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Design and Development of a Cost Model for the Implementation of Process Analytical Technology in the Pharmaceutical Industry

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Abstract: Process Analytical Technology (PAT) is a systems approach for designing, analyzing, and controlling the manufacturing process, during its execution, through measurements of critical processes parameters and critical quality attributes. PAT is now part of pharmaceutical manufacturing (Cárdenas *et al*. 2020), but the costs and financial benefits of PAT have not been thoroughly evaluated. Furthermore, non-financial personnel are usually the promoters of PAT implementation in the pharmaceutical industry. The business case is the most common tool used to justify the investment in PAT, and the cost model is its most critical component. For a cost model to be complete, it is crucial to clearly identify and define the relevant costs and their structure. The cost model must be capable of adapting to the financial requirements of different pharmaceutical companies. A comparison between the different proposed financial analyses of PAT implementation found in the literature was made. A significant list of potential costs was obtained and combined based on the way they were calculated and their sources, resulting in a compacted list. The identified expenses were classified according to the product costs definition found in the literature: Capital Investment, Direct Material Cost, Labor Cost, and Overhead Cost. The cost model obtained allows to evaluate different scenarios, according to the needs of scientists involved in PAT projects.

Keywords: Process Analytical Technology, Business Case, Cost Model, Economic Analysis

1. Introduction

For private companies to be competitive, it is crucial that they control their expenses. Among these, the costs associated with the manufacturing process represent the highest percentage (Basu *et al.* 2008). Cost analysis is a key element when analyzing the implementation of new technologies that promote process improvement, especially in pharmaceutical industry. Cost analysis is essential given the expensive regulatory process when introducing a new product and the limited flexibility to improve the production process (Suresh and Basu 2008). The high cost of goods sold (COGS) of pharmaceutical products is a consequence, in part, of the methods implemented to achieve excellence in the delivered product (Basu *et al.* 2008). The continuous improvement in production processes and, therefore, reduction in manufacturing costs could mitigate this high cost of goods sold (COGS) (Lapinskaitė and Kuckailytė 2014).

Process Analytical Technology (PAT) is an initiative that supports process improvement and manufacturing cost reduction, through the knowledge and control of the manufacturing process. It is a systems approach *"for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."* (U.S. FDA 2004). Generally, scientists are the promoters of the implementation of PAT in the pharmaceutical industry. Scientists need to justify

its implementation and using a Business Case can simplify the process. However, structuring the economic analysis represents a limitation, especially when consolidating the costs involved in implementing PAT. In consequence, the support of industrial engineering is needed to nest each of the financial factors, technical specifications and the process.

The analysis of manufacturing costs in the pharmaceutical industry, was performed in a handful of investigations. In 2006, the manufacturing cost for three products in a pharmaceutical company were defined to determine the economic viability of PAT (Valþórsson 2006). This study evaluated the savings generated by PAT in quality control (QC) tests, the increase in process efficiency and improvements in process performance. Two studies in 2007 focused on analyzing the costs and benefits implied by PAT. The financial return of the combination of PAT with Lean manufacturing was evaluated in the first study. The financial performance was estimated at a hypothetical medium-sized generic drug manufacturer through a case study. Industry benchmarks and published data for publicly traded companies were employed for the case study (Cogdill *et al.* 2007). In the second research, the economic impact of the PAT implementation in the identification of raw materials in the manufacturing of pharmaceutical products was analyzed (Freeman Stanfield *et al.* 2007). In pharmaceutical manufacturing at least one test is required to verify the identity of each component of a drug product. Therefore, raw material analysis often represents a bottleneck in the production line. Within this study, it was highlighted as a benefit that PAT allows to identify the materials in the warehouse without having to send the samples to the quality control laboratory. The transfer of a raw material from the warehouse to a laboratory may result in significant delays, especially in a large manufacturing facility.

As economic evaluation methods of the project, this study considers Net Present Value (NPV), Internal Rate of Return (IRR), and Return on Investment (ROI). These metrics must exceed the growth strategy of the company for project approval (Fontalvo-Lascano *et al.* 2020). The present study describes the design and development of a Cost Model using a template for PAT implementation. The template has been developed with information from literature review and application of fundamental Industrial Engineering concepts to facilitate the development of business cases by non-financial personnel.

2. Literature Review

Through the literature review, it was possible to investigate the relevance of cost analysis for the pharmaceutical industries. This industry is one of the most regulated since it directly affects the health and quality of life of patients. For this, pharmaceutical companies, must meet a series of requirements related to good manufacturing practices (Basu *et al.* 2008)

PAT by itself does not add value to the process; for this, it requires being part of an overall methodology such as Quality-by-design, Quality Systems, or Lean Manufacturing (Alford 2013). PAT allows to reduce manufacturing costs and reduce time in the release of the product. PAT analyzers are automated, non-invasive, and reduce the number of operators. The analyses are directly conducted while monitoring a process, and the sample is not brought to a QC lab for analysis (Cárdenas *et al*. 2020). PAT often requires the application of chemometric techniques and multivariate tools applied to obtain the desired data and develop process knowledge (Challa and Potumarthi 2013). Multivariate (chemometric methods) are still new in many pharmaceutical companies, and the training of personnel is a cost that must be considered.

PAT implementation is considered a capital project given the significant required investment. An investment in the range of $50,000 to $200,000 is generally required for acquiring a system capable of monitoring a process. Therefore, an economic analysis is essential to evaluate its profitability for the company (Fontalvo-Lascano *et al.* 2020). The relevant costs and their structure must be identified and defined. Few investigations focused on cost analysis to PAT implementation has been developed. The identification of costs associated with batch manufacturing by-product for PAT implementation in the pharmaceutical industry was evaluated in 2006 (Valþórsson 2006). Besides, the financial returns of PAT combined with Lean Manufacturing have been assessed, giving relevance to the quality costs (Cogdill *et al*. 2007). The economic impact of PAT in the identification and analysis of raw materials, determining the related costs was evaluated too (Freeman Stanfield *et al.* 2007).

The NPV, IRR, and ROI are the evaluation methods for the economic analysis more commonly used. However, these methods have rarely been used for the economic analysis of PAT projects. The Net Present Value (NPV), compares in the present time the profit obtained with the minimum expected return regarding the expenses generated (Juhász 2011). The Internal Rate of Return (IRR) is defined as the interest rate obtained on that investment that is not recovered (Newnan *et al*. 2012). The return on investment (ROI) compares the investment made versus the benefit obtained focused on investment efficiency (Zamfir *et al.* 2016).

3. Methodology

The research methodology corresponds to the following stages: The Information Consolidation, Analysis and Information Classification, and finally the develop Cost Model for Business Case. A literature review of Cost Analysis, Business Cases, PAT, and other economic elements was first performed. Furthermore, meetings were held with leaders of the

pharmaceutical companies to learn more about PAT, its costs, and the key points for its approval. In the second stage, the information obtained was analyzed, comparing each of the economic models for the implementation of PAT that were found, selecting and classifying the associated costs. A total of thirty-one (31) costs were obtained; the details of how it was done are included in a previous study (Fontalvo-Lascano *et al*. 2020). Finally, using the information from the second stage, the cost model that would be the main part of the Business Case was structured. The cost model is composed of the costs associated with investment capital and operating costs, as well as the economic evaluation methods and the cash flow.

3.1 Capital Investment Cost

The capital investment information was obtained through the literature review and interviews with leaders of the pharmaceutical industry. The information was classified in two principal groups: PAT equipment cost and others. The acquisition cost of the system may be in the range of $50,000 - $200,000, but an additional investment is required in terms of implementation: qualification, validation, and training to use the equipment and to manage the data obtained. The other costs are associated with chemometric model development, multivariate data analysis (MVDA) tools, change management in the quality management system (QMS) cost, among others. The costs were determined according to the amount of equipment required, the critical processes parameters (CPP) and the critical quality parameters (CQP) to be measured and the unit cost for each item.

3.2 Operational Cost

The operational cost corresponds to the operating activities of the manufacturing process. These were classified according to the definition found in the literature: Direct Materials Cost, Labor Cost, and Overhead Cost (Hansen *et al.* 2009). The direct or raw materials cost corresponds to the costs associated with inventory management, such as: capital cost, service cost, storage cost and risk cost (La Londe *et al.* 1977).

The labor cost is related to the salaries and wages paid to the workforce that intervenes directly in PAT implementation and in the use of the equipment required to measure critical quality parameters. PAT often reduces the number of operators that intervene in the manufacturing process. However, it requires the addition of specialized personnel capable of working with the systems installed to monitor the process, and interpret the data obtained. In the overhead cost, the indirect expenses incurred for the operation of the company related to PAT were consolidated: maintenance, quality, utility and ecology cost. These categories are presented in Table 1. The Costs were consolidated in these categories to design a generic structure applicable to any pharmaceutical company regardless of its manufacturing cost structure.

Interviews with financial experts from the pharmaceutical industry were conducted to analyze the operational costs in their companies. As a result, it was evidenced that quality costs are the most impacted with PAT implementation. The disposition of solvents, used to prepare the samples in the High-Performance Liquid Chromatography (HPLC) testing, represents the highest source of solvent waste in many manufacturing sites. PAT methods generally eliminate the use of solvents and leave the materials analyzed intact. Thus, there are important environmental benefits with the use of PAT.

Table 1. Operational Cost Categories

Group		**Cost**	
Operational Cost	Overhead Cost	Maintenance Cost	
		Quality Cost	Internal Failure Cost
			External Failure Cost
			Appraisal costs - Quality Control (QC)
			Prevention costs - Quality Assurance (QA)
		Utility Cost	
		Ecology Cost	
	Direct Materials Cost	Inventory carrying Cost	Capital Cost
			Service Cost
			Storage Cost
			Risk Cost
	Labor Cost	Operating labor cost (PAT)	

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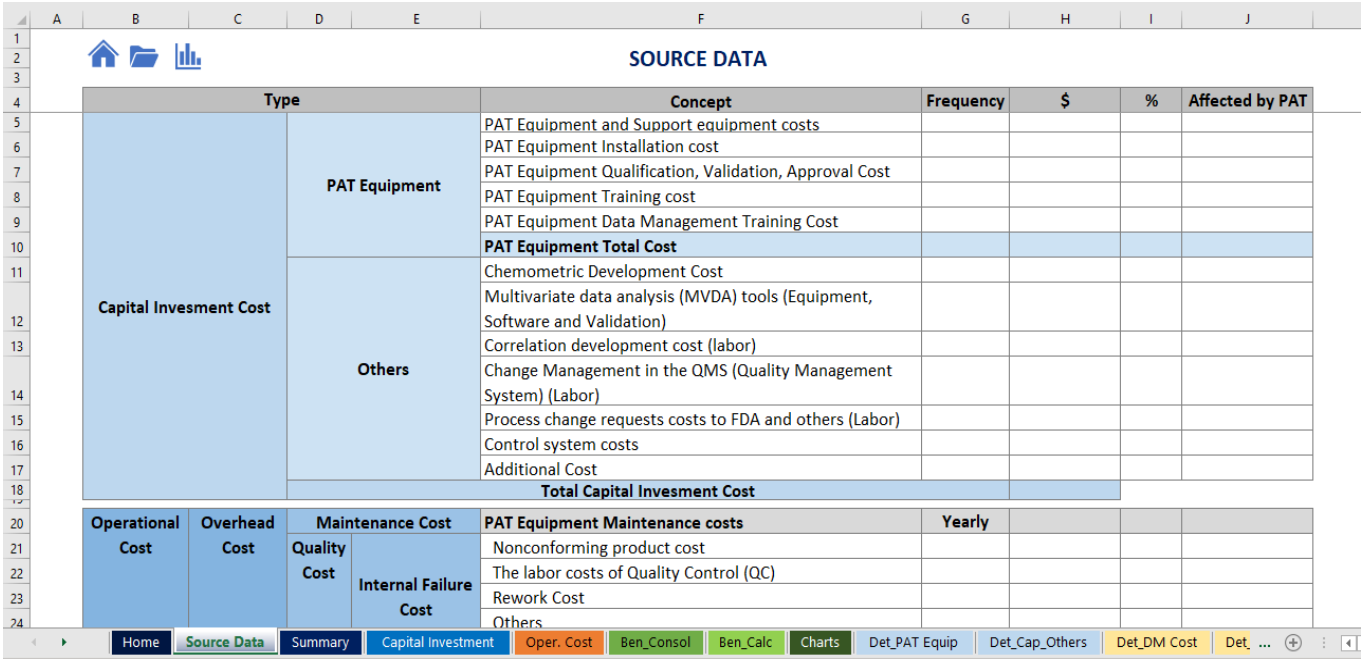
3.3 Cost Model

The model contains the cash flows and the different costs, which are automatically filled by costs previously obtained through a source data section shown in Figure 1. The PAT economic impact was measured using the Net Present Value (NPV), Internal Rate of Return (IRR) and Return on Investment (ROI) methods. The template allows the user to evaluate different scenarios, according to the necessity of the leaders of PAT project implementation. Verification was done evaluating that the NPV, IRR, ROI, and cash flows had a logical and expected order according to the specified assumptions and the theory of how these methods work. Additionally, the model was validated by various financial experts from the pharmaceutical industry.



SOURCE DATA

Type		Concept	Frequency	$	%	Affected by PAT
Capital Invesment Cost	PAT Equipment	PAT Equipment and Support equipment costs				
		PAT Equipment Installation cost				
		PAT Equipment Qualification, Validation, Approval Cost				
		PAT Equipment Training cost				
		PAT Equipment Data Management Training Cost				
		PAT Equipment Total Cost				
	Others	Chemometric Development Cost				
		Multivariate data analysis (MVDA) tools (Equipment, Software and Validation)				
		Correlation development cost (labor)				
		Change Management in the QMS (Quality Management System) (Labor)				
		Process change requests costs to FDA and others (Labor)				
		Control system costs				
		Additional Cost				
	Total Capital Invesment Cost					

Operational Cost	Overhead Cost	Maintenance Cost		PAT Equipment Maintenance costs	Yearly			
		Quality Cost	Internal Failure Cost	Nonconforming product cost				
				The labor costs of Quality Control (QC)				
				Rework Cost				
				Others				

Home | Source Data | Summary | Capital Investment | Oper. Cost | Ben_Consol | Ben_Calc | Charts | Det_PAT Equip | Det_Cap_Others | Det_DM Cost | Det_ ...

Figure 1. Cost Model - Source data section - Excel Template

The cost model was developed as an interactive Microsoft Excel template. This template contains a home page, which was developed in a previous study (Fontalvo-Lascano *et al.* 2020) and is shown in Figure 2. Here, the different menus for accessing costs, benefits and the results section are specified.

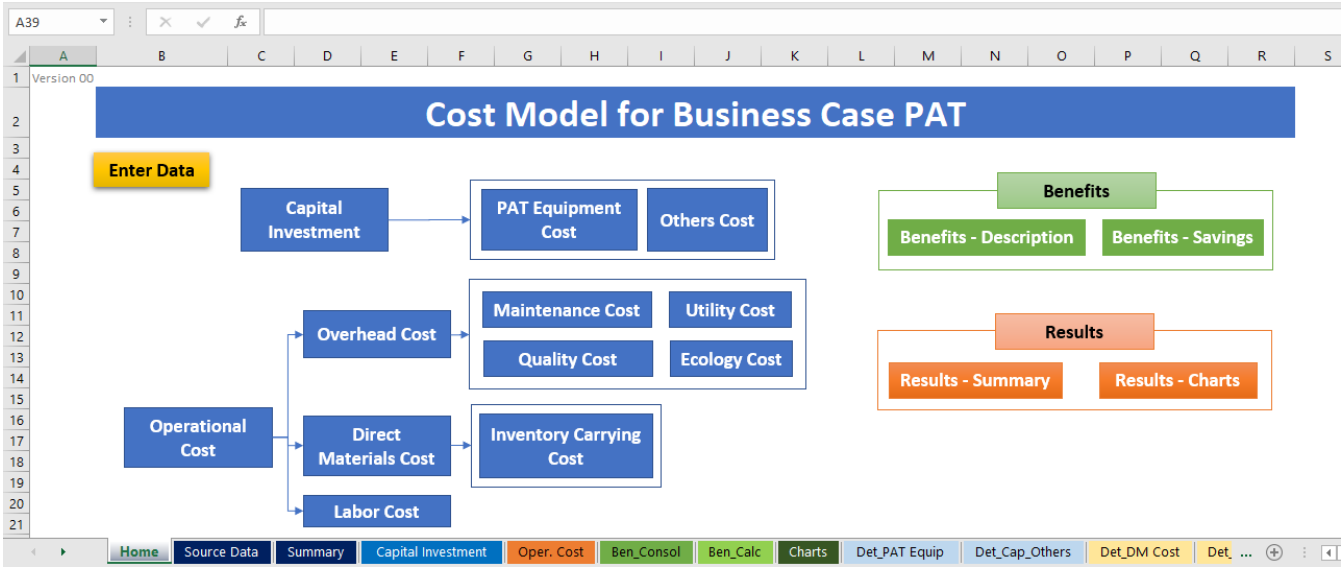


Figure 2. Cost Model - Home Page - Excel Template (Fontalvo-Lascano *et al*. 2020)

4. Conclusions and Future Research

Throughout this study, it was possible to delve into the economic aspects related to PAT implementation. Furthermore, the knowledge related to the Process Analytical Technology (PAT) was strengthened through the cost model development, since the activities and components required for its operation were detailed.

This cost model follows the pharmaceutical industry requirements and economic evaluation methods. It supports the structure of the Business Case to justify the PAT Implementation. Besides, it is capable of adapting to the financial requirements and manufacturing processes of different pharmaceutical companies. The cost model obtained allows to evaluate different scenarios, according to the necessity of the leaders of PAT project implementation. In addition, the cost model could assist the non-financial personnel of the pharmaceutical industry to obtain the required financial information for PAT implementation. The effects of taxes and depreciation, including the tax benefits and sensitivity analysis, should be developed in future studies.

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