

This article reviews the considerations involved to decide whether to outsource any manufacturing activity. Some basics for successful outsourcing are considered. The challenges and benefits of outsourcing, the company's areas that should be involved in the process, and the activities to be developed are discussed.

Outsourcing and Contract Manufacturing in the Pharmaceutical Industry

by Magdalena Nannei and Sandra Rumiano

The pharmaceutical industry is facing new challenges. The need for continually increasing investment both to develop new products and to maintain them in the market following regulatory approval often conflicts with the requirement to keep costs low.

At some point, outsourcing may become a strong candidate for improving the business, and sourcing strategies could allow the pharmaceutical company to focus on its core activities or products. In addition, the technology required may be so specialized that there is no in-house knowledge and expertise and it is more convenient to obtain this from outside the organization.

The possibility of increased cost benefits when a product or process is manufactured by a third party provider should be balanced against the risk that a contract manufacturing organization will not satisfy expectations. Therefore, risk analysis is one of the major activities when establishing an outsourcing manufacturing strategy.

What is Outsourcing?

The FDA indicates in its Guidance for Industry, Quality Systems Approach to Pharmaceutical cGMP Regulations, that *"Outsourcing involves hiring a second party under a contract to perform the operational processes that are part of a manufacturer's inherent responsibilities."*¹

Why Outsource?

There can be many reasons why an organization would outsource, some of which may be planned, including:

- optimizing and controlling operating costs

- strengthening the focus on core business initiatives
- freeing resources
- reducing the time to market

Frequently outsourcing is a consequence of merger and acquisition activities without a clear strategy on the possibility for outsourcing in a continuous operating environment. This could be considered as an example of an unplanned outsourcing strategy.

Gaining focus is one of the major drivers for outsourcing. The "two-digit growth factor" is essential when developing a commercial and manufacturing strategy for a pharmaceutical company. Focus should be applied to the fastest growing products which provide the company with the highest return on investment.

Companies usually have a list of 10 or 20 top molecules on which they prefer to concentrate their commercial efforts, capital investments, and resources utilization. Regardless of the importance of other products to the commercial portfolio, they will not provide significantly to future growth. This is why an outsourcing manufacturing strategy could be designed to maintain them at the necessary regulatory and commercial requirements, while avoiding further capital investments.

Recently, offshoring (substituting foreign for domestic labor) has become a highly interesting alternative when coupled to a Contract Manufacturing Organization (CMO) since substantial savings can be obtained. Currently, Latin America, China, and India represent valid alternatives for global manufacturing with Argentina, Brazil, Colombia, and Mexico as the main contributors within Latin America. These countries have developed all the conditions

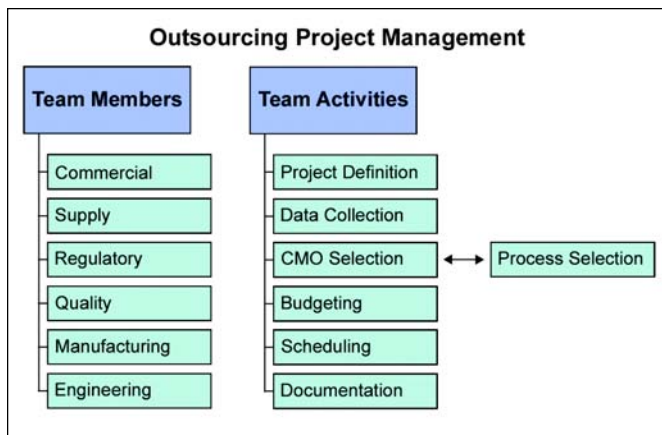


Figure 1. Main areas and activities that are involved in an outsourcing project.

required to become reliable outsourcing alternatives.

Some of the conditions which the countries should possess, in order to be selected as potential countries for manufactured products, are related to a reliable macroeconomic environment and include:

- stable democracy system
- no conflicting borders
- tax and duty benefits (inside the country plus regional benefits like a common trade area)
- a developing and healthy economy
- placid trade unions
- low labor costs
- a high educational level (particularly)

It is not considered reasonable under the current scientific, regulatory, and investment environment to have manufacturing sites designed to manufacture everything. Both capital investment, in areas and services, and significant numbers of highly educated personnel, needed to keep the site updated and compliant, are required when several different areas of expertise are involved.

When asking the question “make or buy?” in the pharmaceutical industry, necessary considerations include:

- the successful experience of other industries, like the automotive industry that is outsourcing 70% to 80% of its total value
- dissatisfaction with outsourcing, due to failures in the outsourcing relationships within short to mid periods of time

An impressive figure in favor of using a CMO is shown in the pharmaceutical outsourcing market, which today is valued at \$22.5 billion, and this is estimated to more than double by 2010.²

What to Outsource?

Practically everything that is manufactured also can be outsourced. From APIs and their intermediates to drug products, bulks, or filled and packaged drug products, the

complete manufacturing chain or single processes, or unit operations, including analytical and QA, as well as distribution and inventory management. With creative thinking, there are many ways to resolve manufacturing constraints using outsourcing³. Usually outsourcing comes after situations like:

- supply chain analysis (bottle necks, non added value activities)
- new products requiring unavailable expertise inside the company
- strong changes in demand requirements
- cost issues

Filling and packaging operations are activities that are commonly outsourced. New packaging configurations and materials often require equipment not available inside a company, and contract manufacturing is a satisfactory solution to overcome the problem without significant issue.

Another regular outsourcing activity is the manufacture of gelatin soft elastic capsules that it is performed at highly specialized sites. Effervescent tablets or powders, lyophilized and sterile products, eye drops, aerosol formulations, and medical shampoos are some of the pharmaceutical forms that are usually manufactured at dedicated manufacturing sites since the processes involved in their production require specialist knowledge, equipment, and facilities.

Penicillins and *beta-lactam* antibiotics, high potent compounds, and hormones are usually manufactured by third parties when they do not belong to the core product list since these products require separate buildings and expensive room classifications.

Another popular outsourcing activity in the pharmaceutical (and other industries) is the logistics function. During the 1980s, the outsourcing in this regard was related only to some elements of the whole range of the logistics operation and it was delegated to one specialist. Then this figure was changed for a more complex environment involving the development of strategic alliances. Thus, the situation turned into “the strategic alliance with service providers.”⁴ In the logistics world, this refers to “logistics service providers,” including functions such as:

- warehousing
- transportation
- electronic information exchange
- packaging process of the goods
- identification (labeling)
- custom clearance

The figure in this case is increasing and was doubled only during the 1990s.⁵ In that way, Kuehne Nagel, Caterpillar, TNT Contract Logistics, are very good international examples.

How to Outsource?

There are many strategies for contract manufacturing for

products, processes, and organizations. However, there are some basic elements that are present, regardless of the selected strategy. Figure 1 provides a summary of the main areas involved and the activities to be performed when selecting a CMO. The participants in the different areas can be either team members or have a type of technical advisory role. There is a tendency to increase the number of team members as a project develops, primarily based on the project complexity. This may cause the transfer of a project to be very difficult to handle.

The commercial departments may not be part of the transfer team or organization although their involvement is necessary. There are many commercial issues affecting a project, like packaging configuration or batch size changes, which in turn can affect shelf life, mainly in low volume products. Response time to peak demand periods also will have an important effect on the commercial areas. Commercial departments are key players since actions taken by the other functional areas are based on their input, needs, and long range forecasts. Without proper feedback, the technical areas might continue to work on a project without an updated perspective:

- what has been developed is no longer sufficient for the company's needs
- does not meet required standards
- the product is no longer of commercial interest

The financial analysis could be led by manufacturing or supply, but many organizations may prefer to have it as a separate group. Financial analysis determines whether the transference to a CMO is justified and it may be more convenient to have an independent member of the transfer team performing this task.

The basic process for implementation of a CMO consists of four principle activities, including:

1. Project definition
2. Collection of data
3. CMO/Process Selection
4. Generation of data

Project Definition

"A project is a sequence of unique, complex, and connected activities having one goal or purpose and that must be completed by a specific time, within budget, and according to specification," as defined by Robert K. Winsock in his book, *Effective Project Management*.⁶

In the case of the CMO, the purpose is to find the most suitable supplier for a specific service or product. Once cost calculations are involved, the specifications for the product and process must be clearly defined.

The Project Overview Statement will summarize the requirements, costs estimations, capital needs, risk, and gap analysis, timelines and milestones, resources allocations, etc. The signatures of the top management of the regulatory, QA, supply, manufacturing, and commercial areas of a com-

pany will reinforce the strategic plan described in the Project Overview Statement.

Table A summarizes some of the possibilities for defining an outsourcing project. Several reasons may combine to strengthen the rationale for implementing an outsourcing project. Tax and cost benefits, mergers and acquisitions, capital related matters, or regulatory issues are various significant factors. However, gaining flexibility and reducing time to market are increasingly key factors for implementing a CMO project.

Collect Data

This is the most critical activity to decide why, what, and when to outsource a product or process.

Data collection implies a significant effort for the entire organization in order to avoid unexpected omissions that could affect progress of the contract manufacturing project. Data collection provides the background for the data generation activities and for the filing process. Regulatory agencies, generally, require more and more data comparisons between the current and the new source to evaluate the impact on product.

All too often, the inadequate background information is handed over to the CMO, and the outsourcing company fails to provide a satisfactory product comparison.

The *ISPE Good Practice Guide: Technology Transfer*, provides valuable guidance for product or processes transfers applicable to contract manufacturing.⁷ Industrial manufacture is the transfer from an R&D area or from one industrial site to another. The Guide's fundamental goal "is to provide value added guidance to industry, which will facilitate timely and cost effective transfer of technology between two parties. Advice and guidance is provided which may be applied to analytical methods, APIs, and dosage forms, and takes ac-

Business Strategy	Operational	Finance	Regulatory
Not a Core Product	Plant Capacity Constraints	Cost Savings	Need to Separate Products
Niche Product	Reduce Time to Market	Avoid Capital Investments	Compliance Issues
Commercial Uncertainty	Packaging Design Issues	Tax/Duty Benefits	Other Regulatory Issues
Political Unrest	Production Technology not Available	Increase Capital Rentability	
Capital Rentability	Rationalization		
Mergers and Acquisitions	Lack of Expertise		
Worldwide Planning	Increase Production Flexibility		
Consolidation and Specialization			

Table A. Some factors to consider in the "make or buy" decision process.

Outsourcing and Contract Manufacturing

count of requirements in the US, Europe, and Asia.” The value of this Guide has been demonstrated in transfer projects within Latin America since many countries closely follow US or European regulations. The value of the Guide also is related to the need to speak a common language with a CMO, and even within an organization.

Regulatory and compliance evaluation should be one of the first steps. In addition, when the project also involves offshoring, the revision of the regulatory status of the receiving country should be evaluated.

As they will affect both the product owner and the CMO, one of the most challenging topics is the post marketing regulatory compliance issues. In the case of contract manufacturing compliance, managing the changes has the potential to increase risk for both organizations. The due diligence process should highlight the characteristics of a manufacturing organization, as well as the risks associated with its business environment. The quality agreement signed between both companies should highlight the need for the owner company to have access to all relevant data and systems. It should be emphasized that any change or issue within the CMO has the potential to impact in the product owner. The quality agreement should clearly identify the method by which both companies will handle product recalls, complaints, change control management, quality reviews, etc. Regardless of how many details are described in the Quality Agreement, the culture of an organization will make a difference when problems arise.

Stability issues and process statistics should be carefully evaluated to focus on potential production problems. In the case of offshoring, transportation times can have an impact on products with short expiration dates.

Collection of data is not only an in-house activity since it also affects the potential sourcing companies. The data collection should start as soon as possible in a selected CMO.

In FDA Guidance for Industry, Quality Systems Approach to Pharmaceutical cGMP Regulations, there is a section dedicated to make some short observations on outsourcing, Control Outsourced Operations, IV, B, 4. One very significant comment is that “Under a quality system, the manufacturer should ensure that a contract firm is qualified before signing a contract with that firm. The contract firm’s personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm’s and contracting manufacturer’s quality standards should not conflict. It is critical in a quality system to ensure that the management of the contractor be familiar with the specific requirements of the contract. However, under the cGMP requirements, the manufacturer’s QU is responsible for approving or rejecting products or services provided under a contract (§ 211.22(a)).” (QU stands for Quality Unit). It is clear from this recommendation that the quality systems for both organizations should be carefully reviewed and gaps and risks identified and ranked. This Guideline is only applicable – as a recommendation – for the US, but the statement on the evaluation of conflicting interests in the quality system is of universal

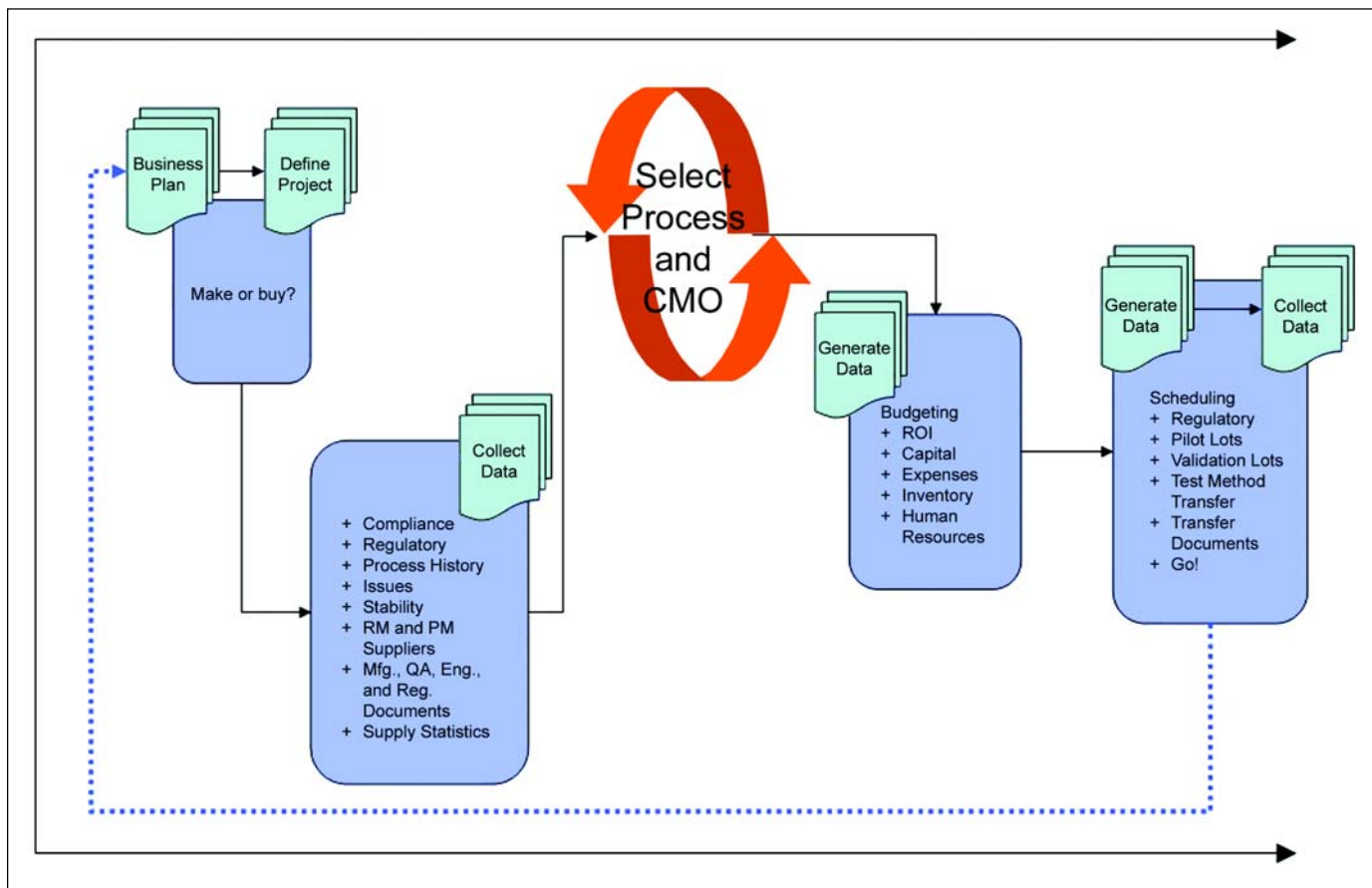


Figure 2. Scheme of the process flow for data generation and data collection pre and post CMO selection.

value. This is a point not easily resolved since it implies challenges for training when cultural or regulatory behavior is very distinct. Therefore, a basic recommendation is to consider the differences carefully in the risk assessment process.

Other documents of very high value to be used as reference are the guidance documents published by the FDA, like the SUPAC-MR: Modified Release Solid Oral Dosage Forms, which have the scope to provide “*recommendations to pharmaceutical sponsors of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Abbreviated Antibiotic Drug Applications (AADAs) who intend to change (1) the components or composition, (2) the site of manufacture, (3) the scale-up/scale-down of manufacture, and/or (4) the manufacturing (process and equipment) of a modified release solid oral dosage form during the post approval period.*”⁸ When multiple changes are required, which can happen easily in an outsourcing project, the document indicates that “*changes not addressed in this guidance, or for multiple changes submitted at one time or over a short period of time, sponsors should contact the appropriate CDER review division or consult other CDER guidance’s to obtain information about tests and application documentation.*” Similar documents exist for other pharmaceutical forms. Other countries also use SUPAC as guidance documents or similar types of recommendation papers with some variations. In the case of offshoring, where the sourcing country and receiving country follows different guidelines, this could be an added complication.

From the manufacturing, QA, analytical, and regulatory point of view, the following elements that are always present, materials, methods, machines, measures, environment, and equipment, are the key factors to consider in the review process.

Materials: materials of natural origin can have a wide variation in their specifications. The Pharmacopeia requirements are usually met for materials of different sources, but the issues are generally related to some physical properties, such as particle size, shape or bulk density; therefore, data should be generated to highlight the differences and estimate the dissimilarity for chemical or physical properties.

Method of manufacture: the selected manufacturing method will be used to generate pilot lots, stability lots, and the technical knowledge and expertise in the CMO. The SUPAC guidelines, mentioned above, help to provide strong support for the selected strategy.

Measurements and analytical techniques: analytical equipment or methodology can be an endless source of conflict. Very small differences can generate large differences in the results and be the cause of delays and conflicts. The test method transfer process starts with the data collection, to review and compare equipment, methodologies, and training, in preparation for the moment of data generation when

the transfer is actually performed. The sending laboratory should provide the experience and analytical know-how to ensure regulatory compliance.

Machines and equipment: the SUPAC guidelines are again a very good reference to be used for the comparison work. Many countries, such as Brazil and Mexico, are developing similar types of guidelines. Both companies should establish the strategy to evaluate any potential difference within written guidelines, since regulatory requirements could have a detrimental impact on the project cost.

Environment: the environment can have a decisive influence, mainly in the case of offshoring. As an example of the influence of the environment in the regulatory strategy, it is interesting to note that there are some regulatory agencies located in tropical areas that could accept previously generated stability data from zone IV areas, but they would ask to repeat the studies if the data was generated in zone II areas.

People: cultural, language, training, experience, and motivation differences are important factors to be considered in an outsourcing project.

Figure 2 attempts to summarize all the activities for data collection and data generation.

Select the Process and the CMO

Once the data has been collected in the manufacturing company and in the CMO, there should be a continuous flow of more data and information to gain a deep understanding of the pros and cons of each explored alternative until a final decision is made and a CMO is selected.

In this selection, the process itself is selected. It may be desirable to change the technology, e.g., the current technology is old and less cost effective. Filing and bioequivalence requirements may prevent the desired change, but the alternative should still be considered. Packaging configuration poses an extra challenge due to the differences in the commercial chain (blisters or bottles). In global sourcing, the CMO should be able to fill and package the products according to the requirements of different customers.

Risk Analysis

Risk analysis is a specific activity that it is present both during data collection and also during data generation activities. ICH Q9 provides, in Annex II, a complete list of activities and issues to consider during the risk evaluation such as: documentation, training and education, design and facilities, flow of material, and personnel. Carney has pointed out that “*there is an expectation that a pharmaceutical company will proactively and systematically identify risks that might negate some deliverable quality attribute of a product and have a program in place to prevent or minimize these identified risks.*”⁹

Outsourcing involves the usual risks of any product trans-

fer project, plus the risks of doing the work through a vendor. The company risk analysis, generally, considers what happens within its organizational boundaries and investigates possible sources of risk in the CMO with the help of auditing and reviewing tools. However, some risks could be completely unknown for activities performed outside the company. Similarly, the CMO should perform the corresponding risk analysis for the impact of the new process or product inside its operation.

The risk description for a regular transfer could be the shift to a new technology, the safety risks in the new areas, the supply delays as the project moves forward, or inadequate yields, etc. The additional risk of an outsourcing project is related to infrastructure and project management skills in the CMO, but also it should consider some issues in the organization like risk of service level reduction, lack of cultural fit, loss of technological connections. In the case of offshoring, the risk analysis should include additional subjects, such as:

- geopolitical stability
- risk of being subject to different laws in another jurisdiction
- language skills
- work culture
- union issues

In the case study, described under “The Value of the Right CMO,” the serious issues that arose as a consequence of improper vendor selections are detailed, as well as the solution with the switch to a convenient contract manufacturing organization where the cultural model was in agreement with that of the owner company.

Generation of Data

When the CMO has been selected, a program of activities is detailed, and the above mentioned *ISPE Good Practice Guide: Technology Transfer* can be used as an example for the information required to prepare for manufacture. The outsourcing company, when located offshore, should be prepared to handle differences that arise in the regulatory requirements of the receiving country.

The project could involve the manufacture of pilot lots, feasibility studies, stability, and bioequivalence studies, API impurity profiles in the case of source change for an API, and thorough evaluation of the manufacturing differences between the original and new source since this difference will be challenged by many regulatory agencies. Transportation studies, and the evaluation of any difference in the temperature profile during transportation, should be addressed and evaluated. The final runs will be the validation lots that, upon approval, will be put into the market.

The Value of the Right CMO - a Case Study

A European company with sales offices in one Latin American country decided to move all the production located in that country from different manufacturing contract organizations

to a single organization because of compliance issues.

The “owner” company did not have local technical support to help with the process and neither did headquarters since the formulations were developed several years ago for the specific needs of that affiliate. The formulations were developed in headquarters.

The “new” CMO was requested to handle the transfer, as well as the technical work to bring products under compliance. The products were several uncoated and film coated tablets.

The review of the available documentation by the “new” CMO showed lack of compliance between the manufacturing, QA, and regulatory documents. Reasons for changes were not available and the change control system in the different companies involved in this transfer was very poor. The evaluation of the lack of compliance made clear that several minor differences were introduced throughout the years in the processes, in the formulations, and in the analytical methods, without proper supporting data or filing updates. Fortunately, the original documents were available as a reference source.

The revision also indicated that the filings were in agreement with the original documents. The differences in the analytical methods were minor and could easily be resolved. There were clearly two possibilities:

1. to build adequate data with the current manufactured formulations
2. to go back to the original products since there was no strong evidence to support the changes

In the first case, the products did not reflect the filed formulation and processes although again it should be stressed that the differences were minor. In the second case, the formulations could be immediately brought under compliance, but the risk could be an unexpected manufacturing failure.

The “owner” and the “new” CMO decided to start the work with the evaluation of the original filed formulations, as the risk analysis pointed out strong evidence in favor of this solution. The main factor was that the original documentation developed at headquarters was clear and adequately supported the formulations, while there was no reason to trust the documents presented by the CMO, which initiated the changes.

It is probably that bad management, inadequate training, and lack of investments were the main reasons to explain the changes. One of the most common differences found was the screen size change for the milling operation: the correct size had been replaced for a closely related screen to avoid expenses.

One pilot lot of each formulation was manufactured and stress stability studies were performed for a short period of time to identify potential failures. The results confirmed the results already filed, thus supporting the alternative selected.

The analytical method validations were updated by the “new” CMO, given that there were analytical equipment

differences and there was no possibility of doing a satisfactory Test Method Transfer with the several former CMOs.

The next step was the manufacture of the engineering runs and the validation lots, which was performed satisfactorily.

The compliance issue was mostly an internal issue since the regulatory requirements did not request so many details of the manufacturing or analytical methods. The “owner” company also was concerned by the lack of a controlled situation and any potential regulatory or manufacturing implication in the future.

This example from real life is not an uncommon situation and emphatically stresses the need of a very good process of selection of a CMO for pharmaceutical products. In this particular case, the “new” CMO took the ownership of the whole project, but it should be noted that the headquarters for both companies, the “owner” and the “new” CMO, belonged to the same European country and they were able to understand each other fairly easily.

Conclusion

The outsourcing activity is a challenging and exciting opportunity to improve the way of doing things for pharmaceutical companies. The economic figures involved in the outsourcing trade have continuously increased during the last few years and the forecasts are more than promising.

The key factors for success are to establish the outsourcing activity as a permanent strategic tool to develop “inbound” confidence in it, to generate a clear and complete Project Overview Statement, and to develop close partnership with the outsourcing company.

Many years ago, it was unthinkable that some activities could be handled outside the manufacturing company, while today there are some companies that outsource all their manufacturing activities. This change in the manufacturing paradigm is giving a strong signal to the market and that market should be listening in order to profit from it.

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