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Putting a price tag on novel autologous cellular therapies

MOHAMED ABOU-EL-ENEIN[1,2], GERHARD BAUER[3], NICHOLAS MEDCALF[4], HANS-DIETER VOLK[1,5] & PETRA REINKE[1,2]

[1]Berlin-Brandenburg Center for Regenerative Therapies, Charité University Medicine, Campus Virchow, Berlin, Germany, [2]Department of Nephrology and Internal Intensive Care, Charité-University Medicine, Campus Virchow, Berlin, Germany, [3]Institute for Regenerative Cures, University of California Davis, Sacramento, CA, USA, [4]Wolfson School of Mechanical, Electrical and Manufacturing Engineering, Loughborough University, Loughborough, UK, and [5]Institute of Medical Immunology, Charité University Medicine, Campus Virchow, Berlin, Germany

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 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, reimburse-

Correspondence: **M. Abou-El-Enein**, MD, Berlin-Brandenburg Center for Regenerative Therapies, Clinical Development Platform, Charité-University Medicine, Campus Virchow, Augustenburger Platz 1, D-13353 Berlin, Germany. E-mail: Mohamed.abou-el-enein@charite.de

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ment 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, 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.