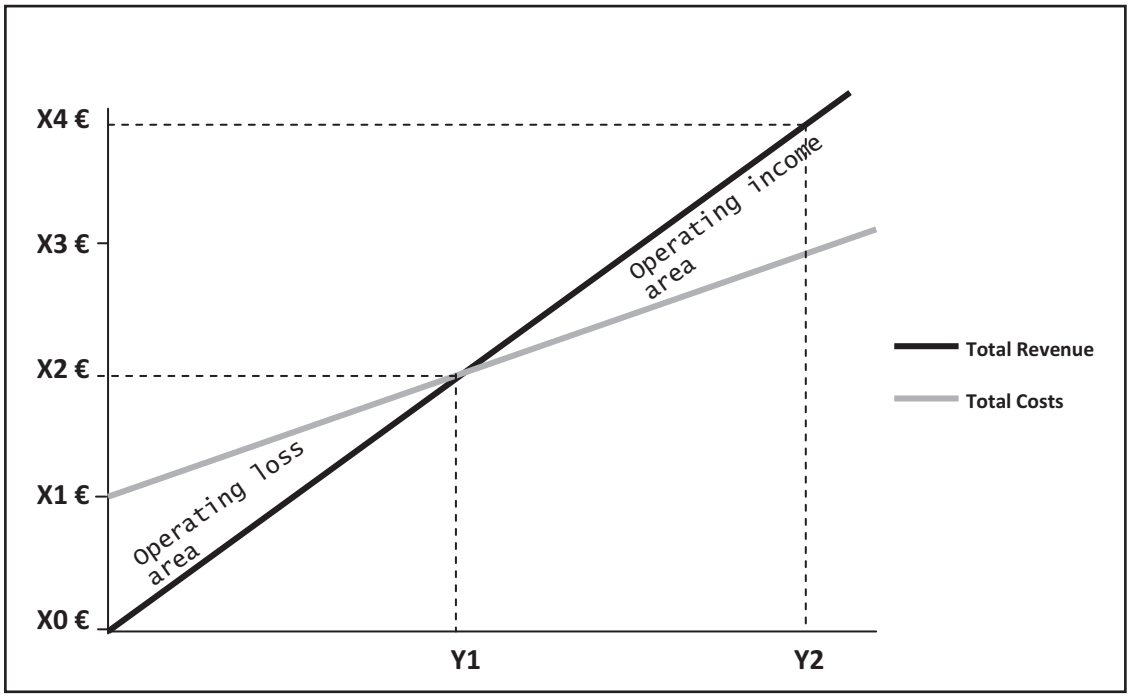

Figure 1. A hypothetical break-even analysis of manufacturing GMP-grade cell therapy products. The figure presents a cost-volume-profit graph for GMP-grade cell lines. Notice that when no cells are produced, fixed costs are X1 €, resulting in a loss of 100% of these costs per year. As manufacturing volume increases, the loss decreases by the contribution margin for each cell line produced. The cost and revenue lines intersect at the break-even point, which means zero loss and zero profit (fixed and variable costs are covered). Then, as manufacturing increase beyond this break-even point, we see an increase in income. The unit contribution of fixed costs decreases by half (X4 €) when the production volume reaches Y2. This point can be reached, for instance, by producing two parallel cell lines in one GMP laboratory using strict spatial separation.

variable costs are the dominant cost share. Nevertheless, other aspects, such as costs for scale-up equipment, dedicated to only some of the manufactured products, can still contribute to a higher percentage of costs than the GMP manufacturing time.

It is apparent that the scale of manufacturing is another important cost driver in the production process of cell therapies [14]. Usually, calculating the production capacity of a manufacturing facility should be based on a supply and demand relationship. In most of the cost modeling efforts, capacity constraints are ignored and production costs are assumed to be linear, thereby limiting the degree to which costs are realistic. This is often done because accounting for production scale economy can significantly complicate the pricing process of a product. Such activity does not come easily to those without prior experience of the process in question or without operational management experience. Since increasing production levels reduces the contribution of the fixed costs of operating GMP facilities to the manufacturing cost per unit, developers always aim to improve their scale-up capabilities. For instance, in a phase 1 or 1/2 clinical trial investigating an autologous therapeutic cellular product, more than two products could be manufactured per incubator given good physical separation and changeover procedures after product manufacturing cycles. If closed systems are used, such as the Octane Cocoon (Octane Biotech Inc.) [16] or the G-Rex M (Wilson Wolf Manufacturing) [17] bioreactor platforms, only spatial limits and points in the process where manual handling imposes a bottleneck will constrain the number of products that could be manufactured in parallel. This relation between scaling up production and reduction of costs is further explained in a hypothetical break-even point analysis (Figure 1). To that end, the identification of the key economic drivers in manufacturing cell therapies and their inclusion in any attempt to reduce the associated manufacturing costs can help to contain escalating prices.

Preparing for lengthy development timelines and stringent regulatory requirement

Due to the media attention that new cell therapy products attract, there is high public expectation for rapid availability of these therapies. In spite of that, developers who are keen on translating novel therapeutic strategies into the clinic need to be well-equipped financially to succeed in their efforts. Some larger commercial developers do not have any expectation of substantial revenue derived from these novel products; they instead rely on less advanced products that have a less

demanding regulatory pathway or that already have an established market share for them to survive financially. However, this mixed-portfolio strategy may not be feasible for small startups and academic institutions that lack a back-catalogue of such products to secure a revenue stream. Even after securing the needed funding for the long development phase, maintaining the highly specialized GMP production facilities is very costly and requires a substantial upfront investment and willingness to support a high burn rate of maintenance costs. This may be responsible for the very low percentage of academic developers who expect their products to be implemented into regular clinical care [18]. Instead, they turn to specific fast track regulatory pathways such as the "Hospital Exemption" and "Specials" routes in Europe [19] to treat patients earlier and without having to go through the burdensome process of getting the cell product to commercial scale. Other small biotech companies rely on addressing unmet medical conditions and the possibility of obtaining an orphan drug designation for their products, which can speed up the regulatory approval pathway [14] and generate adequate cash flow during the pre-market period. However, this does not necessarily guarantee commercial success [20]. One must also note that most academic developers are using public funds in their translational process. Therefore, the development of a much-needed novel therapeutic will be funded by taxpayer money. If attempts are to be made to accelerate the translation of such products to market, it would be necessary to license them to industrial manufacturers at a reasonable price [15], on the basis that affordable pricing should be maintained when selling such products.

The regulatory approach for the clinical translation of any cell or gene therapy product is highly dependent on their intended clinical use, methods of manufacturing and specific national regulations where they are being developed [21]. Although the regulatory framework for cell therapies in Europe may be perceived by some as rigid and exhaustive [22], the regulatory authorities recognize the importance of ensuring patient access to safe, effective medicines and are exerting tremendous efforts to address these concerns [23]. This is evident in the introduction of the new European Union (EU) clinical trials regulation, which aims to harmonize the divergent regulatory requirements of the different member states in case of multistate clinical trials, among other aspects [24]. Moreover, the European Commission has initiated a procedure for consultation on new guidelines on GMP, specific for advanced therapy medicinal products. Although these efforts have been positively perceived by the majority of the scientific community, they do not come without major challenges. For instance, the new EU clinical trials regulation mandates a very strict timeline for the evaluation process of clinical trial applications, which may be difficult to comply with for small academic groups developing advanced therapies [24]. Also, some fear that the new GMP guideline may be intended to create double standards, depending on whether advanced therapies are manufactured by industry or by academic manufacturers [25]. In either way, regulatory guidance should continue to evolve to prevent the growing use of unproven cell therapies that encourages medical tourism [26] and to shorten the development timelines of these therapies, which, in turn, will lower their market prices. For this, academic institutions that are involved in the development of cell therapies should establish collaborations between their centers and engage in a responsible collective dialogue with the appropriate regulatory agencies to speed up their translational processes [21].

Reaching a successful reimbursement rate

Reimbursement of cell and gene therapies is currently one of the most debated topics in the adoption process of novel technologies into the medicinal products market. On the one hand, if developers fail to reach a reimbursement rate that covers their incurred expenses, the product as well as the business structure behind it will never be able to survive in the open market. On the other hand, offering cell and gene therapies as highly overpriced products will not help them to achieve commercial stability through adequate market penetration [27]. Immunotherapies, such as antigen-specific T cells, may actually offer the patients the best chance for less toxicity, higher potency and improved quality of life in comparison with the available anti-viral drug regimen [28]. However, under the current methods of insurance reimbursement, such products, yet with limited well-defined real-world benefits, may not be seen as addressing an unmet clinical need, or their potential benefits may not outweigh their costs. A key consideration when analyzing the health economic justification for cell-based therapies is, therefore, the extent to which they restore function rather than simply maintain the patient or ameliorate the condition. The negation of costs of ongoing patient support, and of managing chronic comorbidities, is one of the best arguments to justify the high initial costs of prescribing cell therapies. Most importantly, not only detailed cost-effectiveness analyses accounting for the alternative costs of long-term palliative care are required for evaluating these novel interventions, but also streamlining the manufacturing process and lowering associated costs for developing such therapies would be critical steps in achieving a positive cost-benefit ratio. The recently suggested considerations to maximize reimbursement potential of cell and gene therapies should also be looked at early on in the development process [15]. Probably some of these

Table I. The variable costs of manufacturing GMP-grade CMV-specific T-cell products.

Variable resources	Description	Variable costs (€)
Materials and supplies	Media and supplements and plasticware	5660
	Reagents for the CliniMacs -PepMix HCMVA (pp65) -PepMix HCMVA (IE-1)	420
	Garments	110 (10 sets)
Personnel	Production personnel	2200
Utilities maintenance	Electricity, water and medical-grade gases Corrective maintenance	350
Quality management system	Depreciation of media-fill, process validation and fees for manufacturing authorization Cleaning and environmental monitoring Batch release testing (testing for sterility, mycoplasma, endotoxin and other items required by the guidelines)	1650
Total		10390

The variable resources of the manufacturing process were identified according to the cost model.

therapies, particularly the autologous ones, are not meant for a large-scale adoption into the medicinal product market. Still, this should not hinder developers, especially academic centers, from continuing their research efforts into finding ways to address devastating diseases. In the long term, when manufacturing technologies reach a higher level of maturity, most of these challenges will be easier to overcome.

A case study: CMV-specific T cells for adoptive immunotherapy

We performed a cost estimation of a CMV-specific T-cell therapy manufactured in an academic GMP facility using the previously indicated costing model (Tables I and II). To the authors' knowledge, no similar costing data exist in the public domain for such autologous cell therapy products. The cost model was used to calculate the costs of manufacturing the cellular product using the recently developed whole protein-spanning overlapping peptide pool-based approach with CMVpp65 and IE-1 peptide [29]. With a GMP manufacturing time of 21 days for a single CMV-specific peptide stimulated T-cell line, we estimated the GMP facility indirect costs at €5670. Direct costs were estimated at €10390. The final price for a single CMV-specific T-cell line was then calculated to be €16000. The GMP facility cost of a single T-cell line was then recalculated with the assumption that another T-cell line could be produced in parallel, however, under strict spatial segregation. In this case, the GMP fixed costs decreased to €2835 for each line. The materials and supplies costs were estimated at €6190. The remaining direct costs (€4200) were split between the two manufactured cell therapy products. The final price for a single CMV-specific T-cell product then came to €11000 (Tables I and II). Our case study thus demonstrates that immunotherapy may offer not only significant clinical advantages to immunocompromised patients, but can also be manufactured at a reasonable cost if an appropriate operational model is adopted. Our findings also mirror results from other studies examining the need to reduce the economic burden of post-transplantation care [9,30].

In summary, commercialization of novel cell therapies, especially autologous products, is not a straightforward process; many challenges must be overcome, particularly for academic developers to succeed in their mission. The challenge for the sector is surviving financially through the lengthy development timelines and overcoming any regulatory hurdles while making a successful transition from a production method that has been developed during academic research to one that is sustainable in manufacturing to satisfy a potentially global market. This needs to be done in the current absence of a consensus view about what operational model to adopt and what the incurred costs will be. Therefore, it is today more important than ever to generate accurate manufacturing cost estimates that can be useful to eventually determine a reasonable price for cellular therapies and achieve the aim of producing a clinical benefit in a larger patient population. Only with the application of robust cost and operational models

Table II. The fixed and variable cost shares in the manufacturing of a single CMV-specific T-cell product.

	Unit fixed costs (€)	Unit variable cost (€)	Total unit cost (€)
CMV-specific CTL (1 line/laboratory)	5670 (35%)	10390 (65%)	16060
CMV-specific CTL (2 lines/laboratory)	2835 (25%)	8290 (75%)	11125

The fixed costs represent 35% while the variable costs represent 65% of the total manufacturing costs. If 2 CMV-specific T-cell products are produced in the same GMP laboratory, the fixed costs represent 25% of the total manufacturing costs.

will it be possible to create the confidence that must underpin the required investment. Academia needs a growing cadre of commercially aware researchers who are willing and able to act collectively at the pre-competitive stages of their work to generate the mature, tried-and-tested approaches to manufacture at scale that will increase patient access.

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