Roadmap to help an organization inserted in the Pharmaceutical Industry to start its transition towards Industry 4.0

Abstract

The world is currently experiencing a fourth industrial revolution, called Industry 4.0, characterised by the use of highly disruptive technologies that promise to revolutionise the way an organisation works. Many industrial sectors have already started their transition to this new paradigm, but, on the contrary, the pharmaceutical industry has felt difficulty in welcoming this new industrial model, due to some existing risks and barriers. Therefore, this study aims to study in detail the Industry 4.0 concept and its application in the Pharmaceutical Industry and to understand how this transformation can be carried out in an effective way, outlining and structuring a strategic plan that allows organisations in this domain to mitigate/supplant all risks and barriers, so that they can exploit all the benefits associated with this new approach to thinking about industry.

The case study of this work will be the organisation XPTO, Indústria Farmacêutica,SA, a pharmaceutical company based in Portugal. Through the completion of a diagnosis aimed at obtaining the main constraints experienced in the production process, some proposals and initiatives will then be formulated that are based on some technologies associated with I4.0, allowing the company to deal with these opportunities for improvement, but also to start its path towards the industrial model envisioned with Industry 4.0 and thus enhance the growth of the organisation in a sustained manner.

It is intended that this work can be used as a guide and thus provide a significant contribution to companies in the pharmaceutical industry, but also in other industrial sectors, which, through the example of XPTO, can also start their digital transformation towards Industry 4.0.

***Keywords**: Industry 4.0, Pharma4.0, Pharmaceutical Industry, Roadmap*

---

1. Background

The Pharmaceutical Industry was and is recognised as a successful industry. However, nowadays, companies within this industry face many challenges in dealing with the constraints imposed by regulatory authorities, the extended time to market a product, the constant changes in customer demands, the difficult and competitive global competition or the high costs inherent in the development and manufacturing of a pharmaceutical product (Barenji, et al. 2019). Thus, even large companies, with great financial capacity, now feel the pressure to look for ways to decrease costs to survive an increasingly competitive and unpredictable economic climate (Mittal 2017).

At the same time, major industries, where pharmaceuticals are no exception, are currently undergoing a profound digital transformation (PWC 2016), with a view to innovation and development. This phenomenon has been given the name Industry 4.0, as it is equated to a new Industrial revolution, the 4ª Industrial Revolution. Briefly, the concept Industry 4.0 represents the adoption by Industry of techniques and processes based on Artificial Intelligence, provision of services over the internet, establishment of communication between equipment and computational analysis of massive amounts of data, with the aim of achieving competitive advantages in domestic and global markets, making processes more efficient and increasing connectivity and productivity.

Thus, it becomes necessary to define a plan that can help companies in this sector to start adopting *Pharma 4.0* (name given to the Industry 4.0 approach associated to the Pharmaceutical Industry), so that they can enjoy all the associated potential benefits and, at the same time, mitigate all the risks and overcome all the existing barriers. Although some large multinationals in the sector have already put their plans into practice, benefiting from their great capacity to capture

knowledge, but also from their financial availability, it is also important that smaller companies and as a focus on specific activities of the sector (Ex: Production) start to do so, in order to keep up with the development and thus remain competitive in an increasingly competitive market.

This transition is not something that can be achieved from one moment to the next, due to the complexity and also the breadth of the issue. Therefore, the main objective of this study was to draw up a simple, practical and easy-to-implement plan that would allow smaller organisations to implement it in successive projects and initiatives until the maximum potential of the I4.0 approach and associated technologies is exploited, which bring with them countless potentialities for the entire supply chain, particularly for the production process.

The case study of this work focuses on a medium-sized company, known as XPTO for confidentiality reasons. This company, based in Coimbra, in addition to fitting in with the characteristics presented above, is going through a moment of development and investment in innovation.

Therefore, through a diagnosis and understanding of XPTO's most critical processes, mainly and with a greater focus on medicine production processes, the main constraints and associated improvement opportunities were identified and mapped. Then, through the various technological options associated with Industry 4.0, solutions were proposed, identifying, describing and prioritizing different initiatives that can be implemented by the organization.

This document is intended to serve as a summary of the dissertation, both documents being, naturally, integrated with the Thesis Project.

2. Case Study - Characterisation

The XPTO Group was born in 2001, in the city of Coimbra, through the purchase of an industrial unit from a German multinational by 4 young entrepreneurs. Starting its activity with only 58 employees, it began its activity with its focus mainly on the national market. Twenty years later, the company occupies a prominent place in the sector, with diversified activities in the area of medicine and employing more than 700 employees. The most representative company of the group, XPTO, Indústria Farmacêutica, SA, develops and bases its business of development and production of medicines, mainly in large international markets, such as the main European countries and the United States of America, with exports representing around 85% of its turnover.

The activity of XPTO focuses on three distinct areas:

- Production of medicines under its own brand and for third parties;
- Research, development and registration of medicines on a global scale;
- Marketing of generic medicines.

The production process at XPTO follows the traditional approach present in most organisations of this sector, i.e., production by batches (*Batch mode*) and by order (*Make to Order*). The main objective underlying this manufacturing mode is, according to the FDA, to produce a specific quantity (batch) of products with common characteristics (uniformity in quality attributes) in a manufacturing cycle. In the pharmaceutical production by batches, the various components of a medicine are assembled through a process of several stages, normally composed of a sequence of unit operations (Figure 1).

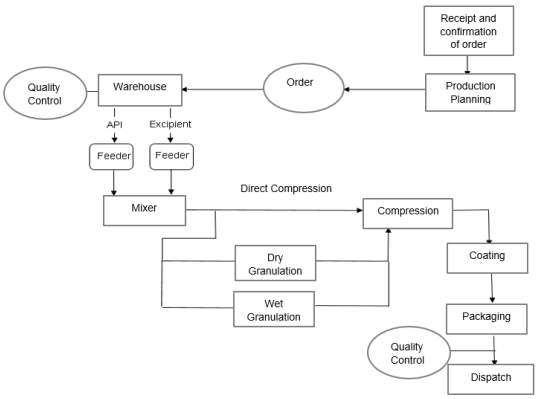

Figure 1-Production Process Diagram of a medicine XPTO Company

3. Identification of limitations

It was possible, as a result of the visualisation of all stages of the productive process, of the discussion with elements of the organisation and also of the collection and analysis of performance indicators directly linked to the productive process, to identify some characteristic constraints of the XPTO productive process. The identified constraints are presented in the following points.

- The production time associated with this type of production is quite high, often affected by *downtime*. As it is a process based on several steps, even with optimised planning, it is frequent to experience downtime in the production process, often caused or aggravated by long cleaning cycles and *set-up* changes between different products;
- To increase production, using batch production, it is necessary to increase production capacity, either by purchasing new equipment or by hiring new employees. This naturally implies a financial effort and, above all, additional space, something that the company does not have at the moment;
- The collection of KPI's related to manufacturing for measuring the area's performance are done manually and their analysis is not done in real time;
- The present production systems are already automatic but not autonomous, not being sufficiently agile or flexible when disturbances occur (manufacturing and packaging)
- Considerable *downtime* associated with Wet Granulation.
- Numerous micro breakdowns in the packaging process.
- Use of only corrective and preventive maintenance strategies, rather than predictive maintenance (manufacturing and packaging);
- Too much time spent on the execution of documents inherent to the production process.
- Execution of documents carried out mainly by hand and with a high associated probability of error.
- Consumption of a lot of paper to carry out these administrative tasks.

The following table summarises the identified constraints, and also describes the direct consequences and consequences on the process of each of the identified constraints.

Table 1-Improvement Opportunities

	Improvement Opportunity	Direct Consequence	Process Consequence
1	KPI's related to manufacturing are collected manually and not in real time	Difficult to precisely know the occupancy rate of each work centre at each moment	Difficulty in defining dates for the delivery of orders on the planning side
		Difficulty in visualising in real-time what is happening at each stage	Greater difficulty in controlling the process
2	Present production systems are automatic but not autonomous, not being agile or flexible enough when disturbances occur (manufacturing and packaging)	Considerable downtime periods, since when human intervention is still needed to solve the existing problems, when failure occurs	Global OEE of the productive process (manufacturing + packaging) is below the expected and higher costs associated to the process
3	Considerable downtime periods associated with Wet Granulation	Higher number of breakdowns in the production process	
4	Countless micro breakdowns in the packaging process		
5	Use of corrective and preventive maintenance strategies instead of predictive (manufacturing and packaging)	Higher number of maintenance interventions (necessary or not)	
6	Much time spent on the execution of documents inherent to the production process	High consumption of resources and time in activities that do not generate value for the company	Lead-Times of each stage of the production process greatly influenced by the execution of these activities
7	Administrative Activities mostly done by hand	Increased time for task execution and higher probability of errors occurring	
8	Consumption of a lot of paper to perform these tasks	Increased costs borne by the organization	Higher costs attributed to the product

4. XPTO Organisational Priorities Definition of improvement proposals

Analysing the table and looking at each of the constraints identified, it is possible to define several points of priorities to be resolved by the organisation, these being:

- Digitalisation of documents associated with the production process;
- Automatic collection of information;
- Optimisation of planning with a view to reducing *downtimes;*
- Better training of equipment operators and implementation of predictive maintenance plans to minimise micro breakdowns;

All these priorities listed above translate into three major vectors:

- **Greater production efficiency;**
- **Cost minimisation**
- **Higher Speed and Agility in Time-to-Market.**

These three goals identified as priorities for the XPTO company, with the new industrial paradigm 4.0, become real objectives that are possible to achieve. However, this transition, as previously stated, is not something that can be achieved from one moment to the next, requiring several implementation projects, since there is a high level of complexity associated, not to mention the investment required.

This way, it was decided to address in this work only the improvement opportunities considered more critical, in order not to run the risk of losing the detail required for a work of this magnitude and importance.

In this sense and once the opportunities for improvement identified in table 1 with the numbers 6, 7 and 8 are directly interconnected (high consumption of resources and time in the execution of tasks that don't add value to the organisation) and aim to improve two of the three priorities identified for the organisation (greater agility and speed in the *time-to-market* and costs minimisation), one of the proposals for improvement to be formulated focus in the implementation of a MES System, software with several functionalities, among them the automatic collection of data and documental management.

A second improvement proposal to be formulated will focus on the numerous micro breakdowns experienced in the packaging stage (Point 5 of Table 1). Being the XPTO group inserted in a sector where the required *time-to-market* is quite aggressive, it is crucial that the organisation has a productive process as efficient as possible, where the causes of potential failures are identified before they have the opportunity to occur and, in this way, have the ability to reduce the times of possible *downtimes* and associated *breakdowns.*

The implementation of a predictive maintenance programme will meet this objective, allowing the XPTO organisation to monitor in real time a system or equipment, gaining the ability to identify and solve possible failures that are about to happen before they actually happen, potentially reducing downtime periods by 50% and consequently increasing the levels of effective use of equipment and OEE (*availability x quality x performance*), indicators that are below the values defined by the organisation in the manufacturing and mainly packaging stages.

Another major gain is related to cost reduction and optimization of maintenance activities. The XPTO organization, with the implementation of a predictive maintenance program, will be able to potentially reduce the costs supported in maintenance activities, being able, according to (Dilda, et al. 2017) , to decrease in almost 25% the maintenance costs, optimizing the time spent in maintenance works, since these activities are only performed when it is really necessary.

5. Methodology

The following methodology was followed, described in the next two points.

1. Process and analysis of identification of limitations and improvement proposals

1.1. Characterisation of the current state of the company in relation to the new challenges presented by Industry 4.0.

1.2. Formulate two proposals for implementing solutions associated with I4.0;

1.3. Carry out a benefit/risk analysis of each one;

1.4. Outline an implementation strategy;

1.5. Assess the potential impacts in operational and financial terms that implementing the two proposals could bring to the XPTO organisation.

2. Cost Benefit Analysis

2.1. Calculate total investment required;

2.2. Prioritise one of the formulated proposals that would be implemented in a first phase according to the need felt by the organisation and investment required.

2.3. Payback calculation of the investment made for each of the proposals.

2.4. Time planning through a Gantt-Chart of the implementation of the two proposals.

The implementation of the methodology presented above allowed formulating two proposals for implementing solutions associated with Industry 4.0, presented in figures 2 and 3.

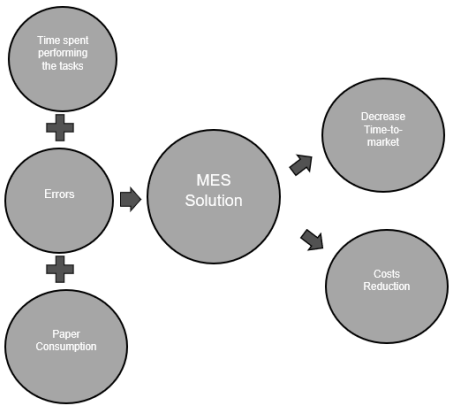

Figure 2- Identification of Improvement Proposal MES System

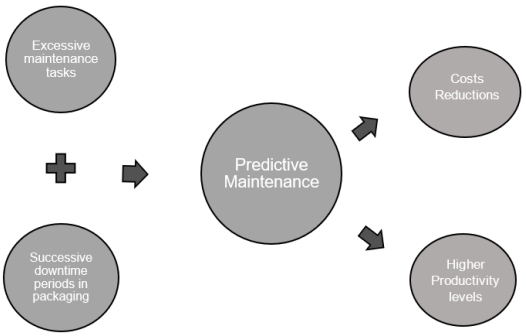

Figure 3- Identification of Improvement Proposal Predictive Maintenance System

On the left side there are limitations identified and that aim to be solved by the two improvement proposals. In the centre is the tool to be implemented and on the right side the benefits that XPTO can achieve with the implementation of each one of these tools.

6. Benefits of implementing the MES system

In order to be able to calculate the operational and financial impacts that an MES system could bring to the XPTO organisation, with a view to justifying its implementation, two scenarios were created to support the analysis. A first scenario denominated the **Inaction Scenario**, where it is assumed that nothing is done by the organization to solve the improvement opportunities associated to the production process documentation and a second scenario, denominated the **MES Scenario,** where it is assumed that the MES system is successfully implemented by the organization, benefiting from all the associated benefits and that are mirrored in the bibliographical revision of the dissertation.

Table 2 then allows a comparison of the two scenarios over a time span of 12 years.

Table 2- Direct Savings from MES Implementation

Scenarios	Cost EUR 2024	Cost until 2036* EUR	Total savings
Inaction Scenario	94 988 EUR	1 695 495 EUR	
MES Scenario	-	499 979 EUR	1 195 516 EUR

**Cumulative* costs *from 2024-2036 considering a 5% yearly escalation (Ex: salary increase)*

Comparing the two scenarios, with the implementation of MES, the company would save around **1 195 516 EUR** over 12 years. The direct savings obtained are due to decreases in the total time spent by employees in the preparation and review of manufacturing and packaging records and also to the decrease in the total number of printed pages, as the documentation will be electronic.

7. Benefits of implementing the Predictive Maintenance System

Following the same logic used previously, two scenarios were created: a first scenario where nothing was done by the organisation to address the improvement opportunities associated with the packaging stage and the non-use of Predictive Maintenance systems (**Inaction Scenario**) and a second scenario where the Predictive Maintenance system is implemented (**Predictive** Maintenance **Scenario**).

Table 3 allows a comparison of the two scenarios over a time span of 11 years:

Table 3-Direct Savings from the Implementation of Predictive Maintenance System

	Baseline	Inaction	Predictive Maintenance
	2023 EUR	2034* EUR	2034* EUR
Revenues (Operating Margin - 15%)	2 474 423 EUR	36 911 288 EUR	45 460187 EUR
Costs	185 794 EUR	2 771 515 EUR	1 600 985 EUR
Total Earnings		**34 139 773 EUR**	**43 859 202 EUR**

**Revenues and Cumulative Costs 2023-2034 considering the assumptions detailed at the beginning of the Cost-Benefit Analysis section*

Comparing the two scenarios, with the implementation of the Predictive Maintenance System, the company would have cumulative gains of around **9 719 429 EUR** over 11 years.

8. Total investment, time needed to implement the two improvement proposals and *payback* period of the investment

Table 4 summarises the total investment, the implementation time for the two solutions analysed and the *payback* period.

For the proposed implementation of an MES system, considering a total investment of 690,000 EUR and an annual saving of 119 551 EUR, it is possible to state a *payback of* the investment made of approximately 6 years.

In the case of the predictive maintenance proposal, with the capacity gain in the packaging sector and the reduction of costs associated with maintenance activities and *downtime* periods, the organisation has the possibility to achieve annual gains of 971 942 EUR, achieving a return on the investment made in just 2 to 3 months.

Table 4- Investment and payback of the solutions under analysis

Solution	Investment	Time	*Payback* period
MES	690 000 EUR	2 years	5, 77 years
Predictive maintenance	200 000 EUR	1 year	0, 2 years

The time planned for the implementation of these two proposed solutions will be 3 years (sequential implementation of the solutions), with the predictive maintenance programme being the first project to be implemented, since it is the project with the lowest investment, shortest implementation time, shortest *payback* and highest return on investment.

9. Conclusions

The Pharmaceutical Industry is currently based on organisational and industrial management models that are still somewhat conservative, particularly when compared with other sectors such as the automotive or electronic components industry, among others. The fact that it is a highly regulated sector of activity, in which traceability and the risks of cross-contamination are critical, along with the characteristics of the products (e.g. short shelf life) and the fact that market demands are not uniform, slows down the adoption of continuous manufacturing processes as opposed to *batch mode* or manufacturing to stock as opposed to manufacturing to meet orders.

These characteristics represent a wealth of opportunities for innovative management approaches and process optimisation, in which the initiatives associated with Industry 4.0 fit.

The aim of this work was to characterise a medium-sized national pharmaceutical industry that could serve as a pilot project for the implementation of some of the initiatives (Pharma 4.0), as well as to illustrate its potential to benefit the competitiveness of such an organisation.

After a period of characterization and analysis of the target company, a set of opportunities for improvement were mapped, from which we highlight the high time spent by the organization in the execution of documents inherent to the production process, many of them done by hand and with high probability of associated error as well as the excessive consumption of existing paper and also the innumerable micro-cutting in the packaging process, which leads to an increase in production time and, consequently, in the *time-to-market*.

For these improvement opportunities solutions have been identified, such as the implementation of an MES system that aims to make all the documentation inherent

to the production process digital, thus reducing the paper consumption of the organisation and the time spent by the organisation's resources in the elaboration and revision of this documentation or the implementation of a predictive maintenance system that, through a real-time monitoring of a system or equipment, will gain the capacity to identify and solve possible failures that are about to happen before they really happen, potentially reducing the downtime periods associated to the packaging stage.

Once the solutions were defined, the operational and financial impacts of each solution were analysed to understand the feasibility of implementation and a plan for its implementation was outlined.

It was clear from this study that in addition to the intangible gains of modernisation and better control of processes by the organisation, direct gains (in the form of real savings) and capacity gains, resulting from the implementation of MES and a predictive maintenance programme, can contribute in a relevant way to an increase in the profitability and competitiveness of XPTO.

The next steps to be taken will be to identify solutions for the remaining limitations identified, and it is important that these are based on tools associated to the industrial model, so that the XPTO organisation continues its transition towards the total adoption of this new industrial paradigm.

10. References

Aksu, Buket, and Gizem Yegen. "Global Regulatory Perspectives on Quality by Design in Pharma Manufacturing." In *Pharmaceutical Quality by Design*, 19-41. Sarwar Beg, Md Saquib Hasnain, 2019.

Barenji, Reza Vatankhah, Yagmur Akdag, Barbaros Yet, and Levent Oner. "Cyber-physical-based PAT (CPbPAT) framework for Pharma 4.0." *International Journal of Pharmaceutics*, 2019, June ed.: 118445.

Dilda, Valerio, Malte Hippe, Lapo Mori, Olivier Noterdaeme, Christoph Schmitz, and Joris Van Niel. "Manufacturing: Analytics unleashes productivity and profitability." *McKinsey&Company.* 2017. https://www.mckinsey.com/business-functions/operations/our-insights/manufacturing-analytics-unleashes-productivity-and-profitability.

Mittal, Bhavishya. "Business Acuity." In *How to Develop Robust Solid Oral Dosage Forms from Conception to Post-Approval*, by Bhavishya Mittal, 155-163. Academic Press, 2017.

Otto, Sean. "The Case for Predictive Maintenance." *Pharma Manufacturing*, 2019.

PWC. "Industry 4.0: Building the digital enterprise." *PwC "Global Industry 4.0,"* 2016, September ed.

Reinhardt, Ingrid Carla, Dr Jorge C. Oliveira, and Dr Denis T. Ring. "Current Perspectives on the Development of Industry 4.0 in the Pharmaceutical Sector." *Journal of Industrial Information Integration*, 2020, February ed: 100131.