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Good Manufacturing Practices (GMP) manufacturing of advanced therapy medicinal products: a novel tailored model for optimizing performance and estimating costs

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Abstract

Background aims. Advanced therapy medicinal products (ATMP) have gained considerable attention in academia due to their therapeutic potential. Good Manufacturing Practice (GMP) principles ensure the quality and sterility of manufacturing these products. We developed a model for estimating the manufacturing costs of cell therapy products and optimizing the performance of academic GMP-facilities. *Methods.* The "Clean-Room Technology Assessment Technique" (CTAT) was tested prospectively in the GMP facility of BCRT, Berlin, Germany, then retrospectively in the GMP facility of the University of California-Davis, California, USA. CTAT is a two-level model: level one identifies operational (core) processes and measures their fixed costs; level two identifies production (supporting) processes and measures their variable costs. The model comprises several tools to measure and optimize performance of these processes. Manufacturing costs were itemized using adjusted micro-costing system. *Results.* CTAT identified GMP activities with strong correlation to the manufacturing process of cell-based products. Building best practice standards allowed for performance improvement and elimination of human errors. The model also demonstrated the unidirectional dependencies that may exist among the core GMP activities. When compared to traditional business models, the CTAT assessment resulted in a more accurate allocation of annual expenses. The estimated expenses were used to set a fee structure for both GMP facilities. A mathematical equation was also developed to provide the final product cost. *Conclusions.* CTAT can be a useful tool in estimating accurate costs for the ATMPs manufactured in an optimized GMP process. These estimates are useful when analyzing the cost-effectiveness of these novel interventions.

Key Words: *advanced therapy medicinal products, clean-room technology, Good Manufacturing Practices, micro-costing, performance optimization*

Introduction

Advanced therapy medicinal products represent a new medicinal product category that comprises gene, cell-based and tissue-engineered therapies as defined in the European Regulations (1,2). These products provide a variety of clinical opportunities for diseases that currently have limited or no effective therapeutic options (3–7). These products are regulated in the United States as human cells, tissues and cellular-based and tissue-based products (8). Cell processing for therapeutic applications requires product manipulations under aseptic conditions (9). Regulatory agencies worldwide require that such products be manufactured in a strictly controlled environment to ensure the absence of contaminants (10). These requirements have been primarily defined in the United States (11) and Europe (12) as Good Manufacturing Practices (GMP) standards. Although there are variations between the U.S. Food and Drug Administration and the European Medicines Agency in approaching GMP standards, the basic concept is to ensure that manufacturing of cell therapy products follows the ideals of appropriate clean-room technology. Clean-room technology is complex and requires great effort to be implemented appropriately, which imposes significant financial investment in the manufacturing process.

Many academic centers are now involved in clinical trials applying GMP-grade cellular, tissue or gene therapies. As a result, researchers have recognized

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the need for a practical and optimized approach on how to meet GMP requirements during manufacturing of cellular therapies (13). Because a great deal of expense is involved with the application of GMP methods, cost analysis can help in improving the efficiency of resource use during a GMP manufacturing process. Cost analysis, a tool for health technology assessment (14), is also relevant for both economic evaluation (15,16) and setting reference prices (17) for new therapeutics. Emphasizing the importance of health technology assessment, new legislation became effective in Germany in 2011 stating that all new drugs entering the market should be subjected to a health technology assessment with detailed costs of treatment (18). This process is not in effect in the United States.

When performing cost analysis for new medicinal products, manufacturers usually estimate the costs within the framework of a business model. For pharmaceutical companies, conventional models handle the therapy as a uniform product mass that is produced in industrial-type GMP facilities on a large scale (19). This approach is suitable for allogeneic cellular therapy products. Other academic laboratories have developed patient-based business models, usually during a clinical trial phase, to handle autologous cellular products for a small cohort of patients (19). Nevertheless, none of these modeling efforts were designed originally in accordance with GMP processes, and no studies, to the best of our knowledge, have addressed this subject before. The aim of the present study was to design a tailored model, called clean-room technology assessment technique (CTAT), not only to estimate the manufacturing costs of GMP-grade products accurately but also to measure and optimize the performance of GMP facilities. In this article, we describe the structure of the model and report the results of its application to two different academic GMP facilities in Germany and in the United States. Additionally, we explore the difference between using traditional business models and using the CTAT model in an academic GMP facility. Most importantly, we demonstrate for the first time how to determine practically the cost of a cell therapy product using a mathematical equation based on the CTAT assessment.

Methods

Study overview

The CTAT model was conceived at the newly constructed GMP facility of the Berlin-Brandenburg Center for Regenerative Therapies located at the Charité University Medicine Campus in Berlin, Germany. Prospective cost and performance analyses using the structured model were conducted at the same facility for GMP manufacturing of advanced therapy medicinal products. Retrospective analyses were conducted at the GMP facility of the University of California Davis to strengthen the credibility of the model.

Structure of CTAT model

The CTAT model aims to identify all the physical parameters and components of a GMP manufacturing process. Because of the complicated nature of this process, in which resources are not dedicated to only one activity in isolation, the model also aims to analyze and quantify the interdependency that exists between the various activities. For this specific reason, the CTAT model was designed as a two-level model: (i) Level one identifies the activities that are responsible for operating a GMP facility, which are referred to as core processes. The value measured of these activities represents the fixed manufacturing cost, also referred to as indirect cost. (ii) Level two identifies the activities that are varied with the production procedures, which are referred to as supporting processes. The value measured of these activities represents the variable manufacturing cost, also referred to as direct cost. The model integrates both performance optimization and financial estimation tools to ensure efficient delivery of the stated goals.

The model starts with building a supplier-input-process-output-customer (SIPOC) diagram (20). The diagram identifies all key activities in the GMP life cycle, listing their inputs and identifying their outcomes, and identifies who would benefit from each activity. The life cycle starts with setting up a GMP facility, passes through all the operational and production processes and ends with having an applicable product that meets the required specifications. After obtaining this information, the next action is for the user to determine which activities fit into each level of the model. An interdependent activity with shared resources should be analyzed and broken into finer details to determine how its individual resources can be categorized.

The model uses a process evaluation chart (PEC), a quality improvement tool that helps to monitor the implementation of best practice standards that are established for the core and supporting processes (e.g., least amount of resources or time each process should usually take). The performance of these processes can be strained by several factors including, but not limited to, use of a poor quality management system, ineffective use of personnel and failure to coordinate between