



Development and Application of a Business Case Model for a Stream Sampler in the Pharmaceutical Industry

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Abstract

Purpose A template to prepare a business case for Process Analytical Technology (PAT) and Continuous Manufacturing (CM) projects is presented in this study. Business cases are necessary tools used in different organizations to present new projects for management evaluation. As new ways of working under PAT and CM constitute a significant investment of capital, time, personnel, and other resources, a solid business case will facilitate the organization, presentation, and justification of these innovative strategies to management for their evaluation. The authors understand that this is the first study that considers the implementation of PAT in a specific manufacturing facility, including potential tax benefits associated with the manufacturing location.

Methods A financial analysis template was used to develop a business case for an innovative stream sampler for pharmaceutical powder blends. The business case financial model included the capital investment and associated costs for implementing this powder sampler. The case study modeled three different potential tax benefits modalities. The definition of the financial model parameters, assumptions, and constraints are followed by the recommendations of pharmaceutical industry leaders and tax advisors.

Results The financial model provided the evaluation of the listed relevant costs and benefits. The analysis evidenced a significant influence of tax incentives on the economic evaluation. As a result, the financial model estimated a net present value (NPV) range of \$420,957 to \$578,896, an internal rate of return (IRR) with a minimal of 65% and a maximum of 89%, and a return of investment (ROI) of 82 to 133% for the proposed PAT investment. The most significant benefits representing additional savings between \$14,157 and \$234,157 per year were presented applying the tax incentives.

Conclusion The PAT Business Case template facilitates evaluating different scenarios, costs, and benefits for a proposed project. Each company may adopt the business case model according to its cost structure and manufacturing processes. The tax benefits contribute further to this case study, especially the super deduction, followed by the R&D tax credit. Furthermore, the tax incentives effects can be evaluated by entering the input data without an additional step in the business case template.

Keywords Sampling · Process analytical technology · Continuous manufacturing · Business case · Cost model · Economic analysis

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Introduction

Process Analytical Technology (PAT) implementation is a key element in improving drug manufacturing processes. 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” [1]. The expectation is that PAT will support innovation and efficiency in pharmaceutical process development, manufacturing, and quality assurance. However, the implementation of PAT requires a significant investment; and constitutes a capital project [2].

The improvement of manufacturing through PAT requires the approval of new investments to monitor or control a process or work with the information obtained. PAT projects require careful evaluation because their outcomes will directly impact the organization’s profitability [3]. Scientists can justify PAT implementation through a business case, which is the most used tool to justify a capital investment [4, 5]. The business case is an instrument that describes the problem, cost, benefits, possible solutions, facts, and data required to make a decision [6, 7]. The cost/benefit model is the most critical component of the business case to make capital investment decisions, as companies will select and invest in projects that maximize profitability. The profitability of PAT projects will be compared to other proposed projects as companies evaluate possible investments.

Currently, there is a need to provide new powder sampling systems as alternatives to sample thieves. There are numerous examples of the problems associated with sampling of static powder beds by a sample thief [8–12]. This study presents a series of business case scenarios using a newly developed stream sampler based on the principles of the “Theory of Sampling” [13]. The Fundamental Sampling Principle states that all the material or batch must have the same probability of being sampled and that the material is not affected by the sampling process [13]. The stream sampler allows for the non-destructive analysis of powders flowing within the sampler through a sapphire window using spectroscopic techniques such as near infrared (NIR) or Raman spectroscopy.

The PAT literature focuses on scientific and technical considerations, with minimal discussion of fundamental financial aspects [18–21]. However, several articles discuss the economic analysis for PAT applications [2, 14–16]. The economic feasibility of the PAT implementation based on a production strategy for three products of a specific pharmaceutical company was evaluated in 2006 [16]. This

research observed significant savings in quality control (QC) testing, increased process efficiency, and improved process performance. The cost-efficiencies generated through the combination of PAT and Lean Manufacturing could generate savings by improving process capability and supply chain management [14]. The economic impact of the PAT implementation in the identification of raw materials in the manufacturing of pharmaceutical products was analyzed [15]. This study highlighted PAT’s benefits by identifying the raw materials at the warehouse without sending the samples to the QC laboratory. Previous studies have shown that process understanding is increased through PAT, providing valuable information for a real-time release testing (RTRT) strategy [17]. Process understanding may also facilitate product approval and help a company reach the market quickly and increase its sales. The larger pharmaceutical companies now have PAT groups that provide information that contributes to new products approval. The value of PAT in product approval and development is clear, and the cost/benefits of in-line monitoring and RTRT were discussed by a BioPhorum committee [18].

The authors are not aware of any studies considering the costs associated with PAT implementation within the quality system of the manufacturing site subject of this technology transfer, including the effects of the tax credit incentives for that specific region or country. The financial models obtained in the studies related to the economic analysis of PAT depend on the cost structure and expectations of each company. Economic analysis related to the PAT for monitoring and control of blend uniformity may have been developed within companies but not shared or discussed with the PAT community.

For the first time, this article presents the application of a business case template, considering the manufacturing site subject of the PAT technology transfer. This study takes into consideration the costs of changes in plant procedures that are necessary for PAT implementation. The template also calculates the effect of tax incentives on the net present value (NPV), internal rate of return (IRR), and return on investment (ROI) of the proposed PAT investment. The business case template provides the financial evaluation of a new stream sampler currently under development and the financial assessment of acquiring supporting instrumentation, including a near-infrared or Raman spectrometer or the implementation of continuous manufacturing. The template could be used to evaluate many other PAT or continuous manufacturing investments and is not limited to the stream sampler in this case study. The business case template presented in this study will be available as a tool for advancing PAT and CM within the pharmaceutical industry.

Materials and Methods

Stream Sampler

The stream sampler consists of a powder inlet, a sapphire window, a powder collection port, and the powder exit. The flow area within the sampler is consistent with the spot size of the spectroscopic equipment used ensuring all the material has equal opportunity of being analyzed [19]. Figure 1 shows the applications of the stream sampler when determining drug concentrations in a manufacturing process or in its development phase. The stream sampler can be used to analyze powder mixtures in a continuous or batch process. In both scenarios, the sampler could be placed before a tablet press for real-time monitoring of drug concentration through near-infrared or Raman spectroscopic measurements. The real-time drug concentration results obtained from the NIR or Raman spectra could be provided to a feed forward control system to accept or reject tablets at the tablet press. The stream sampler would eliminate the use of a sample thief, which requires an interruption of the manufacturing process and possible powder segregation [8].

The stream sampler also has a sample collection port to remove a cross-section of the material flow area without interrupting the powder flow. These samples can be subject to analysis by a reference method such as high-performance liquid chromatography (HPLC). This feature could be useful for companies that are developing new processes as shown in Fig. 1. After the sample collection port, the material completely exits the stream sampler ensuring new material is continuously analyzed. Once the material exits the sampler,

it can continue to next process step as shown in Fig. 1. The sample collection port was designed for use during process development or validation.

Business Case Excel Template

The business case discussed in this study considers the use of the sampler for real-time monitoring. The template works as a user-friendly calculator where the user enters the data in a source data section. This section feeds the subsequent parts of the template (Capital Investment, Operational Cost, and Benefits Computations). The cost/benefit model consists of fourteen sections described in Table 1.

Economic Evaluation Methods

The economic evaluation methods used in the business case model correspond to net present value (NPV), internal rate of return (IRR), and return on investment (ROI).

The NPV allows evaluating the profitability of an investment or project; it is calculated given a discount rate i , and net cash flow CF_j , at the year j , using Eq. 1 [20]:

$$NPV = \sum_{j=1}^n \frac{CF_j}{(1+i)^j} - \text{Initial Investment} \quad (1)$$

The NPV represents the sum of the equivalency of the expected cash flows at the present time. The interest rate that causes a discounted breakeven point by making this sum equal to zero is called the internal rate of return (IRR). This is shown in Eq. 2 [16]:

Fig. 1 Diagram of the stream sampler applications in process and development for the determination of drug concentration

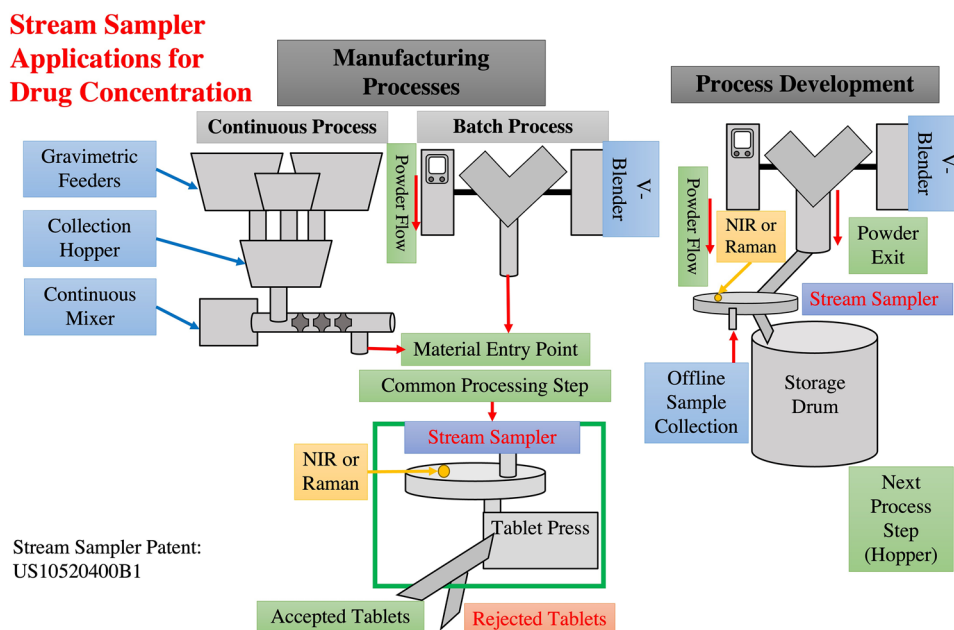


Table 1 Cost/benefit template section list

	Name section	Description
Main sections	1. Home	This section includes the overall map of the cost/benefit model template structure
	2. Source data	The information corresponding to the inputs that will feed the template subsequent parts (capital investment, operational cost, and benefits computations)
	3. Capital investment	A detailed list of cost categories related to the capital investment (3), operational cost (4), and benefits applicable when PAT is implemented (5) and its computation (6)
	4. Operational cost	
	5. Benefits—description	
	6. Benefits—savings	Presents results graphically in cash flows and the Pareto diagram
	7. Charts	
	8. Depreciation	Used to apply the Modified Accelerated Cost Recovery System (MACRS) depreciation method in two scenarios: (1) without research and development (R&D) credit, and (2) with R&D credit
	9. Tax benefits	Describe and calculate the tax benefits
	10. Comparison	Compares the three for tax benefits available in Puerto Rico
	11. Cash flows depreciation	Provides the before-tax cash flow (BTCF) and the after-tax cash flow (ATCF) for three different tax incentives scenarios: depreciation and tax benefits (11), depreciation, tax benefits, and R&D Credit (12), and tax benefits and super-deduction without R&D Credit (13)
	12. Cash flows depreciation + R&D	
	13. Cash flows taxes + super deduction	
Support sections	14. Computations help	Detailed and specific computation tables are suggested to find each cost requested in the source data section

$$NPV = \sum_{j=1}^n \frac{CF_j}{(1 + IRR)^j} - \text{Initial Investment} = 0 \quad (2)$$

The ROI is a profitability metric that compares the accumulated net of total of benefits (profit) obtained, P_j , and all expenses, E_j , with the capital investment made. The ROI evaluates the investment performance or efficiency, as shown in Eq. 3 [21]:

$$ROI = \frac{\left[\sum_{j=1}^n \frac{(P_j E_j)}{(1 + i)^j} \right] - \text{Initial Investment}}{\text{Initial Investment}} \times 100\% \quad (3)$$

Tax Incentives and PAT

The investment alternatives must consider the impact of taxes and tax incentives to obtain better estimates of the cash

flows and the economic evaluation methods. Most governments, especially developing countries, have implemented tax incentives to promote foreign investment and stimulate economic development in their country. These initiatives offer more favorable tax treatment to specific economic activities [22]. Taxes and tax incentives can affect the profitability of the investment, reducing or increasing the return of investment, respectively. PAT implementation could be a research and development (R&D) activity conducted at the manufacturing site which qualifies for tax credits.

Case Study

Design of Analysis

Table 2 describes the case study inputs for the pharmaceutical manufacturing site evaluated in this study. The operation city for the manufacturing plant corresponds to Mayagüez,

Table 2 Case study inputs related to pharmaceutical manufacturing site (yearly)

Inputs	Value	Source
Yearly revenue billing	\$1,272,260,000	Public Audited Financial Statements, Multinational Company—Puerto Rico Branch, Puerto Rico State Department Report 2019
Total Inventory Value (Finished Goods)	\$869,842	Public Audited Financial Statements, Multinational Company—Puerto Rico Branch, Puerto Rico State Department Report 2019
Percentage of Contribution by municipality	8.58% (Mayagüez)	Municipal Revenue Collection Center (CRIM) of Puerto Rico, 2020
Minimum attractive rate of return (MARR)	30%	Estimated
Quality specialist salary (\$/ Hr)	\$40	Estimated
Inspector salary (\$/ Hr)	\$40	Estimated
Operator salary (\$/ Hr)	\$16	Estimated
Unit sample cost	\$100	Estimated

Puerto Rico. The site size is 1000 employees, roughly the standard size of the manufacturing companies of solid oral dosing drugs established in Puerto Rico [23]. The yearly revenue billing of this manufacturing site is over \$1 billion and corresponds to the sales of products in the USA, including Puerto Rico. The Puerto Rico branch of this company has a finished good inventory estimated at \$869,842, representing 37% of total company inventory. This inventory data and revenue came from a similar manufacturing site in the island and its name is being protected due to a confidentiality agreement.

The contribution to the government is defined by a percentage based on the municipality over the real property (PAT equipment cost). This contribution has a 75% tax exemption according to the 2062.02 section of the Puerto Rico incentive code. This tax exemption is explained in detail in Table 5.

The minimum attractive rate of return (MARR) was 30% for this case study, but lower MARR values can still be attractive to management in projects of high-volume production. The MARR corresponds to the minimum profit a company expects to make from an investment, considering the investment risks. Thus, a MARR of 30% corresponds to an acceptable investment. Higher values for the MARR are used by companies short of capital or at industries where volatile prices increase the risk of poor returns for projects, as in the petroleum industry [20]. The MARR allows the managers to compare and evaluate investment alternatives with the same risk level.

The labor cost input related to the production line, and process quality monitoring included the salaries of a quality specialist, an operator, and an inspector position. The cost per hour for each position defined in this case study is roughly the standard salary of the manufacturing companies established in Puerto Rico. The salary for a quality specialist and an inspector was estimated at \$40 per hour, while the operator salary corresponds to \$16 per hour.

The sampling process in a manufacturing company implies a unit sample cost, which in this case study is equal to \$100. This cost includes the material used cost, consumable cost, inspection holding times, and labor cost of the QC laboratory personnel.

Table 3 shows the cost associated with the stream sampler, its installation, and production line setup. The case study will consider an investment in one stream sampler, estimated around \$70,000, and one spectrometer capable of doing real-time analysis, which costs approximately \$150,000. The estimated installation and maintenance costs are 5% of the equipment cost and include transportation and equipment adaptation to the line by the supplier. The maintenance cost includes the labor cost of the maintenance personnel, spare parts, and holding times. The monitoring process using the stream sampler is in-line, which implies changes in the manufacturing line. The changes considered in this case study corresponds to changes in the quality management system (QMS), given the sampler is not an invasive equipment. This cost was included in the heading other capital costs (refers to Table 7).

The implementation of the stream sampler and NIR spectrometer will require equipment utilization and data management training. The estimated supplier training cost is \$150 per hour for data management training. The training cost will be recurrent as an operational cost when the PAT implementation is completed and will be realized by the company personnel that the supplier trained.

The real-time monitoring of drug concentration in blends also requires developing a calibration model, which implies the preparation of blends at several concentrations, typically five concentrations. The case study assumed a formula for a direct compression process for 10% w/w of an over the counter (OTC) drug. The material cost employed for building all chemometrics models corresponds to 10 kg of active pharmaceutical ingredient (API) and 75 kg of excipient [24]. The API cost is equal to \$148 per kilogram, given it corresponds

Table 3 Case study inputs related to stream sampler implementation

Inputs	Value	Source*
Stream sampler cost	\$70,000	Estimated
Spectroscopy equipment cost	\$150,000	Estimated
PAT equipment installation cost	5% of equipment cost	Estimated
PAT equipment maintenance costs	5% of equipment cost	Estimated
Supplier training cost (\$/ Hr)	\$150	Estimated
Pharmaceutical Validation Specialist (\$/ Hr)	\$50	Estimated
Chemometrician salary (\$/ Hr)	\$58	Estimated
Material cost (employed for building chemometrics models)	\$2755	Estimated
License MVDA	\$8000	Estimated
Laptop	\$2000	Estimated

*These estimates come from experience in similar projects

to a popular OTC of common use. This cost could vary according to the API specialty reaching a sale price of \$2520 per kilogram [25] The excipient cost corresponds to \$17 per kilogram, for a total material cost employed for building chemometrics models of \$2755. Preparation of the calibration model requires one chemometrician. The chemometrician standard salary of the manufacturing companies in Puerto Rico is equal to \$58 per hour.

Multivariate data analysis (MVDA) tools are often installed when PAT equipment is installed to aid data collection and data analysis. These MVDA tools included equipment (Laptop) estimated at \$2000 and software (Licenses MVDA) with a cost of \$8000.

The work-in-progress (WIP) inspection allows monitoring the product through its processing [26]. The WIP is a term that specifies the partially finished products awaiting completion. The WIP inspection consists of inserting a sampling thief, removing powder, and placing it in vials for sending them to QC laboratory. Procedures for storing, cleaning, and training of personnel in the proper use of the sample thief are required. However, this inspection implies holding times by interrupting the manufacturing process when the sampling thief is used. The implementation of the stream sampler implies a 100% cost reduction of the WIP inspection cost. The stream sampler allows the collection of samples without interrupting the flow of the WIP. PAT equipment allows identifying the critical quality and performance attributes of WIP without sending the samples to the QC laboratory.

PAT implementation generates many benefits. PAT reduces the labor of the QC laboratory personnel since measurements are made during production [1, 14]. This reduction was estimated at 90% of the labor cost of QC laboratory. The improvement in production yield is another benefit, resulting from the minimizing product losses due to nonconformance. A reduction of 90% was estimated based on nonconforming batch reduction as the prevention of rejected products helps the production yield. This improvement is achieved through the process understanding that is gained in PAT, and ensuing control strategies to allow process adjustments to assure

product quality. Besides, savings of 50% on inventory carrying cost may result from the decrease of inventory hold-ups and reduction in batch release time related to QC delays [4, 16, 27]. Table 4 describes the expected stream sampler benefits defined as savings, corresponding to a percentage reduction applied to the operational cost.

Tax Incentives

The template takes into consideration tax incentives for investments. For this case study, the current tax incentives laws of Puerto Rico, which have offered tax incentives for more than 50 years, were used [23]. China, Singapore, India, Ireland, and other sites also offer attractive tax incentives for pharmaceutical manufacturing. The tax benefits can be substantial and an important incentive for investment in PAT and advanced manufacturing in any country. The template could be applied using the tax incentives laws of other manufacturing sites, given the template structure. The template may also be used without considering tax benefits.

Scenarios Considering Tax Incentives

The template structure may be used to evaluate different scenarios according to the tax incentives that the pharmaceutical company could apply. This study considers incentives established by the Government of Puerto Rico to promote activities that generate sustainable economic development on the island. The list of the pharmaceutical industry’s incentives resulted from the literature review, feedback from tax advisors, and interviews with leaders of the Department of Economic Development and Commerce (DEDC) of Puerto Rico. Currently (as of 2020), tax incentives are governed by the Puerto Rico Incentive Code, Act 60 established in 2019 [28]. The analysis of different scenarios is essential for pharmaceutical companies because it allows evaluating the best and efficient way to use the tax credit incentives. Besides, the tax incentives help to reach the project’s purpose of saving money, making it more attractive for managers. This case study includes three different tax credit

Table 4 Estimated benefits of PAT with stream sampler

Concept	Headings	% Cost Reduction Expected (savings)*
Overhead cost: quality cost	Nonconforming product cost	90%
	The labor costs of quality control (QC)	90%
	Work-in-progress (WIP) inspection cost	100%
Direct materials cost: Inventory carrying cost	Capital cost	50%
	Service cost	50%
	Storage cost	50%
	Risk cost	50%

*These estimates come from experience in similar projects

scenarios. Table 5 provides a summary of the tax benefits taken into consideration in each scenario:

Scenario I: Depreciation and Tax Benefits

The depreciation method used corresponds to the Modified Accelerated Cost Recovery System (MACRS) because it allows for more significant accelerated depreciation over a given time. Alternatively, the business case template allows using the straight-Line depreciation method according to the financial guidelines of the company. For the stream sampler, the useful life used to calculate the depreciation corresponds to 5 years. This useful life is established in asset types classification for MACRS in Publication 946 by the Department of Treasure of the United States [29].

Scenario II: Depreciation, Tax Benefits, and R&D Credit

This scenario corresponds to an extension of Scenario I but with differences in the tax incentives used. Scenario II considers the benefits for the pharmaceutical companies associated with research and development activities. The tax credit related to this benefit affects the depreciation base, reducing it by 50%. The depreciation base corresponds to the equipment cost, which in this case study is equal to \$220,000. Therefore, the base amount for depreciation calculations will be \$110,000.

Scenario III: Tax Benefits and Super-deduction Without R&D Credit

The third scenario considers the tax incentive of the super-deduction currently (as of year 2020) available in Puerto Rico. This tax incentives corresponds to the 100% Exemption for Investment in Buildings, Structures, Machinery and Equipment. The super-deduction base corresponds in this case study to the total equipment cost, which is equal to \$220,000. The tax incentive of super-deduction does not consider depreciation cost. The super-deduction and the depreciation are mutually exclusive.

Assumptions and Constraints

The following assumptions were defined for the case study according to the results obtained in meetings with pharmaceutical experts and the Puerto Rico Incentive Code [28]. The assumptions and constraints are shown in Table 6.

Results and Discussion

All the scenarios considered a base structure related to the capital investment, operational cost, and benefits associated with the PAT implementation. The study period, defined to evaluate the cost-effectiveness of the project, corresponds to 7 years, based on current business practice documented in the literature for similar applications [15, 16]. According to previous studies, the PAT implementation could reach a break-even point after as little as 6 years [16]. The useful life of the stream sampler should be longer than the 7 years of the study period. The depreciable life is defined by the depreciation method; MACRS establishes a 5-year depreciation period for this kind of equipment. The following results correspond to the outputs of the business case template:

Capital Investment Cost

According to the inputs used in the source data section, the total capital required for implementing the stream sampler corresponds to \$330,827. Table 7 provides a list of the cost items. The PAT equipment cost group corresponds to the cost associated directly with the equipment and the activities required for its operation. The qualification, validation, approval cost corresponds to the development of protocols and their execution to determine whether the equipment meets the specifications of its intended purposes and requirements related to product quality. PAT equipment must be qualified and calibrated before being utilized. This qualification and calibration cost corresponds to the salary and expenses associated with one Pharmaceutical Validation Specialist who performs the instrument qualification in 40 h

Table 5 Selected tax benefits used by scenario in the business case template

Puerto Rico's Incentives Code (Act 60–2019) Section	Description	Scenarios		
		I	II	III
2062.01	4% income tax rate	✓	✓	✓
2062.02	75% property tax exemption	✓	✓	✓
2062.03	50% municipal patents and other municipal taxes	✓	✓	✓
2062.06	100% exemption for investment in buildings, structures, machinery and equipment (super deduction)			✓
3030.01	50% tax credit for science and technology (R&D credit)		✓	

Table 6 Assumptions and constraints list

	Template operation	Puerto Rico’s Incentives Code (Act 60–2019)
Assumptions	<ul style="list-style-type: none"> • A single capital investment is made at the beginning of the analysis (in year zero (0)) • Tax benefits are applied at the first operation year. They are not distributed in different periods • Operational costs are computed as an annuity (a constant annual amount) equal to the first year of operation. These are related to the operation of PAT after the implementation • Benefits are computed as an annuity (a constant annual amount) equal to the second year of operation • Tax benefits for dividends, royalties, and construction were not contemplated in the template 	<ul style="list-style-type: none"> • Super deduction scenario cannot include the depreciation, both are mutually exclusive • Computations of the super deduction and the R&D credit are not carried out with the same amount. (Sect. 2062.06 (d)—Sect. 3030.01 (a-7)) • Total operational cost cannot exceed the total revenue per year • R&D Credit can be used in one year or more periods. The R&D Credit in the cash flows is applied at the first operation year. (Sect. 3030.01 (a-4))
Constraints	<ul style="list-style-type: none"> • Costs/benefits model analyzes the PAT implementation according to the type of information that is entered into the template (single product, or a single manufacturing line) • Drug sales volume and drug production volume are not considered as an input in the economic analysis 	

per week, during twelve workweeks. Training in equipment utilization and data management is required to use the equipment and the data obtained correctly. The PAT equipment training cost was estimated at \$3756, which corresponds to supplier cost and the man-hours of two operators, considering that the supplier would provide the initial training for the sampler. The PAT Equipment Data Management training cost was estimated at \$2656. This corresponds to a supplier cost of \$150 per hour, 8 h per day, during two workdays, offered for two employees (operator).

The other costs included in the capital investment correspond to the additional requirements and changes in the production line. The stream sampler in this case study requires

a calibration model to calculate the drug concentration with the near-infrared spectra obtained. The PAT implementation requires the development of chemometric models. This development requires the preparation of blends at several concentrations, spectral acquisition, and calculation of the calibration model. The time required for these activities was estimated at 24, 8, and 16 h per week, respectively, for twelve workweeks. Major pharmaceutical companies now have personnel focused on PAT and with expertise in chemometrics. Three employees are required to complete the three activities. The material employed for building chemometrics models in the first activity has a cost equal to \$2755. Spectral data analysis with chemometrics requires MVDA

Table 7 Capital investment cost results

Type	Concept	Total cost	
Capital investment cost	PAT equipment	PAT equipment and support equipment costs: <ul style="list-style-type: none"> • Stream sampler (\$70,000) • Spectroscopy equipment (\$150,000) 	\$220,000
		PAT equipment installation cost (for stream sampler)	\$3500
		PAT equipment qualification, validation, approval Cost	\$24,000
		PAT equipment training cost	\$3756
		PAT equipment data management training cost	\$2656
		PAT equipment total cost	\$253,912
		Others	Chemometric development cost
	Multivariate data analysis (MVDA) tools (equipment, software, and validation)		\$16,960
	Change management in the QMS (quality management system) (labor)		\$880
		Process changes request costs to FDA and others (Labor)	\$640
	Others total cost	\$76,915	
Total capital investment cost		\$330,827	

software [16]. The MVDA capability requires equipment (Laptop), software (Licenses MVDA), and the labor cost of one chemometrician 40 h per week, for three workweeks.

PAT technology implementation requires activities related to the company's quality system [1]. The quality systems that require changes include the Quality Management System (QMC) and Change Control System. The cost associated with these activities was calculated according to two specific activities: prepare and review documents and training of two employees (quality specialists). These activities require 10 and 6 h respectively, in 1 week.

Operational Cost Associated with PAT

After its implementation, the costs associated with PAT correspond to the maintenance cost, PAT equipment training cost, and PAT equipment data management training cost. These costs are in addition to the current costs required for the tablet production line operation and they are recurrent costs (overhead cost). The implementation of new equipment at the production line implies yearly maintenance after its first operation year. The literature review provided an estimate of cost for maintenance. The maintenance cost was estimated at \$3500, which corresponds to the 5% equipment cost (stream sampler). The stream sampler operation can be done by the pharmaceutical process operator, therefore there is no additional cost incurred. The cost of training at PAT equipment and PAT Equipment Data Management, was estimated at \$256 per year for each. These costs correspond to the man-hours of two employees (operators) per training, 8 h per day, during one workday. These employees received the training from the supplier. The total operational cost calculated with the inputs used at the source data section corresponds to \$4012 per year.

This estimate does not include losses related to testing inaccuracy or “false negatives” that may occur in the early stages of the PAT implementation. However, this application

is focused on real-time determination of drug concentration of a pharmaceutical blend, a PAT application that has been widely studied where the occurrence of false negatives is less likely [30–32]. False negatives are often related to sampling errors which would be reduced with the stream sampler [33, 34]. The false negatives may also be related to lack of understanding of real-time results. Companies that move from off-line methods to real-time methods will see process variation that was never observed since it was not measured. False negatives could be an excellent subject of future studies, but is outside the scope of this study.

Benefits Associated to PAT Equipment Operation

The total savings per year using the stream sampler was estimated as \$381,753 (refers to Table 8). The 57% of total benefits, equal to \$217,461, correspond to the effect of the reduction of inventory levels. The decrease of inventory hold-ups and the reduction in release time related to QC delays could help reduce inventory levels [4, 16, 27]. An efficient manufacturing process could help to prevent significant inventory hold-ups and avoid stock-out risks. The evaluation considers only a single product at a single manufacturing site. The reduction of inventory costs would be much greater if PAT is applied throughout to all processes done at the company.

The savings of in-process control (IPC) laboratory costs would be 100% of the sampling and testing cost (WIP inspection cost). The stream sampler allows real-time process monitoring without interrupting the flow of the WIP at the batch production line. The cost reduction consisted of the avoidance of IPC laboratory activities with the in-line tests [14, 16, 27, 35]. It would no longer be necessary to pull samples from a blender with a sample thief and bring them to the laboratory for analysis.

The WIP inspection cost was estimated for a worst-case scenario. This inspection corresponds to two inspection

Table 8 Savings associated to PAT equipment operation

Benefit categories	Headings	Cost reduction (savings)		
		Percentage of reduction (%)	Value	
1. Low inventory levels	Direct materials cost: inventory carrying cost	Capital cost	50%	\$73,937
		Service cost	50%	\$60,889
		Storage cost	50%	\$52,191
		Risk cost	50%	\$30,444
	Total low inventory levels			\$217,461
2. IPC laboratory costs for PAT products	Work-in-progress (WIP) inspection cost	100%	\$107,160	
3. Production yields for each batch will increase	Nonconforming product cost	90%	\$54,540	
4. Quality control (QC) investigations	The labor costs of quality control (QC)	90%	\$2592	
Total savings			\$381,753	

types using a sample thief: characterization and validation. Each type of inspection requires two employees (inspector) per shift for sample collection. Three shifts were estimated for the production operation in this case study. A total of 4 h per shift per week were required for each inspection type, for a total of 384 man-hours per shift per year per inspection type. The analysis of three batches in characterization inspection was estimated. Equally, the analysis of three batches was estimated for validation inspection. Forty samples per batch were estimated for each inspection type. The sample cost corresponds to \$100. This cost is totally reduced with the stream sampler use, representing savings equal to \$107,160 per year, 28% of the total savings. The benefits per year when implementing the stream sampler are shown in Table 8 and represented graphically in Fig. 2. Figure 2 shows that the main benefits are related to lower inventory levels, followed by the IPC laboratory costs. The line in Fig. 2 emphasizes the cumulative percentage of each benefit of the total savings by PAT operation.

The implementation of PAT using the stream sampler allows for the prevention of non-conforming products accounting for an increase in production yield. The estimated benefit accounted for by the increase in production yield was \$54,540 per year. The prevention of product rejection can be attributed to PAT implementation and increased process understanding [1, 14]. The continuous and frequent blend evaluation through the stream sampler/PAT system facilitates taking real-time corrective actions, contributing to prevention and risk management throughout the product manufacturing lifecycle [36, 37].

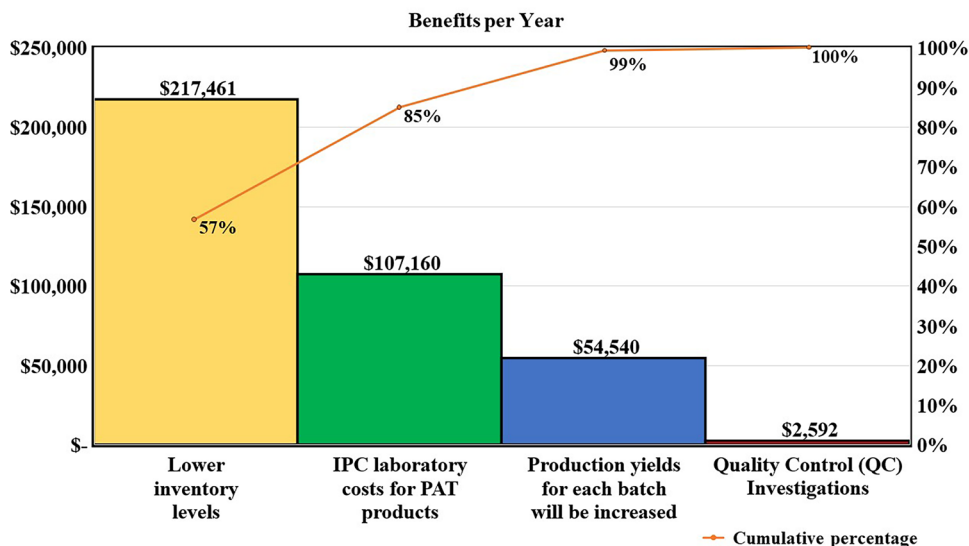
PAT also reduces the cost associated with quality cost labor for investigations of process deviations. Any out-of-specification result obtained from a sample thief, a

genuine blend homogeneity failure, sampling, or testing error requires an investigation. The implementation of the stream sampler and PAT system reduces the probability of having a sampling and testing error, resulting in a reduction of the frequency of investigation events [16, 38]. The estimated benefit of reduced investigations was a 90% reduction of investigation events per year, accounting for a saving of \$2,592 in this case study.

The real-time monitoring of the blending process through the stream sampler in combination with NIR or Raman spectroscopy also adds a significant advantage in terms of the immediate detection of a variation in the drug concentration in the blends. Thousands of measurements would be available for a continuous process, providing information that could be used for process improvement [32]. In contrast, the sample thief, and the off-line determination of drug concentration in blends by a QC laboratory occurs after a batch blending process is completed.

The stream sampler facilitates the statistical evaluation of the blend uniformity data [39]. The sampler with the spectroscopic technique and chemometrics permits multiple determinations of drug concentration in the flowing blends where all parts of the blend now have the same opportunity of being selected and the material is not affected by the sampling process. Compared to the thief sampling, which uses pre-defined sample locations and affects the material, the stream sampler increases the aleatory nature of the samples, making it possible to perform variographic analysis and characterize the process variance and materials heterogeneity. Variographic analysis provides an estimate of the sampling and analytical errors and makes it possible to differentiate between them and the variation related to the heterogeneity of the powder blends [19, 39]. This can be very beneficial in the development of a process. The benefits

Fig. 2 Pareto diagram—savings per year by benefit categories



could also include the faster transfer of a new product from research and development to manufacturing. No company wants to delay the approval of a new product due to a sampling problem typically observed by using a sample thief. R&D groups wish to have all the technology necessary to bring products to market faster, and manufacturing units want to implement them successfully in the shortest possible time.

Benefits Associated to Tax Incentives

The results of tax benefits are divided by scenario according to the case study assumptions. Figure 3 shows the benefits per year associated to tax incentives by scenario. Even though the financial analysis results of the three scenarios evaluated are favorable from NPV, IRR, and ROI perspectives, the super deduction scenario showed maximization potential for benefits. An NPV value that is significantly positive, in this case above the level of capital investment, provides the basis of favorability by which a company should consider this technology. In addition, deduction and tax scenarios, which are location-specific, add to the financial favorability. The first scenario considers the most common situation in which the depreciation method is applied with tax incentives and is favorable with a total tax benefit of \$14,157. The most significant tax benefits came from the third scenario with the super deduction, \$234,157, followed by the second scenario related to Puerto Rico’s R&D Tax Credit with a total of \$96,864. The tax benefits are location specific as they consider government tax and research incentive programs as the PR R&D credit code in this case. These tax benefits must be requested, they are not automatic, and the companies must also meet requirements to apply

Table 9 Economic evaluation methods by scenario

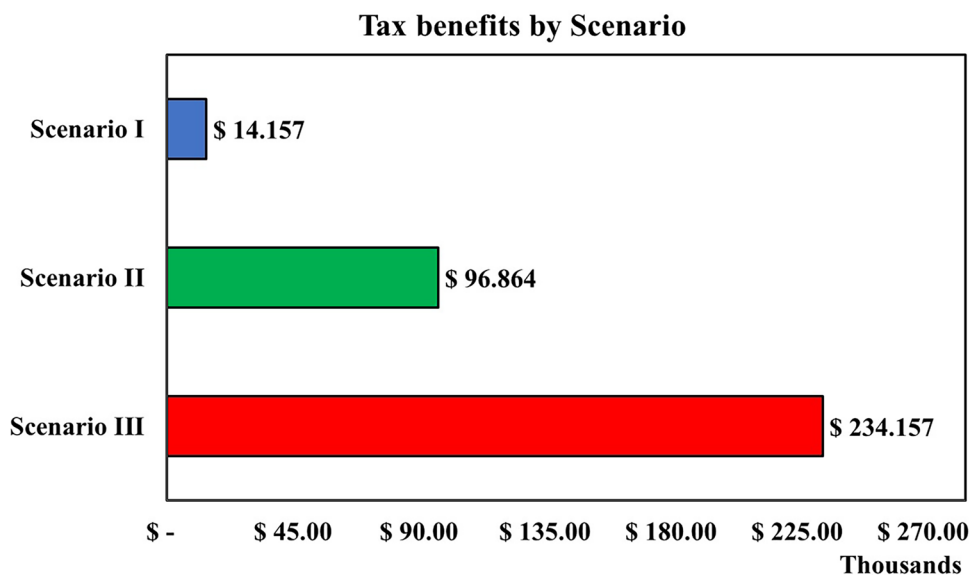
	Scenario I: Depreciation + tax benefits	Scenario II: Depreciation + tax benefits + tax credit R&D	Scenario III: Tax benefits + special deduction
NPV	\$420,957	\$526,753	\$578,896
IRR	65%	78%	89%
ROI	82%	116%	133%
Payback period (years)	1.9	1.5	1.3

for them. These requirements are contained at the Incentive Code, Act 60 established in 2019 [28].

Results by Scenario

Table 9 provides the results for the economic evaluation methods by scenario. All the scenarios are favorable for implementing the stream sampler/PAT system for what we understand is a typical pharmaceutical manufacturing operation. Although it has the lowest economical metrics, the first scenario has a positive impact with a NPV positive of \$420,957. A positive NPV implies that this project will generate benefits: the higher the NPV value, the greater the project’s profitability. An IRR of 65%, a ROI of 82%, and a payback period of less than 2 years for the first scenario make it financially attractive. For the second scenario, the metrics are more favorable than the first scenario, with a NPV of \$526,753, an IRR of 78%, a ROI above 100%, and a payback period of 1.5 years. The third scenario is the most attractive of the three possible options with an NPV of \$578,896, an IRR equal to 89%, an ROI of 133%, and a payback period of 1.3 years.

Fig. 3 Benefits according to scenario I—Depreciation and tax benefits; II—Depreciation, tax benefits, and R&D credit; III—Tax benefits and super-deduction without R&D credit



The IRR must be compared with the MARR to evaluate if the stream sampler implementation is profitable [20]. The implementation of the stream sampler is a profitable project because the IRR is higher than the chosen MARR of the case study (30%). IRR allows measuring the growth rate that is expected from the project. The higher the IRR, the more profitable the project would be, and this case study obtained an IRR that is over three times the MARR [15].

The ROI compares the initial investment versus the benefits obtained by the project. A positive and high ROI reflects that the stream sampler implementation is profitable, in this case, based on the first-year return. Hence, the stream sampler becomes more desirable for a company because its returns are higher than the invested resources.

A relatively short payback period makes the project more attractive because the time needed to recover the capital investment is brief. In any of the studied scenarios, the investment recovery occurs in less than 2 years.

Conclusions

The costs and benefits associated with the stream sampler are also applicable to many other projects involving PAT, continuous manufacturing, and emerging technologies. The stream sampler has been used as example of a PAT investment to further investigate the costs and benefits associated with its implementation in manufacturing. The authors are certain that this study will catalyze much needed progress in evaluating the costs and benefits of introducing new technologies in pharmaceutical manufacturing.

The reduction in inventory levels and decrease of IPC laboratory activities are positive effects of the implementation of the stream sampler and monitoring with NIR or Raman spectroscopy. Besides, the stream sampler implementation could be a very profitable investment project, with a rate of return between 65 and 89% and a payback period between 1.3 and 2 years approximately. The return on investment may represent a difference between 82 and 133% versus the capital investment for this project which is economically attractive.

The tax benefits contribute further to this case study, especially the super deduction, followed by the R&D tax credit. The case study evidenced the ease of using this business case model, including analyzing and reviewing the results. This business case template allows evaluation in real-time of any change generated during the project's analysis and its effect on the project's economic evaluation methods. Furthermore, the tax incentives effects can be evaluated by entering the input data without an additional step in the template.

As future work, we need to consider evaluating the sampler/PAT system implementation in manufacturing lines associated with other types of products. Likewise, we should consider

the evaluation of PAT implementation in medical device production and the food industry. The economic impact that PAT implementation shall consider is the exploration these kinds of industries and the benefits associated with sustainability, testing simplification, and quality system requirements.

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Author Contribution MAF-L: Coordinated this research and carried out all experiments, data analysis, and drafted the manuscript. BBA-H: Drafted the manuscript, prepared figures, and data analysis. CC: Aided in manuscript revisions and establishing theoretical data needed. EJS: Aided in manuscript revisions and establishing theoretical data needed. MIMP: Coordination of the research, helped establish methods for data analysis, and aided in the conception of the study. RJR: Conceived this study and participated in coordinating the research.

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Data availability All data is available as supplementary material of this article.

Declarations

Consent for Publication All the authors mentioned in the manuscript have agreed for authorship, read, and approved the manuscript and given consent for submission and subsequent publication of the manuscript.

Conflict of Interest The authors declare no competing interests.

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