

# Development of a Business Case Model for Process Analytical Technology Implementation in the Pharmaceutical Industry

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## Abstract

Leading pharmaceutical companies are implementing Process Analytical Technology (PAT). PAT is defined as a system for designing, analyzing, and controlling the manufacturing process through the real-time measurement of critical processes and critical quality parameters. The economic analysis and cost-effectiveness of PAT has not been evaluated in-depth and is the subject of this research. The knowledge gained is being used to develop a Business Case Model for PAT analysis, justification, and implementation, following pharmaceutical industry requirements including the cost model, benefit estimates, and the economic evaluation based on the Net Present Value (NPV), Internal Rate of Return (IRR), and Return on Investment (ROI) methods. The template developed may be adapted by each company according to its cost structure and manufacturing processes. A literature review was performed on Business Cases, PAT, and other economic aspects, and ten manufacturing experts were interviewed. A comparison between the different proposed structures of the cost-benefits and business case model was made selecting the relevant elements. The template was structured with the source data of the associated costs, capital investment, and estimated cash flows. The PAT Business Case template allows to evaluate different scenarios, costs, and benefits, of a proposed project.

## Keywords

Process Analytical Technology, Business Case, Cost Model, Economic Analysis.

## 1. Introduction

Process analytical technology (PAT) 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). The analytical methods used in PAT may be “*viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner*” (U.S. FDA 2004). The goal of PAT to enhance understanding and control the manufacturing process, to achieve Quality-by-design.

PAT may be illustrated using the drying of an active pharmaceutical ingredient (API) as an example. Without PAT every batch would be dried for 8 hours, and then samples would be brought to a remote Quality Control (QC) lab to determine whether the moisture content of the API has reached the level required for the product. However, with PAT a near infrared spectrometer would be installed at the dryer for real time monitoring of the moisture content. Drying could be reduced to 5 hours or less, according to the efficiency of the dryer used. PAT involves a change from procedure-based manufacturing (always 8 hours of drying) to drying until the moisture of the final product is obtained.

Thus, the sample is not brought to a remote off-line QC lab for testing. The product release time may be reduced, since it is not necessary to wait for the QC lab to analyze the product. This example shows how PAT may reduce energy consumption and operational costs and increase productivity. Process knowledge is also increased as the real time monitoring shows the progress of the drying process. The economic analysis of PAT merits investigation given the significant capital investment required for its implementation. Furthermore, the potential financial return that PAT can generate must be analyzed to verify if it is profitable for the company.

Few studies have made efforts to assess the financial benefits of the PAT implementation. In 2006, the PAT economic impact was analyzed for three products in one specific pharmaceutical company (Valþórsson 2006). This research structured the PAT implementation plan, costs and benefits associated with PAT for this company. Significant savings due to PAT were observed as a result of time saved in quality control (QC) testing, increased process efficiency, and improved process performance given the reduction in the number of out-of-specification products. The profitability that may be generated through the combination of PAT and Lean Manufacturing was evaluated in a second study in 2007. Through a case study, the financial performance of this combination in a hypothetical medium-sized generic pharmaceutical manufacturer was estimated. The study was structured using industry benchmarks and published data for publicly traded companies (Cogdill *et al.* 2007). Another study developed a business case for the implementation of PAT on raw material identification and analysis (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. These analyses would require sending samples from the warehouse to a QC laboratory where one or more wet chemistry methods are followed. The raw materials are not available for production until the QC laboratory completes the analyses and releases them. PAT makes it possible to identify the materials at the warehouse without having to send the samples to the QC lab. The PAT methods contribute to a reduction in analysis time and inventory. This study considered Net Present Value (NPV), Internal Rate of Return (IRR), and Return on Investment (ROI) as economic evaluation methods of the project. These metrics must exceed the growth strategy of the company for project approval.

However, the financial models obtained have been specific since they depend on the cost structure of each company. A generic Business Case that supports scientists in proposing PAT projects in pharmaceutical companies is needed. Scientists must contemplate, the scientific aspects and all the possible expenses, including the unforeseen and additional costs corresponding to process modifications to implement PAT. The Business Case presents a cost/benefit model which is essential for making decisions. However, this model is complex to develop, given the difficulty of collecting the information. Equally, the strategy to obtain approval from upper management is also difficult to design.

The present study describes the development of a Business Case Model using a template for PAT implementation. The template has been developed with information from conversations with pharmaceutical industry leaders, literature review and application of fundamental Industrial Engineering concepts to promote the use of PAT within the pharmaceutical industry.

## **2. Literature Review**

The literature review revealed that Process Analytical Technology (PAT) is based on the concepts of Process Analytical Chemistry (PAC). The term PAC was replaced for PAT by the FDA, to avoid limiting its concepts to the chemistry of processes (Cárdenas *et al.* 2020). PAT considers obtaining process information in real-time at a point on the manufacturing line where it can be used to control a critical quality parameter. The critical parameter could be a simple measurement, e.g., determining temperature with a thermocouple, to more complex measurements. This latter type required using chemometric techniques (Hailey *et al.* 1996), multivariate tools, process analyzers, and process control tools (Challa and Potumarthi 2013) which will allow a better understanding of the process.

The pharmaceutical industry and the FDA have given relevance to the benefits that PAT offers for each company. When PAT is part of an overall methodology such as Quality Systems, Lean Manufacturing, and Quality-by-design, these benefits materialize (Alford 2013). Among these benefits, the most prominent corresponds to being able to control the process while the manufacturing process continues (Calhan *et al.* 2017). PAT allows saving time and money since sample preparation is not required in the QC lab (Simon *et al.* 2015).

The implementation of PAT is not straight forward. A risk analysis is needed to identify the failures that PAT may have to mitigate the risk effect or eliminate it (Lee *et al.* 2015). PAT often involves the development and implementation of new analytical methods. PAT generate changes in the production area using new instruments, techniques, such as Near Infrared and Raman spectroscopy. In turn, PAT implementation follows the Quality-by-

Design concept, and it requires exploring different methods that ensure maximum process performance (Vogt and Kord 2011). Delays may occur in the implementation of these new analytical methods. A PAT-team is required in which there are members from different disciplines. They must have knowledge of the manufacturing process, the analytical method for process monitoring, chemometrics, data management, and experience in the financial and manufacturing process (Romañach 2008). A number of PAT systems employ near infrared spectroscopy and Raman spectroscopy, and multivariate data analysis (chemometrics) to extract information from the data obtained. Training in these multivariate methods is often required, as most of the currently used methods in the QC lab rely on univariate data analysis.

PAT projects imply a significant capital investment, and the evaluation of its economic impact to justify the investment (Fontalvo-Lascano *et al.* 2020). Some research in the last decade has focused on supporting this justification. The economic feasibility of the PAT implementation by-product in the pharmaceutical industry was evaluated in 2006 (Valþórsson 2006). Furthermore, the financial return caused by PAT implementation combined with Lean Manufacturing has been assessed (Cogdill *et al.* 2007). Equally, the business case structure of the application of PAT on raw material identification and analysis was developed (Freeman Stanfield *et al.* 2007).

The literature reviews exposed the evaluation methods for the economic analysis used more frequently are the NPV, IRR, and ROI. The Net Present Value (NPV), compares in the present time the investment made with the net cash flows to be generated in the future (Hopkinson 2016). The Internal Rate of Return (IRR) is the profitability offered by the project and is usually related to the net present value (Hopkinson 2017). The return on investment (ROI) compares the benefit obtained with the investment made evaluating the investment efficiency (Zamfir *et al.* 2016). All the above supports structuring a business case considering the costs, benefits, and information that allows evaluating the economic impact of the PAT implementation in the pharmaceutical industry.

### 3. Methods

The research methodology consists of three stages, as shown in Figure 1: The first stage consisted of a literature review focused initially on PAT, its beginnings, implementation in the pharmaceutical industry, benefits, and related economic aspects. The general concept of Business Cases was researched and its use on pharmaceutical companies. Other topics, such as Quality-by-design, supply chain, and cost models employed by the pharmaceutical industry, were also researched. Additionally, meetings were held with pharmaceutical companies' leaders to learn more about PAT, the lessons learned, and key points when seeking approval of the PAT implementation.

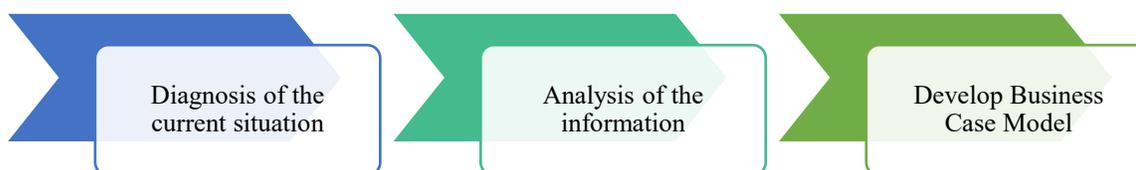


Figure 1. Research methodology.

The second stage consisted in an information analysis. The information obtained at the first stage was compared, classified and evaluated. The third stage involved the develop of Business Case Model. It started with its global structure and then with the cost-benefit model.

#### 3.1 Business Case Structure

The global structure of the Business Case Model for PAT implementation was obtained from a literature review. Five different proposed structures were selected and compared for its content and description. The relevant elements were chosen according to analyzed in the literature review and the recommendations from experts' pharmaceutical industry. Table 1 shows the comparison of the Business Case structure, which consists of twenty (20) sections.

Table 1. Comparison of Business Case structures.

Sections		Reference				
		Schmidt (2003).	Maes et al. (2006).	Brindle (2009).	ITM Madrid (2017).	Stratton (2004).
1	List of Costs / Cost Model / Financial Model	✓		✓	✓	✓
2	The Benefits / Benefits Rationale	✓	✓	✓		✓
3	Business Risk	✓		✓	✓	✓
4	Sensitivity Analysis	✓				✓
5	Investment Evaluation			✓		✓
6	Justification		✓		✓	✓
7	Objectives				✓	
8	Purpose	✓				✓
9	Executive Summary	✓				✓
10	Assumptions	✓				✓
11	Scope & Boundaries	✓		✓		
12	Scenarios	✓				
13	Full Value vs. Incremental	✓				
14	Data Sources & Methods	✓				✓
15	Analysis of Results	✓				✓
16	Non-Financial Results	✓				
17	Contingencies & Dependencies	✓				✓
18	Conclusions and Recommendations	✓				✓
19	Introduction and Overview					✓
20	Schedule					✓

The Business Case structure requires the eleven (11) sections described in Figure 2. The Cost Model, Benefits, and Risk Analysis are the backbone of the Business Case. They are fundamental for the approval of the PAT implementation initiative.

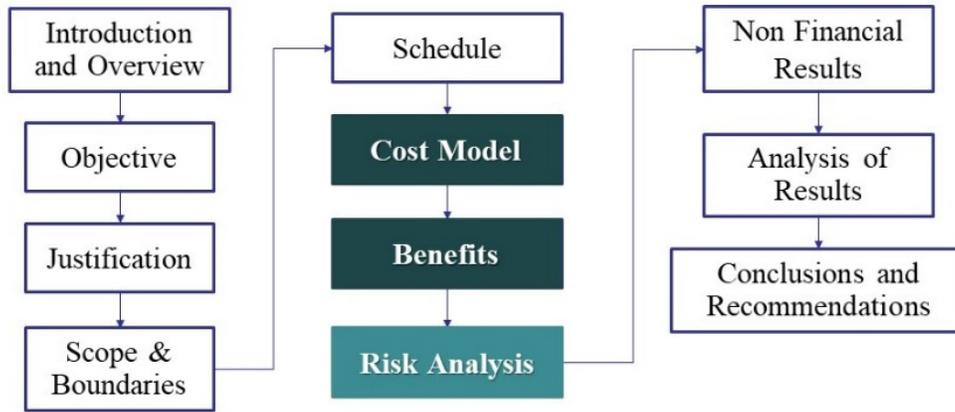


Figure 2. Structure of Business Case Model Proposed.

### 3.2 Costs

The information consolidated was evaluated according to the cost, benefits, and relevant elements that allowed the development of the cost-benefit model. Seven (7) references on economic analysis of PAT in the pharmaceutical industry were found and a list of sixty-one (61) variables emerged. These variables correspond to the costs associated with each financial analysis. The number of variables was reduced to thirty-one (31), after identifying similar variables.

The chosen variables were classified as shown in Figure 3, according to the Product Costs definition found in the literature: Capital Investment, Direct Material Cost, Labor Cost, and Overhead Cost (Hansen *et al.* 2009). The frequency and computation were defined once the definitive list of variables was determined.

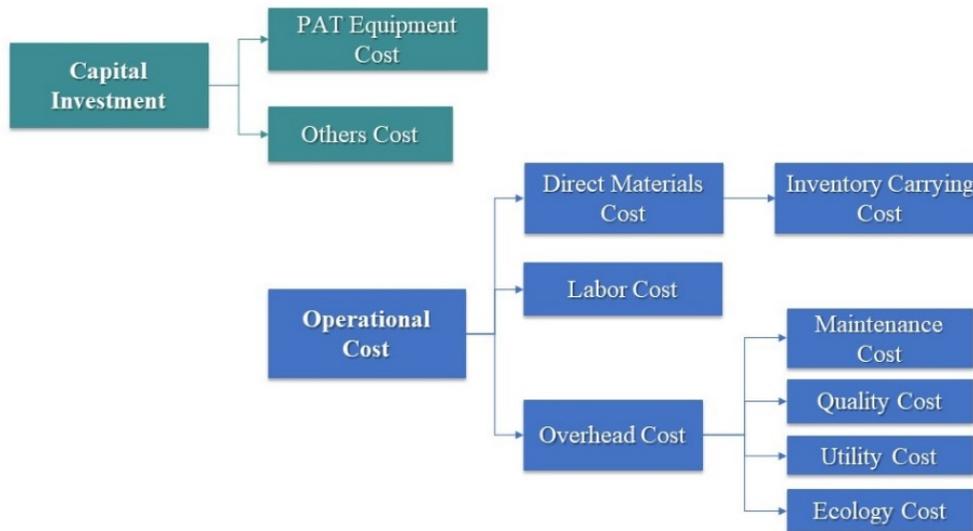


Figure 3. Relevant variables (Cost) Classification.

### 3.3 Benefits

The list of benefits of PAT was the result of the literature review and interviews with leaders of the pharmaceutical industry. A total of twenty-seven (27) benefits were identified and classified as measurable and not measurable. The benefits classification was made according to the item in which it generated the savings. The list of benefits was grouped by their similarities and went from twenty-seven (27) to eleven (11) benefit groups, which is presented in Table 2. The benefits were associated with cost savings or with corporate indicators to demonstrate its gain in the

Business Case. The savings were calculated, by applying a percentage reduction to the specific cost-related in the corresponding years of the cash flow.

Table 2. Benefits Groups of PAT Implementation.

No	Benefits		
1	Savings in QC costs	1.1. In Process Control (IPC) lab costs for PAT products will be eliminated (Reduction in QC testing, leading to real time release).	
		1.2 Investigations	1.2.1. Reduced time for investigations
			1.2.2. Fewer investigations
		1.3. Savings due to fewer Food and Drug Administration (FDA) audits	
2	Reduced throughput time (Process Time + Inspection Time + Moving Time + Wait Time)		
3	Real time release (The product is released when completing the last stage of the manufacturing line due to the analysis of the process data (Skibsted <i>et al.</i> 2007))		
4	Increased process efficiency (value-added time associated with a process /total lead time of the process)		
5	Production yields for each batch will be increased (eliminating material losses) (number of good units produced / number of units going into the start of the process)		
6	Lower inventory levels		
7	Reduce impact of raw material variability		
8	Improved process capability		
9	Ease of technical transfer		
10	Greater process understanding		
11	Greater assurance of product quality		

### 3.4 Cost-Benefits Model

The cost/benefit model was developed, after costs, benefits, and overall business case structure were determined. The model contains the cash flow, which is automatically fed by costs and benefits previously obtained. The Net Present Value (NPV), Internal Rate of Return (IRR) and Return on Investment (ROI) are the methods selected to measure the PAT economic impact. This model was developed as a Microsoft Excel template, the home page is shown in Figure 4. The template allows evaluating different scenarios, relevant costs, and benefits according to the necessity of the leaders of the PAT implementation. The model was verified to assess that it works correctly according to the projected, an easy to access and use tool. Verification was done entering data calculated according to the literature found, and the NPV, IRR, ROI, and cash flows had a logical order expected according to the assumptions. Equally, For the model to be recommended in the analysis of PAT implementation, it was validated by financial experts in the pharmaceutical industry.

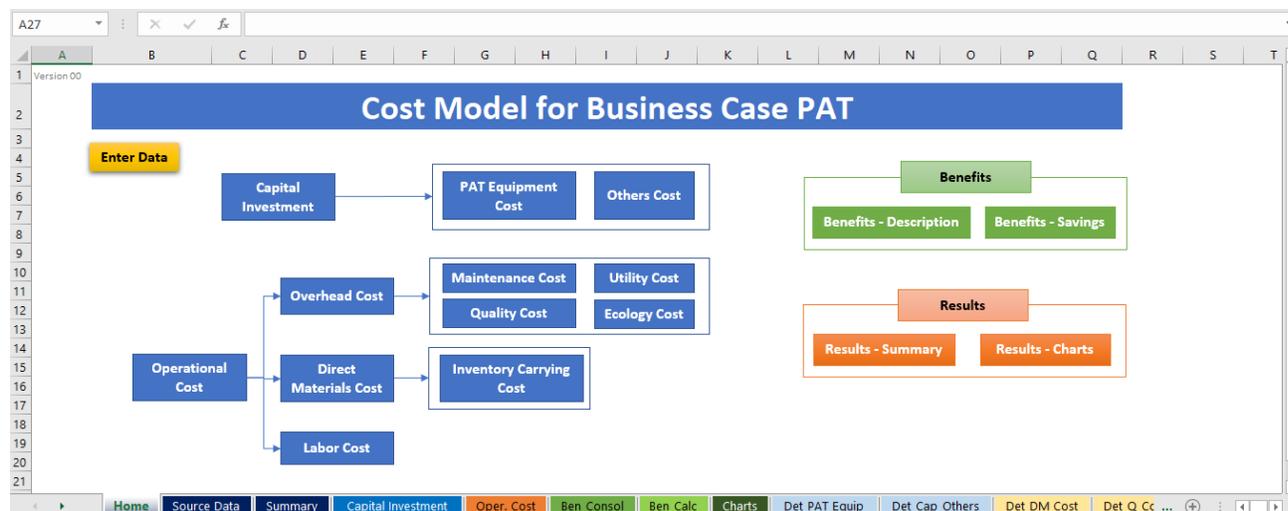


Figure 4. Cost Model for Business Case PAT - Excel Template.

#### 4. Conclusions and Future Research Direction

This research has allowed delving further into the Process Analytical Technologies (PAT) concept, ceasing to be abstract for those without a chemistry background.

Improving the processes before the use and the approval of PAT and more profound knowledge of this tool should be considered in PAT future research. Therefore, from this research, it is proposed for the PAT implementation project, the development of a Business Case Model using a customizable template. This model follows pharmaceutical industry requirements, and it includes the cost model, benefit estimates, and economic evaluation methods. The Business Case Model adapts to the cost structure and manufacturing processes of each company. Different scenarios, relevant costs, and benefits can be evaluated according to the necessity of the PAT implementation leaders. Besides, it could support pharmaceutical industry scientists in searching, recording, and obtaining the required financial information to justify the PAT implementation.

The effects of taxes, depreciation, and the tax benefits should be developed in future works. Equally, a sensitivity analysis could be implemented. This analysis will help in identifying which are the specific costs that impact the profitability of the project, thus generating significant benefits.

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## **Biography / Biographies**

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