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THESIS ON THE SUBJECT

"Quality risks of outsourcing manufacturing activities in the pharmaceutical industry; a lean approach"

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(περιλαμβάνεται ως ξεχωριστή (δεύτερη) σελίδα στο σώμα της διπλωματικής εργασίας)

«Δηλώνω υπεύθυνα ότι η διπλωματική εργασία για τη λήψη του μεταπτυχιακού τίτλου σπουδών, του Πανεπιστημίου Πειραιώς, στη Διοίκηση Επιχειρήσεων για Στελέχη : E-MBA» με τίτλο
.....Quality risks of outsourcing manufacturing activities in the.....
.....pharmaceutical industry: a lean approach.....
έχει συγγραφεί από εμένα αποκλειστικά και στο σύνολό της. Δεν έχει υποβληθεί ούτε έχει εγκριθεί στο πλαίσιο κάποιου άλλου μεταπτυχιακού προγράμματος ή προπτυχιακού τίτλου σπουδών, στην Ελλάδα ή στο εξωτερικό, ούτε είναι εργασία ή τμήμα εργασίας ακαδημαϊκού ή επαγγελματικού χαρακτήρα.

Δηλώνω επίσης υπεύθυνα ότι οι πηγές στις οποίες ανέτρεξα για την εκπόνηση της συγκεκριμένης εργασίας, αναφέρονται στο σύνολό τους, κάνοντας πλήρη αναφορά στους συγγραφείς, τον εκδοτικό οίκο ή το περιοδικό, συμπεριλαμβανομένων και των πηγών που ενδεχομένως χρησιμοποιήθηκαν από το διαδίκτυο. Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου».

Υπογραφή Μεταπτυχιακού Φοιτητή/τριας.....

Ονοματεπώνυμο.....Τρίχα Μαρία - Νικολέτα.....

Ημερομηνία.....04/02/2021.....

EXECUTIVE SUMMARY

The respective essay presents, analyzes, and assess the basic quality risks may arise when pharmaceutical industries decide to outsource their manufacturing activities. The whole subject is being examined from a lean perspective.

The provision of the relevant literature review concerning the topic, not only indicates its importance, but also proves the timeliness of the subject.

Lean methodology's tools such as Failure Modes & Effects Analysis (FMEA) and Failure Mode, Effects, and Criticality Analysis (FMECA), are being herein utilized, for the quantification of the criticality of the potential quality risks identified during outsourcing manufacturing activities, (from an Internal Plant – IP – to a Contract Manufacturer – CMO), to be feasible.

The results, outcome and hypothesis, (H1), stemmed from this FMEA / FMECA analysis, are then being expanded and applied to a case study taken from everyday pharmaceutical life, for the capability of the industry to properly implement the basic rules of lean outsourcing, (as far as production is concerned), to be assessed.

The conclusions stemming from the reported case study, aim to indicate how pharmaceutical companies will be able to avoid the occurrence of unsuccessful outsourcing; the difficulty around the proper implementation of the basic rules of lean outsourcing along with the future of its existence within the pharmaceutical industry, may be a fruitful field of interest for further studies.

CONTENTS

ABBREVIATIONS

For readers' convenience, the following abbreviations will be used within this paper:

- CMO stands for Contract Manufacturing Organization
- IP stands for Internal Plant and will be used for the medicine's donor site to be described
- GMP stands for Good Manufacturing Practices
- EMA stands for European Medicine's Agency
- FMEA stands for Failure, Modes & Effect analysis
- RPN stands for Risk Priority Number
- GDPR stands for General Data Protection Regulation
- OOS stands for Out of Specifications results
- API stands for Active Pharmaceutical Ingredients
- QTA stands for Quality Technical Agreement
- AQL stands for Acceptance Quality Level

  QRM stands for Quality Risk Management
- CAPA(s) stands for Corrective and Preventive Action(s)
- EHS stands for Environmental, Health & Safety issues

1. INTRODUCTION

1.1. The importance of Pharmaceutical Industry as a field of interest

This essay examines the area of outsourcing within the general field of pharmaceutical industry; big pharmaceutical industries included in the case study to be reported below, had not been randomly chosen.

The pharmaceutical industry has become the most effective mean through which medicines' production is being accomplished during the last years, (Nalimov Pavel A., Rudenko Dmitry Y., Skripnuk Djamilia F., 2015). Large pharmaceutical companies not only aim to produce medicines compliant with the registered quality standards, able to save human lives, but they also play a vital role in the economy of nowadays, (Rizwan Raheem Ahmed, Jolita Vveinhardt and Dalia Streimikiene, 2018).

As per the above, it is easily understood, the increase of life expectancy due to the industry's efforts has vastly contributed to the fact the pharmaceutical industry steadily became a key player in the development of world's global economy, (Nalimov Pavel A., Rudenko Dmitry Y., Skripnuk Djamilia F., 2015).

So, if the pharmaceutical industry is such a profitable and successful player within global economic markets and if all its foundations are well grounded and established, then which is the basic reason making it a field for expanded analysis among scientific cycles?

During the last decade, the pharmaceutical sector has faced multiple changes and challenges with the most serious one to be its inability to produce new medicines which would replace the already exported ones for which patents gained were to be expired. As a result, many pharmaceutical companies were being uncompetitive and the whole sector tended to become unprofitable, (Ron Bradfielda and Hany El-Sayedb, 2009).

As per the above, production's decline along with market's constantly new needs and great competition between the already existing firms, make the future of pharmaceutical sector seem very vulnerable. So, what is the industry's answer to survive? Outsourcing.

1.2. Outsourcing and the concept behind implementing it

Prior to our trying to understand which are the basic elements of an outsourcing activity, as well as why an IP decides to outsource its processes to another CMO, let us provide the definition of the term “outsourcing” which seems to be the solution to the survival of pharmaceutical industry’s profitability. “Outsourcing” or “contract manufacturing”, (in this essay both terms describe the same activity), takes place when an organization makes a contract with another one, in order for the latter to provide its services to the first one, (Monica Belcourt, 2006).

More specifically, concerning the pharmaceutical industry, contract manufacturing can be expanded throughout several activities of the sector, and it may also involve the completion of medicines’ manufacturing process from another firm; the latter activity is conducted under the brand of the IP, based upon the formulation, specifications and requirements IP has provided to the relevant CMO, (E. J. Pandya, K .V. Shah, 2013). So, apart from the fact the final products must be in compliance with all abovementioned aspects provided from the IP, they should also be in accordance with the relevant registered specifications provided from the legislation of the country the goods are to be exported to. This is a basic rule for a medicine to be sold to a market.

Basically, what happens in action when a pharmaceutical company decides to outsource its production to another firm is that the first one pays the latter one to manufacture products belonging to the first one; these products used to be manufactured from the IP.

Despite the fact the significance of outsourcing has been increased during the last years, the whole process is not considered to be something new within the industry. What however is an innovative trend within the pharmaceutical world, is the augmented tendency regarding outsourcing partial operations of their basic functionality; this tendency could lead smaller firms to increase their competitive advantage within the pharmaceutical market, (Anthi Vaxevanou, Nikolaos Konstantopoulos, 2014).

So, apart from the fact outsourcing can increase the profitability of the CMO, which are the other benefits stemming from contract manufacturing

activities, as far as the IP is concerned and which are the basic reasons actually leading a firm to the “outsourcing” decision?

The basic reasons for outsourcing can be recognized to be the incredibly rapid technology’s development, the re-structuring of global economy, as well as the hugely existing and constantly growing market’s competition; all of these changes along with the constantly changing consumers’ needs and with the fact pharmaceutical legislation for goods’ export is becoming more and more stricter, have totally modified traditional perspectives around the functionality of the pharmaceutical firms, (B.S. Piachaud, 2002).

What comes forward from the relative literature review is that an IP decides to outsource when some of the following issues arise; the manufacturing process required for medicines’ production cannot be in-house completed, (equipment’s constraints), new products’ development must be performed due to market’s needs from the IP, (insufficient room, time or resources for old medicines’ production), or when capacity constraints are observed within production’s department, (sales – production misalignment), (E. J. Pandya, K .V. Shah, 2013).

Now that we have examined the reasons behind outsourcing, let us see the benefits gained from it.

Firstly, IP can increase their resources since their employees are free to work in the business’s core competences. Secondly, outsourcing is a cost-cutting activity and an opportunity for the IP to increase their profitability. Finally, IP’s responsiveness regarding market’s needs is increased since outsourcing is generally faster than initiating an in-house production, (Anthi Vaxevanou, Nikolaos Konstantopoulos, 2014).

The process of outsourcing can be separated into 5 stages: *“Preparation, Vendor Selection, Transition, Relationship Management and Reconsideration”,* (Anthi Vaxevanou, Nikolaos Konstantopoulos, 2014).

So, which is the best way to search for a CMO, (vendor), and where should they be located for the contractual relationship to be fruitful and successful?

First, it should be pointed out outsourcing must be nowadays seen as a *“strategic selection process”* and not as an opportunistic case of contracting manufacturing activities to low-cost countries for the IP to be financially

benefited. CMO to be selected must be considered a partner and the today ability of companies to seek and choose the proper CMO is one of their assets, (Gunter Festel, Mikko De Nardo and Timo Simmen, 2014).

This essay describes a contractual activity taking place in Greece. For outsourcing in the Greek market, the main rationale was found to be the reduction of the IP's standard costs, the increase concerning personnel's know-how around technological advances and the reduction of the initial capital, (Nikolaos K. Liapopoulos, Socrates J. Moschuris, 2013). The above point, along with business flexibility facilitated from the general mentality of Greek people, make the in-case Greek CMO, a fruitful example for analysis

Conclusively, apart from the above, outsourcing as all activities, includes risks and dangers. This essay will try to recognize all these quality risks and provide an outcome for the proper implementation of contract manufacturing in the pharmaceutical industry; the need for the identification and resolution of the dangers to be reported below, stems from the opportune and timeless interest indicated from the global market regarding the subject of outsourcing, due to the importance and profitability able to be gained from a sub-contracting activity, as indicated from the above presented literature review.

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2. LITERATURE REVIEW

2.1. Lean outsourcing and the concept of Quality in the Pharmaceutical industry

This essay examines the implementation of outsourcing from a lean perspective. This is not only due to the fact both the IP and the CMO to be reported in the case study of the following chapter have already established a lean manufacturing system, but also due to the importance of lean mindset's presence within the pharmaceutical industry nowadays.

Lean concept is a well-known system of methods of eliminating waste, (such as big lead times and inventory), may appear during several stages of manufacturing activities, whereas at the same time improving several processes performed within an industry; lean techniques which aim to form strong leaders and to timely satisfy customers' needs while delivering fully qualitative products, may have their foundations in the automobile industry, (TOYOTA PRODUCTION SYSTEM – TPS), although due to their beneficial impact, they have been during the last years spread to other industries as well, (Qun Zhang, Muhammad Irfan, Muhammad Aamir Obaid Khattak, Xiaoning Zhu, Mahmood Hassan, 2012).

In this essay we are not going to analyze lean methodology tools; this essay aims to show how the general mindset of lean methodology should be applied while outsourcing.

Literature review indicated a firm can implement lean outsourcing when applying training programs to the chosen CMO's workers regarding the manufacturing process IP demands from the CMO to be followed; this training can only be performed from the IP since they have the know-how of the applied manufacturing process required to be outsourced. Additionally, teamwork between the IP and the CMO for lean outsourcing to be achieved must be enforced since transparency and trust must be built between both parties. Finally, IP's management mindset must take into serious consideration the constraints, (e.g.: cultural, language, way of working), might arise during such an outsourcing cooperation and they should apply an open-minded strategy for the implementation of lean outsourcing to be feasible, (A. Adnan, M. Safa, A. W. M. Lung, S. Muppala, 2013).

So how is this lean approach, linked with quality perspective in the pharmaceutical industry?

Quality in the pharmaceutical industry is a main field of interest worrying the scientific community during the last 50 years. Pharma Quality is nowadays linked to GMP regulations, defining relationship's nature between the patient and the product to be consumed. Quality does not only concern the ability of a firm to deliver a medicine compliant to the registered specifications, but it also concerns the way all firms' activities are conducted, in a way with which product's safety and effectiveness, timely delivery and patients' safety can be reassured, (Reham M. Haleem, Maissa Y. Salem, Faten A. Fatahallah, Laila E. Abdelfattah, 2013).

Throughout the years and as quality management in the pharmaceutical industry has become of vital importance, many lean tools have been developed for this management to become easier and feasible, (5Whys, Six Sigma); this essay does not aim to examine each of them separately since the bibliography behind this issue is already large enough. However, it should become clear that, the implementation of lean management tools for the elimination of waste identified during several manufacturing activities has been proven to be vastly beneficial for the firm's quality management, (Boppana V. Chowdary Damian George, 2011).

As per the above, it can be concluded the expansion of the implementation of lean management's tools during outsourcing manufacturing activities, can lead to a successful and solid cooperation between firms who seek for quality to be their top priority.

2.2. Quality Risk and Quality Risk Management in the Pharmaceutical Industry

The definition of the term "quality risk" in the pharmaceutical industry is crucial for the comprehension of this study. According to the bibliography, quality risk is a combination of how possible an incident is to occur, along with how severe the consequences of its occurrence might be, (Amrita Das, Praveen Kadwey, Jai Kumar Mishra, Sudheer Moorkoth, 2014).

The general concept behind the occurrence of any quality risk within the pharmaceutical industry is that such a risk may be hidden or may happen any time an aspect or an activity is incompliant with the fact product's quality must be the same during any stage of its lifecycle; the acceptance level up to which quality must be maintained is provided from the relevant legislation as well as from product's registered specifications. Any identified risk

causes the deviation of the product from the abovementioned fact must be faced as a quality one and its criticality must be assessed and mitigated, for the safety of both the product and the patient to be reassured; this is the general scope under which Quality Risk Management, (QRM), has been established, (Muhammad Nauman, Rehana Bano, 2014).

Quality Risk Management is a process of assessing, controlling, communicating, and periodically checking the quality risks may arise during the conduction of any activity completed within a pharmaceutical industry, (V Vijayakumar Reddy, N Vishal Gupta, H V Raghunandan, U Nitin Kashyap, 2014).

Many tools have been created throughout the years, for the industries to be helped to establish successful Quality Risk Management programs. None of them is obligatory to be followed from the firms included in the industry, although each of them must have a defined QRM process, based on the general methodology, providing like that, documented, quantitative evidence regarding the criticality and the mitigation of the risks identified and assessed. In the respective essay, the tool used for the assessment and quantification of the criticality of the risks identified in the reported case study is FMEA / FMECA. This tool has been chosen due to the nature of the herein presented case study which actually concerns a product's manufacturing process; FMEA / FMECA are suitable for the identification of the risks associated with a product's manufacturing process or with the equipment / facilities used for its completion, (Joymalya Bhattacharya, 2015).

QRM is a dynamic and systematic process, becoming successful only when its performance includes team-work; QRM cannot be completed from a single person and even if the risks identified are mitigated, (through CAPAs implementation), the process itself requires them to be re-evaluated throughout the years for the efficiency of the actions caused the abovementioned mitigation to be re-assured, (Muhammad Nauman, Rehana Bano, 2014).

The basic principles of a QRM are generally that the assessment of risk's criticality must be based on scientific data and that it should be proportional to the harm its occurrence may cause to the patient, (V

Vijayakumar Reddy, N Vishal Gupta, H V Raghunandan, U Nitin Kashyap, 2014).

2.3. Risk Analysis – FMEA

The basic QRM tool used for the analysis & quantification of the criticality of the risks identified during the examination of the herein presented case study is FMEA / FMECA.

FMEA is a method aiming in the identification and assessment of a process's failures during its early stages where it is obviously easier to apply CAPAs helping in the prevention of failures' occurrence; as per the above, the most proper stage of a process during which the conduction of an FMEA must take place is either the initial product's design step, or product's development one, without this excluding the possibility for FMEAs to be also conducted during routine process's implementation, (Lefayet Sultan Lipol & Jahirul Haq, 2012).

The basic difference between FMEA & FMECA is that FMEA only includes the presentation of process's steps and the identification of the potential failures hidden beneath them, whereas FMECA gives emphasis to the quantification of failures' criticality through RPN's calculation, as well to the CAPAs required to be implemented for the confrontation of potential failures' occurrence.

RPN represents the quantification of risks' criticality analysis and it is the product of the multiplication of a failure's (O)ccurence, (how often this failure might occur) x (D)etectability, (how easily a failure's occurrence can be detected) x (S)everity, (how harmful failure's occurrence can be either for the consumer or for the product itself); so RPN = O x D x S and the scale of its measurement is a ten-points one, (no threshold is obligatory), defined each time differently, as per the needs of its organization, (Lorenzo Ciani, Giulia Guidi, Gabriele Patrizi, 2019).

Finally, depending on the criticality of the risks, the relevant CAPAs are then defined and assigned to the responsible members of the industry.

The usage of FMEA / FMECA, ameliorates a process's development, from the incredibly early stages, helps the industry easily meet customers' needs & contributes to the long-term financial impact stemming from product's development; nevertheless, it cannot be reassured all failures of a

process will be thoroughly recognized and assessed and RPN might not provide a representative result since rankings are subjected to each of the participants subject's knowledge, (Lefayet Sultan Lipol & Jahirul Haq, 2012).

According to the above, it is undoubtedly concluded, the need for the conduction of an FMEA / FMECA prior to the initiation of an outsourcing activity is more than an imperative one, for the basic risks hidden beneath a manufacturing process or a sub-contracting activity to be identified, assessed & mitigated. The usage of an FMEA / FMECA, can be expanded to any activity performed within a pharmaceutical industry and must accompany every product's design.

2.4. Quality Risks during Outsourcing

Subject's literature review provides several opinions around the kind of the quality risks may arise when a pharmaceutical industry decides to outsource its manufacturing processes to another CMO.

The basic risks of outsourcing can be summarized to be the following ones: *Lack of Control* regarding the whole process especially when outsourcing offshore; *Intellectual Property Loss* since the IP is obliged to provide all confidential information around the product to the relevant CMO, (along with the first one's core competencies and personnel's know-how); *Capacity Constraints & loss of flexibility – responsiveness to the market* since IP's needs might be de-prioritized from the CMO, depending on the financial portion IP represents for the CMO and finally, *Knowledge-transfer* issues concerning the whole information required to be transported and understood from the IP to the relevant CMO, (John V. Graya, Aleda V. Roth, Michael J. Leibleina, 2011).

All abovementioned risks are quality ones since they can all lead to the deterioration of the quality of the products manufactured from the CMO.

This conclusion is furthermore supported from the following formula indicating how market's demand influences quality:

$$d = a – bp – rt + eQ$$

where d= demand, a= standard market's demand, bp= price elasticity & retail price, rt= delivery's time sensitivity & eQ= sensitivity of outsourcing in regards to Quality perspective; as it can be easily seen, if a, bp and rt which are known parameters remain stable, when product's demand increases, the sensitivity of Quality parameter increases too, (Xiaowei Zhu, 2016).

This is something easily understood from the people knowing the outsourcing industry who, in an environment of constant changes required from the IP, have already experienced the deterioration of products' & services' quality.

While trying to examine the fields where risks stemming from outsourcing might be observed, the following three areas have been recognized to be the most crucial ones, according to the relevant literature review; specifically, outsourcing's risks' presence can become evident in 3 main levels presented below:

- Organizational level:
  risk in the identification between core competences and abilities to be outsourced / risk regarding the control of the CMO and the relationship between both parties / risk regarding the creation of the proper quality agreement between the IP and the CMO
- Pharmaceutical sector's level:
  risk regarding the implementation of national control over the pharmaceutical sector / risk regarding the limitless development of outsourcing companies which gain power over the authentic pharmaceutical patterns
- National level:
  potential risk of unemployment / conflicts of cultures and mindsets, (Christine Harland and Louise Knight, Richard Lamming, Helen Walker, 2005).

Summarizing all abovementioned citations, we might end up to the following table, (Table 1), where the basic advantages and risks of outsourcing implementation are being presented:

Benefits	Risks
Outsourcing is a cost saving activity	IP loses control over their product since the CMO will manufacture the product according to their strategy
Outsourcing represents a	Vulnerable Relationship between the CMO and the

Benefits	Risks
steady and healthy cooperation between both parties since a contract bringing stability is being created for a long period of time	IP; IP must consider CMO's other customers along with the fact the latter one cannot be forced to manufacture IP's products before competitor's ones
Knowledge exchange between both parties leads to the improvement of both parties' technical skills	Intellectual Property Loss since the IP provides full product's details for the manufacturing to be successful
Quality can be improved since each CMO has their own methods of testing in place, able to detect counterfeit	Quality can deteriorate since the IP must constantly make sure there are not conflicts between their standards and CMO's ones; product delivered to the market should always be in compliant with the predetermined quality specifications registered within its official dossier. The IP must rely on CMO's suppliers, manufacturing & analytical methods for their product to meet the relevant acceptance criteria
IP can focus on their core competencies	Outsourcing to low-cost countries can create risks such as language barriers, cultural & mindset's differences which may finally lead to difficulties between final cooperation and management
CMOs can offer reduced costs in acquiring raw materials – economies of scale Establishment of both parties' global presence within the industry	Capacity Constraints De-prioritization of IP's needs might be observed Potential loss of Flexibility and Responsiveness to market's needs since the IP loses control over the time & actual manner their product is being manufactured

Benefits	Risks
Responsiveness & flexibility might also be increased regarding market's needs, in case good collaboration has been established between both parties	Lack of control regarding suppliers' performance and their evaluation might occur since these activities are performed from CMO's side
Improvement regarding Technological updates and innovation might occur during knowledge exchange between both parties	The need for new management's mind set and the lack of knowledge sharing, either due to uncontrolled barriers or due to other deliberate conceptions, can also be considered outsourcing risks

Table 1: Benefits & Risks of Outsourcing

Source: Author

It is common knowledge, quality performance's ambiguity, (from IP's side), directly influences the level of CMO's quality conformance to IP's standards, (John V. Graya, Sean M. Handley, 2015).

The fact outsourcing vastly affects product's quality, firm's productivity and profitability cannot be doubted; despite the fact outsourcing activities represent a major player of nowadays' market, their true effect upon quality and CMO's performance is yet to be studied, (Bin Jiang, Gregory V. Frazier and Edmund L. Prater, 2006).

2.5. The crucial decision of choosing a CMO

One of the most crucial steps when having decided to outsource a process, is the selection of the relevant CMO; this is a very serious selection, not only from a qualitative, as well as from a financial point of view, since it actually defines whether or not the key factors of outsourcing are met between both parties, (Festel, G., Nardo, M.D., & Simmen, T., 2014).

Numerous factors are to be taken into consideration when a firm, (IP), decides to choose a CMO; most of the criteria to be met from CMO's point

of view, are to be answered while posing several of the questions tabulated below, (Table 2):

Question's Nature	Question
Questions bearing a commercial interest	Is the potential CMO financially healthy?
	Does the management team have the appropriate qualifications and experience in working in such positions?
	Is contractual working part of the core activities of the potential CMO?
	Is the company sensitive to merging acquisitions?
	Will the IP be obliged to proceed to any extra capital investments?
Questions bearing a legal interest	Is the contract to be made a dynamic document which can be altered and modified as per the interest of both parties?
	Is IP's intellectual property in danger?
	Is the potential CMO ready to actively and timely respond to the IP's changing environment and requirements which might include regulatory changes as well?
Questions bearing a regulatory interest	Which regulatory & quality systems are in place and valid in the relevant CMO company?
	Are GMP requirements in place? Is the site of the relevant CMO frequently inspected from the relevant Authorities?
	Is the site of the relevant CMO compliant with the current legislation?
	Is the potential CMO compliant to the latest EHS legislation applied to the relevant countries?
Questions concerning equipment's compliance	Is there equipment's capacity for the required production to be met?

Question's Nature	Question
	Is the existing equipment appropriate and adequately validated for the production to take place?
	Is frequent maintenance in place and in compliance to the relevant legislation?
	Is the existing equipment capable to fulfill the requirements of a future similar production?
Questions concerning CMO's personnel	Are the potential CMO's personnel adequately trained and numerically enough for product's manufacturing to be completed?
	Is there a project management team established in the CMO's site?
	Can cross-functional collaboration be established?

Table 2: Questions to be answered when choosing a CMO

Source: Author

Conclusively, it can be considered contractor's selection is a strategic process; suppliers' qualification is time consuming and costly so the IP must be incredibly careful during the choice of their contractors. Finally, the contractual relationship must be defined before the initiation of any sub-contracting activity and the potential risks existing must be mitigated, otherwise the outsourcing activity might collapse, (Vijay Wadhwa, A. Ravi Ravindran, 2007).

2.6. Why Outsourcing might fail

Despite outsourcing's benefits, there are several cases, (one of them is the case study reported below), indicating outsourcing might fail and this failure might lead to the re-insource of product's manufacturing from the IP.

In general, and according to the relevant bibliography, the main reasons for which a sub-contracting, outsourcing activity might fail are the following ones; firstly, because both parties are continuing to collaborate without

having achieved the main purpose of the outsourcing activity, secondly, because both parties face difficulties which cannot be easily resolved and may lead to collaboration's collapse and finally, because their initial target has been altered somewhere in between their collaboration, (S. Cabral et al., 2014).

Apart from the above, one of the most common reasons for which outsourcing activities fail to succeed, is the ambiguity and the untrustworthy relationship developed between the IP and the CMO; the selfish and non-collaborative approach many industries adopt during a sub-contracting activity is of no help for it to be successful, (Torsten Steinbach and Carl Marcus Wallenburg, Kostas Selviaridis, 2018).

For an outsourcing activity to be successful and productive, the presence of the following key aspects is necessary; information exchange must be constant and transparent between both parties, quality criteria must be clear and met between both parties, just-in-time orders' delivery must be in place and supported from both parties and capacity constraints' management must be accurate and faced with mutual understanding from both parties as well, (Tuuli JYLHÄ, Seppo JUNNILA, 2012).

Conclusively, it becomes obvious, none of the abovementioned pre-requisites should be neglected from the parties collaborating to the outsourcing activity; contract manufacturing is a mutual effort and a multidisciplinary process. This is something the pharmaceutical industry has many times failed to achieve; therefore, the future of outsourcing has become uncertain.

2.7. Outsourcing – Future Directions

The future of outsourcing was undoubtedly very prosperous during the past decade; most companies seemed to seek offshore solutions for outsourcing and this was the trend during the last ten years – the tendency for outsourcing could not have been reduced due to the tremendously large financial impact its implementation offers, (Zafar Iqbal, Aasim Munir Dad, 2013).

Nevertheless, the difficult question of which activity to actually outsource, which is the crucial one required to be answered from all firms thinking to proceed likewise, has made the future of outsourcing seeming

doubtful; companies' upper management should be aware there is a specific number of activities able to be outsourced, as well as that the formula connecting outsourcing and a firm's financial improvement is curvilinear, (Carlos Sanchís-Pedregosa, María-del-Mar Gonzalez-Zamora, María-José Palacín-Sánchez, 2017).

Outsourcing will continue to exist as a tool used from firms for their financial boundaries to be broaden, as well as for their economies to be improved; nevertheless, the risks and the problems already identified throughout the years of outsourcing's implementation have already provided the knowledge for the latter to be used as a tool of amelioration and not as a random choice for a firm's future to be saved.

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3. CASE STUDY & ASSESSMENT

Important notes:

- Specific names and actual numbers will not be reported herein due to confidentiality issues
- All aspects of this report are real and can be found within the basis of EMA as far as the decisions raised from IP's side are concerned
- All information provided within this essay are authentic and they are herein presented since the essay's author was the one who handled the case during working for the respective CMO as part of its team of Quality experts
- All reports already written for the respective case are CMO's literary property and strictly confidential; none of their aspects will be herein reproduced

3.1. Basic Description

For the below presented case study to be properly understood, the provision of the following clarifications is imperative:

- Product concerned will be called PS
- IP will be called G
- CMO will be called F

F was chosen from G as the most suitable CMO to produce PS. Transfer process has been completed, validation batches have been produced and analytically tested only to provide results within the registered specifications. Product's commercialization has been initiated. F supplied various markets with PS. No deficiencies have been observed for over 10 years of product's manufacturing.

Between 2016 and 2017, one already exported batch of PS produced back in 2016, was found to be OOS regarding assay's parameter, for the interval of 12 months.

Assay is calculated to be API's concentration within the final product, and it is one of the most crucial aspects for a drug to be released to the market.

According to the pharmaceutical legislation, each pharmaceutical manufacturer should provide adequate analytical evidence the drugs they manufacture are stable during their registered shelf-life. As per the above, each pharmaceutical manufacturer is obliged to analytically test their

marketed products, at least annually, so that they can provide this piece of information, until their being expired. This means, a representative sample is being annually kept & analytically tested from CMO's side. These tests are named stability tests. In case any of the stability testing specifications are found to be OOS, drug's stability is doubted, and it needs to be recalled from the market. This is a critical and very unpleasant situation for both parties since not only the CMO needs to immediately provide investigation around the root cause of the incident or to urgently apply corrective & preventive actions for occurrence's avoidance and to stop drug's production until the actual root cause has been found, but also IP needs to immediately report the incident to the relevant Authorities.

In our case, F immediately informed G regarding the occurrence of the incident and the latter one immediately raised a letter of notification to the relevant Authorities. Finally, recall's process harms the trust and the collaboration between both parties and generally the CMO's fame.

Investigation timely conducted from the CMO, concluded the manufacturing process of PS was inadequately validated; this was further supported from the statistical evidence having stemmed from annual analyses indicating great variation regarding assay's parameter. It should be pointed out, these reports were being annually provided to G and F had made clear the need for process's re-validation, prior to the occurrence of the incident, however, no actions were taken. Finally, the defective batch has not been recalled from the market since G issued a medical report indicating the OOS result, did not actually impact the final consumer, due to drug's nature.

In 2017, F started to produce OOS PS batches, as far as assay's parameter is concerned. Defective batches were too many and no correlation could be found between assay's values for a conclusion to be reached since they appeared to be different from finished product's tablet to tablet. Great variation was being observed. Other stability tests concerning other 2016 batches were also found to be OOS regarding assay. No recalls occurred, since other medical assessments have also been prepared from G. All defective batches produced although found to be OOS during release testing were being rejected from F. Mutual discussions have been initiated for the re-validation process to be initiated, after F had made several proposals regarding aspects of ameliorations potentially existing during the

process. It should be pointed out, G has visited F, for the resolution of the issue to be facilitated.

Finally, in the end of 2017, G & F concluded to the following agreement: all batches of PS produced would be tested regarding assay's parameter prior to their being coated or packed. In case they were found to be OOS, they would be immediately rejected, and G would be charged with rejection's cost. Additionally, some extra tests and some mutually agreed short-term CAPAs were applied to the manufacturing process of PS for the issue to be temporarily confronted, until F re-validation's proposal has been assessed from G side.

Practically, the above made decision had the following meaning for F:

- PS manufacturing process became costly and time consuming since analytical tests have been increased and production needed to wait for analytical results to proceed to the final tablets' coating step
- OOS batches' rejection was additionally costly for F, despite the fact the process was charged to G, since all raw materials and APIs needed to be ordered once more; each batch costed approximately 4K
- Delays and re-scheduling of the whole production & packaging plan needed to be made from Planning Department since batches could not be packed prior to the completion of all analytical tests required from G
- Quality Control Department was overloaded with excessive workload due to the massive modifications required for the extra analytical tests to be conducted – capacity constraints; this also had a huge impact to the testing / release / export of other significant drugs produced from F
- Quality Assurance Department was overloaded with excessive workload since multiple investigations of the same content had been written for all OOS batches prior to their rejection, for F to be in accordance with the relevant legislation demanding all rejections of OOS batches, even during the release or during stability testing to be accompanied from a relevant investigation

Despite multiple reminders performed from F for the re-validation to be urgently conducted, the situation remained the same, up until the end of 2018, when F underwent a scheduled audit from G.

During this audit, conducted from an external sub-contractor, on behalf of G, the significance of the matter came back to the fore with the auditor emphasizing how crucial the contribution of the IP was for the permanent resolution of the issue to be accomplished. Auditor pinpointed what F had already pointed out; the manufacturing of a product cannot be continued if the process fails to meet critical aspects.

This audit forced G to assess and initiate re-validation process; re-validation costs are to be paid from the IP since the product belongs to the latter one and when a manufacturing process is found to be unstable, responsibility is always split between both parties, due to the fact all potential failures should have been identified & assessed in the initial FMEA, conducted during transfer process.

Finally, re-validation has been conducted. Validation batches also came to be OOS.

G decided to take the product out of F portfolio, along with plenty other ones and to proceed with insource manufacturing again.

3.2. FMEA / FMECA concerning PS outsourcing's initiation

The respective FMEA / FMECA, in-detail describes each phase of PS outsourcing's initiation process, (from the very beginning to the production of the first trial batches from F), along with the quality risks potentially occur within its phase, (although not in-detail describing the technical parts of product's manufacturing activity, since this is something supported from a different FMEA), as well as the existing mechanisms F or G may have in order to predict them from happening. This FMEA / FMECA is being conducted under the condition F has been carefully selected from G to be the appropriate CMO for PS manufacturing to be completed.

The criticality of each quality risk is quantified based on the RPN score to be analyzed below. Criticality is being categorized as minor, major, or critical. Aspects for which criticality is between major and / or critical need to be assessed and CAPAs need to be set for the risks to be mitigated. Upon risks' mitigation and when all aspects of the transfer process are of minor

criticality, (RPN gets lower), the initiation of the outsourcing manufacturing activity is then considered to be safe.

RPN calculations included in the following FMECA, are based on the risk rating scale tabulated below, (Table 3):

Parameter	RISK RATING SCALE (FMECA)			
	2	**4**	**6**	**8**
Severity	No impact either on the product or on the final consumer	Indirect impact on the final consumer	Reversible although direct impact on the final consumer	Irreversible and direct impact on the final consumer
Occurrence	Improbable	Rear	Frequent	Constant
Detectability	100 % automatic inspection	Automated systems in place although requiring human intervention	100% manual inspection	No inspection

Table 3: Risk Rating Scale, (FMECA)

The above-mentioned scale is representative to the one used from F, for criticality's assessment to be valid. Numbers and some other confidential aspects have been altered due to GDPR restrictions, although the general concept of RPN calculating remains the same. According to the scale presented above, the following RPN calculations, (Table 4), as well as the explanation of their criticality, (Table 5), are tabulated below:

		Detectability			
		2	**4**	**6**	**8**
Severity x Occurrence	**64**	128	256	384	512
	48	96	192	288	384
	36	72	144	216	288
	32	64	128	192	256
	24	48	96	144	192
	16	32	64	96	128
	12	24	48	72	96
	8	16	32	48	64
	4	8	16	24	32

Table 4: RPN calculations

C	Risk identified is unacceptable – **CRITICAL** (**C**) and requires mitigation
MJ	Risk identified is generally acceptable, (**MAJOR – MJ**), although it should be mitigated
MN	Risk identified is acceptable, (**MINOR – MN**) – Mitigation might be a recommendation

Table 5: Criticality's explanation

Taking into consideration all abovementioned points, the relevant FMECA is tabulated below, (Table 6) [1]:

Table 6: PS Outsourcing's Initiation FMECA

Process Step	Potential Quality Risk	Potential Effect(s)	S	Potential Risk's Cause(s)	O	Failure's Detection's System	D	RPN
PS full dossier & previous validation studies are provided from G	Lack of essential information concerning PS manufacturing, analytical, packaging & exporting specifications	Difficulties during production / OOS results / batches' rejection	**4**	Misunderstanding between IP & CMO / Unwillingness of G to provide the whole dossier to F / Product's age or lack of the whole dossier (from G side) [2]	**6**	Quality Department ensures dossier's completeness – dossier is a pre-requisite for the outsourcing activity to be initiated from F	**6**	**144**
All production's steps are included within an FMECA; any potential failures observed are defined and their risk is mitigated, prior to the initiation of PS commercialization	Unknown or blind spots of manufacturing operations may cause severe problems during production / equipment might end to be improper	Difficulties during production / OOS results / batches' rejection / validation batches OOS / project's failure	**4**	Misjudgment of manufacturing steps during FMECA's conduction / Lack of experience from F / G absence during FMECA's conduction	**6**	No automatic / manual detection; in case this happens, it can only be revealed during the production of PS validation batches	**8**	**192**

Process Step	Potential Quality Risk	Potential Effect(s)	S	Potential Risk's Cause(s)	O	Failure's Detection's System	D	RPN
F equipment & resources, from a manufacturing, a packaging, an analytical and a quality point of view have been examined & their condition, availability and capacity has been checked prior to the initiation of the outsourcing process	Lack of basic aspects for the proper completion of PS manufacturing process / lack of resources may cause severe obstacles during PS production	Difficulties or delays during production / OOS results / batches' rejection / financial inability to solve issues may occur	**4**	F intended conceal of resources' lack for them to acquire the project / G intended neglection to recognize any shortages in case PS is of low value for them, or in case there is much pressure from the market to proceed with exports	**4**	No automatic / manual detection; in case this happens, it can only be revealed during the production of PS validation batches	**8**	**128**
Evaluation of the suppliers of the APIs to be used during PS manufacturing & recommendations regarding those to be used for the raw materials' supply are provided from G	Suppliers not being in complete compliance with the standards provided from the F might be selected from G / Inadequate suppliers' quality performance	PS incompliant with the dossier / batches' rejection / delays during production / multiple market's complaints	**6**	Raw materials might not be key ingredients and proper attention might not be given to them / selection of raw materials from F facilitates cost's reduction so G might leave the choice to be open (economies of scale)	**4**	All regulations require APIs' manufacturers to be selected from the IP and to be included in product's dossier / Raw materials' suppliers' performance can be checked through F quality system or during audits performed	**6**	**144**

Process Step	Potential Quality Risk	Potential Effect(s)	S	Potential Risk's Cause(s)	O	Failure's Detection's System	D	RPN

QTA between the F & G is present prior to the initiation of PS commercialization	Basic elements of the sub-contracting collaboration might not have been determined	Quality issues / Lack of knowledge regarding issues' resolution from F side / Interplay collapse / Lack of trust between F & G	**4**	Market's pressure for PS export and financial benefits may not allow this step to be timely accomplished since a QTA needs to be reviewed and signed from various departments of both parties, (time consuming activity)	**6**	The presence or the absence of a QTA can only be identified from Quality or from Business Development Department of each of the parties	**8**	**192**
AQLs & Acceptance criteria have been established in the QTA prepared from G side	F will not be aware how to categorize the defects may occur during any stage of PS manufacturing / the way G categorizes the defects may be different from the way F does since legislation defines various levels of categorization	Release of a non-compliant batch to the market / batches' recall / project's failure	**6**	This aspect might be forgotten during all others required to be discussed and G might take it for granted F categorizes batches' defects the same way they do	**4**	Only quality department can evaluate the potential lack of specific AQLs prior to the initiation of PS validation batches' production	**8**	**192**

Process Step	**Potential Quality Risk**	**Potential Effect(s)**	**S**	**Potential Risk's Cause(s)**	**O**	**Failure's Detection's System**	**D**	**RPN**

Each already identified proposition for production's amelioration, or each already identified product's / production's deficiency has been communicated to the F even if not required in the beginning of the outsourcing collaboration	Lack of knowledge from F side / communication between both parties lacks transparency	Multiple re-validation exercises meaning cost and time for F / batches' rejection / project's failure	**4**	Failure from G to understand the importance of the provision of this type of information / intended conceal of this information from G side	**6**	There is no system to detect the potential lack of this piece of information – only a very upgraded Quality Department can evaluate this aspect	**8**	**192**

As indicated from the above presented FMECA, all steps of outsourcing's initiation process are crucial and all quality risks hidden beneath their improper completion result in failures of major criticality; as a result, no step can be neglected and the proper completion of all mitigation's activities are a pre-requisite for the outsourcing activity to successfully become effective.

Hypothesis to be set and analyzed below is the following one: ***PS outsourcing's Initiation FMECA has been completed prior to PS commercialization and all Quality risks identified have been assessed and mitigated from both parties (H1)***

(1): This FMECA has been conducted under the condition the need for outsourcing PS manufacturing process has been deemed necessary from G side. The steps to be followed prior to the initiation of the outsourcing process are known within the pharmaceutical industry and they are a product of work experience.

(2): There are cases where a product has been bought from the IP whereas the initial dossier belonged to another pharmaceutical company. In that cases, which are mostly cases concerning old formulations although very well-known ones, the dossier might

not be following the current standards and there is a high possibility for it to lack essential information around the manufacturing process. This must be taken into consideration from the IP and the dossier must be certainly revised prior to be given to the CMO, for it to contain all chapters required from the current Pharmacopoeia.

3.3. Case Study: Gap Assessment

For the key points of the above-mentioned Case Study to be assessed, the following Gap Assessment combining information taken from the literature review and from the FMECA presented in the previous section, has been conducted, (Table 7):

What should have been done	What was done	GAP
Initially recognized OOS stability batch should have been recalled despite the cost this would have had for both parties & PS production should have been stopped under G directions.	Medical assessment indicating the incident had no impact upon final consumer's health was filed to the relevant Authorities. No recall took place. Production has not been stopped.	Incident's significance has been underestimated. Both parties took advantage of the fact this was initially considered as an isolated incident for a drug being manufactured for many years, as well as from the fact a "recall" situation is not profitable from neither of them.
A team of experts coming from both parties should have been immediately formed for the manufacturing process, (as implemented from F), to be deeply examined and for all potentially defective practices leading to the occurrence of the incident to be properly identified.	A team of 2 people with Quality and Production background visited F premises for the Workshop around the issue to be performed. Team's sample was not representative and the lack of knowledge regarding key aspects of PS manufacturing process was essential. Team included no	Significant key points of the manufacturing process were not assessed or taken into consideration during short-term actions' implementation. The general treatment of the subject can be characterized as superficial.

What should have been done	What was done	GAP
	validation or analytical experts.	
Immediate assessment of long-term re-validation's proposal from G point of view.	1.5 year passed until re-validation's proposal has been assessed. This has been performed only after the auditor applied a significant amount of pressure upon G, requesting for incident's permanent resolution.	The production of other profitable drugs from G side, along with the focus they have given on their core competences, did not allow the timely assessment of re-validation's proposal. The fact G did not consider the respective drug to be of such importance for their profits, they allowed the case not to have been treated with the proper attention.
F should have given much more attention and should have provided an accurate and proper long-term re-validation's proposal. For this to be accomplished, a team of experts should have been formed.	Re-validation's proposal has been provided only from one F employee: the site's process engineer. Proposal has been assessed from Production's Department and the communicated to G.	F did not give the proper attention while providing long-term re-validation's proposal to G. Lack of knowledge from F side, as well as lack of resources and of adequately trained personnel, for the failures of PS manufacturing process to be scientifically documented and recognized, did not allow the proposal to be a proper one.
Annual reports and warnings from F side regarding the occurrence of great variation concerning assay's parameter should have been assessed and taken into consideration from G.	No attention has been given from G side to the respective warnings. Every discussion for re-validation from F side has not been accepted from G.	The costly proposal for PS re-validation has not been accepted from G, since a significant amount of time and money, as well as significant delays in production and market's needs would arise in such a case.

Table 7: Gap Assessment concerning issue's confrontation

Conclusion (1):

Too many gaps have been identified from both parties, as far as the confrontation of the issue, (upon its occurrence), is concerned. It has also become clear PS outsourcing' initiation completion has not been completed as per the theoretical background presented in the Introduction of this paper. Criteria presented in the FMECA provided in the relevant section of this essay have not been met.

3.4. Gap Assessment – FMECA

This is a gap assessment indicating the gaps identified during PS outsourcing's initiation process while taking into consideration the steps identified in the FMECA provided above. For H1 to be assessed, each step of the above provided FMECA is analyzed in the extended case of PS, (Table 8):

What should have been done	What was done	GAP
PS full dossier & previous validation studies should have been provided to F from G	All information has been provided to F	No GAP has been identified
All PS production's steps should have been included within an FMECA prior to PS commercialization; any potential failures observed should have been defined and their risk should have been mitigated	**There is no documented evidence this initial FMECA study has been completed.** PS commercialization has been conducted many years ago when the need or the knowledge around FMECA conduction might have not been available	Potential failures of each step of PS manufacturing process had not been accurately assessed; as a result, failures potentially leading to OOS assay's issues had not been identified and resolved during PS outsourcing's process initiation. This made the investigation around the OOS case even more difficult since no information of what could potentially go wrong during the process has ever been provided.

What should have been done	What was done	GAP
		Additionally, the absence of an initial FMECA regarding PS manufacturing process had been identified only after OOS result's occurrence. None of the parties ever paid attention to this crucial piece of information since this is something able to be identified only from PS dossier's full study, (it should be pointed out this initial FMECA should be included in products' dossiers nowadays – according to the relevant legislation) **(GAP 1)**
F equipment & resources, from a manufacturing, a packaging, an analytical and a quality point of view should have been examined & their condition, availability and capacity should have been checked prior to the initiation of PS outsourcing process	There is no documented evidence this point has been completed during PS outsourcing's initiation process	This is a general gap identified during most products' cases; PS is not an exception since there is no part of the dossier indicating F meets all relative criteria regarding equipment & resources for them to manufacture PS – this indicates, full F's capability has not been accurately assessed during PS transfer phase; this, can be linked with quality issues not evaluated from G **(GAP 2)**
Evaluation of the suppliers of the APIs to be used during PS manufacturing & recommendations regarding those to be used	APIs' suppliers have been evaluated and included within PS dossier; no information has been included regarding raw	Raw materials are crucial to produce medicines. Nevertheless, OOS results are always related to APIs; in our case, gap identified regarding raw materials' suppliers'

What should have been done	What was done	GAP
for the raw materials' supply should have been provided from G to F	materials' ones	evaluation, does not seem to be the one to blame for incident's occurrence
QTA between F & G should have been present prior to the initiation of PS commercialization	QTA has been in place	No gap has been identified
AQLs & Acceptance criteria should have been defined in the QTA between F & G	AQLs & Acceptance criteria have been defined and quantified in the existing QTA between F & G	No gap has been identified
Each already identified proposition for PS amelioration, or each already identified product's / production's deficiency should have been communicated to F even if not required during PS outsourcing's initiation process	Even though G was aware of several changes required to be made during PS manufacturing process, no relevant communication has been made with F, since product developed at the time was of acceptable quality for both the market and the consumers	Gap has been identified since severe lack of information around several stages of PS manufacturing process may have led to OOS incident's occurrence; G has either deliberately or not, concealed this information due to market's pressure for PS commercialization or due to their misjudgment concerning information's provision necessity **(GAP 3)**

Table 8:

Gap Assessment concerning PS outsourcing's initiation process while assessing FMECA's key points

Conclusion (2):

All steps identified in FMECA provided above concerning PS outsourcing's initiation process are crucial and all quality risks hidden beneath their improper completion result in failures of major criticality; as a result, no step can be neglected and the proper completion of all

mitigation's activities are a pre-requisite for the outsourcing activity to successfully become effective.

As per the above presented statement, which stemmed from a valid, quantified analysis and since some of the abovementioned criteria had not been met, (specifically, 3 out of 7 criteria were found not to have been properly completed during PS outsourcing's initiation process), the following outcome regarding H1 becomes obvious:

PS outsourcing's initiation FMECA has not been successfully completed and all Quality risks identified have not been timely assessed and mitigated for the sub-contracting activity to be successfully initiated (original H1 has been contradicted & collapsed)

4. CONCLUSION

The basic quality risks may stem when outsourcing manufacturing activities within the pharmaceutical industry have been herein identified and assessed while using lean methodology's tool FMEA / FMECA.

There is one main hypothesis derived from this essay. A case study taken from everyday life has been used for hypothesis H1 to be assessed and for the basic quality risks of outsourcing manufacturing processes stemmed from the relevant literature review to be confirmed and evaluated. H1 has been contradicted and collapsed.

The basic quality risks of outsourcing have been found to be Lack of Control, Intellectual property loss, Capacity constraints – response's flexibility to market's needs, as well as issues during product's knowledge and know-how transfer from the IP to the CMO. Their presence has been confirmed from the outcome of the case study presented above.

The necessity of examining the criticality of these quality risks, from the very beginning of the outsourcing activity, prior to product's commercialization has been confirmed; all risks hidden beneath a sub-contracting activity were found to be of major criticality and it was confirmed the mitigation of all of them should not be neglected.

FMECA and gap assessment above performed indicated risks' identification and assessment has not been timely or accurately performed in the respective case study.

Basic Case study Conclusions

- PS transfer process has not been accurately completed; there is no documented evidence lean methodology's tools such as FMECA, which could have helped in the recognition of potential failures concerning PS manufacturing process, had been used at the time of PS transfer process. This happened either due to the fact the knowledge of these tools' usage was not enough, (PS is an old product), or because the significance of the tools has been misjudged from the participants of product's launching team.
- G knowledge regarding PS manufacturing process & blind spots potentially already identified from their side which could have been ameliorated prior to PS commercialization had not been communicated to F; this happened either because the significance for the implementation of this action has been misjudged from G or because this piece of information has been deliberately concealed from G. ***Quality risk identified here has been confirmed to be inadequate knowledge transfer from the IP to the CMO.***
- Even though the above-presented case study assumed F has been selected from G as the most appropriate CMO for PS production, the criteria for this selection, such as the assessment of the equipment, the capacity & the

resources of the first one, do not seem to have been properly investigated upon CMO's selection.

- All F warnings, communicated to G prior to the occurrence of OOS incidents, concerning the observation of great variation regarding assay's parameter, have been neglected from G; F proposal for process's re-validation has been deemed as unnecessary. Neglection might be explained either from the fact G misjudged the significance of the variation observed regarding a crucial drug's release parameter, or due to the fact market's needs were being adequately covered since no OOS production has been observed at the time. ***Quality risk identified here has been confirmed to be total lack of control regarding PS production's conditions, from IP's side.***
- PS production has not been paused after OOS incident's occurrence, a fact which caused delays in the problem's resolution, the production of more OOS batches, as well as the implementation of costly decisions from both parties; significant delay in the assessment of the OOS issue from G, inadequate knowledge provided from both parties during the meeting conducted for the OOS issue to be investigated were other parameters also affected the proper resolution of the matter. ***Quality risk identified here has been confirmed to be loss of market's responsiveness from IP's side due to significant delays reported above.***
- Delays in the assessment of the final validation's proposal from G side, inadequate scientific knowledge provided from F side upon proposal's preparation along with its improper and non-scientifically documented acceptance from G led to final validation's failure, to collaboration's collapse as well as to PS discontinuation after G decided so since no resolution could be found and none of the parties could afford to produce OOS batches.

The overall conclusion stemming from the case study presented herein which can be expanded to the general field of outsourcing is the following one:

An outsourcing activity for which all potential quality risks stemming from its initiation have not been accurately assessed from both parties will not end up as a successful one.

If lean tools, such as QRM, FMEA / FMECA, do not get timely and effectively used, quality issues potentially arise may devastatingly shake the collaboration between both parties and may also lead to the breakup of the sub-contracting activity. Good collaboration between the IP & the CMO, transparency

& flowless sharing of knowledge & information should be top priorities for both parties. Even though the significance of each product differs for the market, (from a financial point of view), this should not influence the time or the strictness with which decisions under pressing circumstances should be made not only from the IP but also, from the CMO as well. Defective batches and failures during manufacturing processes are the results of an unsuccessful outsourcing activity which has its roots back in the beginning of product's launching. In our case, where the issue was not a matter of contradictory cultures or mindsets between the IP & the CMO, the non-resolution of the problem had a tremendously negative impact, financial & ethical, upon both parties.

Outsourcing activities should be first subjected to honesty, transparency, understanding, mutual effort & interest from both parties. The CMO must face the product manufactured as its own "child" and IP must give the proper attention to every single word reported from the CMO regarding the quality of the product being manufactured. A collaboration based on trust is the only one able to survive and succeed. It is therefore crucial for both parties to understand an outsourcing activity is of their common interest and all of their efforts should be centered around how to constantly manufacture a product of the best quality which will safely provide its services to the common health. If this is not the case, the collaboration will somehow end in the future. There is no prioritization when it comes to product's quality; this is the first aspect to be considered both from the IP and from the CMO.

It is surely understood the financial margins & the potential profits stemming from outsourcing activities between pharmaceutical companies are huge. The timely character of the issue examined herein cannot be doubted. It is also very easy for a CMO to provide a marginally acceptable product, regarding quality, which can be easily exported to the market since it meets basic release parameters set from the IP, especially when the latter one is not able to control CMO's full activity.

These are two of the most crucial mindsets required to be diminished both from the IP, as well as from the CMO, for the heart of outsourcing to be understood; this is the core element of outsourcing required to be deeply established prior to any trial for the initiation of any outsourcing activity takes place. The difficulty in doing so, is possibly another aspect to be studied in future papers.

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