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DETECTING THE COST OF POOR QUALITY: CONTRACT MANUFACTURING BEST PRACTICES

In this article, Leigh Toole, Director, Quality Assurance, The Tech Group (West Pharmaceutical Services), provides some useful advice on how to assess and evaluate key aspects of a potential contract manufacturer partner in order to avoid pitfalls and to ensure the most fruitful relationship for both parties.

Medical device or combination product contract manufacturers are engaged by pharmaceutical companies to deliver safe and effective products. Selecting the right contract manufacturer (CM) can help to ensure a drug product's ultimate success, so several factors must be considered before entering a contractual partnership. By defining specific requirements that a contract manufacturer must have, pharmaceutical companies can narrow the options that ultimately lead to the best choice to ensure a rewarding partnership.

The first step when selecting a contract manufacturer is to perform a comparative analysis of the various CM options. Such an analysis can be completed quickly with minimal expense, and will narrow the list considerably. Additionally, prior to entering into a contractual partnership, site audits must be conducted to further compare the CM's ability to meet specific needs. Site audits can prevent a selection that might result in the high costs associated with poor quality.

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In order to avoid pitfalls and make a data-driven decision when comparing CMs, pharmaceutical companies should evaluate the following key aspects that, when used in conjunction with a comparative analysis and site visit, will identify the potential risks associated with outsourced manufacturing:

- Quality Management System
- Risk management
- Manufacturing capability
- Design control system
- Root cause analysis
- Quality agreement.

QUALITY MANAGEMENT SYSTEM

Performing an audit of a potential CM's Quality Management System (QMS) can establish the firm as an approved, certified or qualified supplier. To start, request a copy of the organisation's quality manual in preparation for a potential audit. Use comparative analysis as a filtering tool to compare the quality manuals of three to six potential CMs. Differences will surface during this exercise, and some firms may deny the request, which may be indicative of the transparency (or lack thereof) to be expected if the relationship moves forward. Comparing quality manuals from multiple firms can identify differences and determine how the CM will meet the predetermined requirements.

Mr Leigh Toole
Director, Quality Assurance
T: +1 480 281 4553
E:leigh.toole@westpharma.com

The Tech Group
14677 N. 74th St.
Scottsdale
AZ 85260
United States

www.westpharma.com/en/techgroup

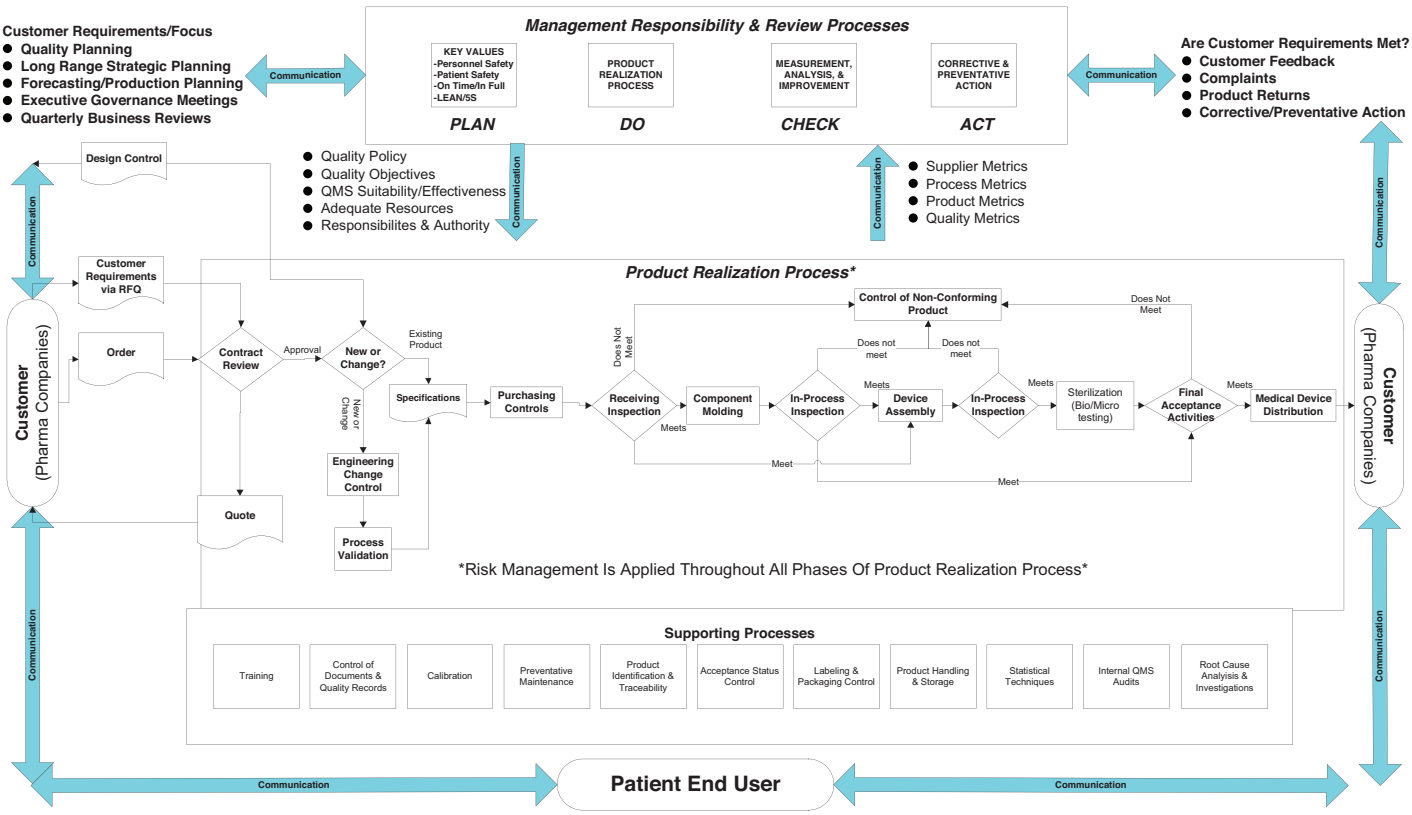

Figure 1: Quality Management System flowchart.

During a QMS evaluation and comparison, focus on how the CM has elected to meet the ISO 13485 requirement established in section 4.1 (a) to "identify the processes needed for the quality management system and their application throughout the organisation", and section 4.1 (b) which requires the CM to "determine the sequence and interaction of these processes". Many firms have failed to define key processes, let alone the sequence, interaction and associated control strategy for these processes. When a firm attempts to meet this QMS requirement, it is typically expressed as a diagram referred to as the "model of a process-based quality management system" with graphic representation of Plan-Do-Check-Act methodology. Although not the intent of the guidance, the example from the standard is often copied into a quality manual. Comparative analysis can determine if the requirement has been missed or if the firm has invested the time required to define key processes, sequence and interaction, and the control strategy associated with these processes (see Figure 1). This requirement has implications on the quality culture of the organisation and the strength of its management team.

Review the quality policy and quality objectives with the management team. Ensure there is documented, objective evidence that all employees have been trained to the quality policy and objectives. Evidence of training does not necessarily translate to training effectiveness. Ask the management team to demonstrate that the quality policy and objectives are understood and have been implemented throughout the organisation. An all-employee survey that includes a written response where employees describe what the quality policy and objectives means is an effective tool to ensure that the principles have been internalised. Reviewing the strength of the QMS can be an early indicator of things to come. Pharmaceutical companies should look for a CM whose approach aligns with its own QMS.

RISK MANAGEMENT

Evaluate the strength of the CM's risk management program. In ISO 13485 section 7.1 (d) the requirement states that "the organisation shall establish documented requirements for risk management throughout product realisation". This section also indicates "ISO 14971 [for] guidance related to risk management". It is not uncommon for an organisation to struggle with compliance to these requirements, and it can be a challenge to establish rules regarding when to use a particular risk management tool. Questions to ask include: When should a preliminary hazard analysis be performed? When should a design Failure Mode and Effects Analysis be generated? What are the rules of engagement for risk priority numbers (RPN) in terms of when risk mitigation activity is appropriate?

Since one entity may be more risk tolerant than another, it can be difficult to align the risk management approaches of two companies. If the potential CM's comfort level of residual risk varies greatly, they may be more accepting and comfortable with higher RPN outcomes than the pharmaceu-

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tical company's system allows without the need for mitigation, reduction or the elimination of the source(s) of the risk.

When reviewing the strength of a risk management programme, evaluate how the firm has applied risk management into some of the key QMS elements: internal audits, nonconforming product, complaints, corrective and preventive action (CAPA) and change management. Evaluate whether the firm applies a risk assessment that provides a documented evaluation based on frequency and severity that establishes a documented, defendable rationale regarding when issues will be investigated and when issues will be escalated to the CAPA system. When seeking a medical device contract manufacturer, look for evidence of the best practices described above as another early indicator of future success. Upon reviewing these policies, determine if the CM has the freedom to operate with little to no intervention. Recognise that shortcomings in this area will translate to greater oversight along with a secondary review and approval of the issues if a partnership were entered into with this entity.

MANUFACTURING CAPABILITY

Quite often, medical device or combination product CMs are sought based on technical fit/manufacturing capability core competency. When using comparative analysis to evaluate manufacturing capability, evaluate the answers to the following questions to help reduce risk:

- Is this particular product need a core competency or is the technology associated with product realisation a stretch for this potential CM?
- Has the CM produced product with similar features and characteristics?
- Does the CM's technical staff possess the education, background, training and experience to be successful with this endeavour?
- Does the facility and infrastructure align with the overall contamination control strategy for the product?
- Does the CM have a history of successfully producing the projected volumes?
- Does the CM have a robust equipment calibration, qualification, process validation, preventive maintenance and statistical process control system in place?
- Does the CM have the ability to perform manual, semi-automated and/or fully automated assembly; final acceptance activities; final packaging, drug handling and labelling?

Most often, past performance is a predictor of future performance and dealing with a company that has a history of high costs associated with poor quality is not a decision that should be taken lightly.

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DESIGN CONTROL SYSTEM

A potential CM must be evaluated on the strength of its design control system. Has the firm established and does it maintain a compliant design control system that could be leveraged in an effort to design and develop components, sub-assemblies, medical devices, pharmaceutical primary packaging components, combination product constituents and combination products? If a design control system has been established, does the system end with product launch or does it include post-market surveillance activities designed to provide input to management review to drive continuous improvement as the product and process is "monitored and measured" in accordance with section 8.2.3 and 8.2.4 of ISO 13485?

ROOT CAUSE ANALYSIS

Any organisation can appear to be in a state of control for a period of time, but the true measure of control associated with sustaining manufacturing is long-term supply "on time, in full" and "right the first time" without disruption. When problems arise, how will the organisation respond? How has it responded previously? Problems offer an opportunity to demonstrate the organisation's ability to deploy root-cause analysis tools established for such an occasion.

An effective CM will deploy resources based on risk derived from a risk assessment that defines the frequency and severity associated with a given issue. Although an investigation can be performed at any time per The Tech Group's QMS, Level 1 (low occurrence, low risk) issues per procedure do not require investigation. Level 2 issues require a documented justification if an investigation is not performed. Level 3 (high occurrence, high risk) issues require investigation and a documented justification if the issue is not escalated into the corrective and preventative action (CAPA) system. These principles and methodologies, along with a robust investigation process that combines proven quality tools, enable a CM to be compliant while at the same time drive efficiency while applying risk management throughout all-product realisation.

When evaluating a potential CM, spend adequate time in the critical quality systems to determine the strengths or weaknesses associated with the firm's ability to: recognise a problem; quickly and methodically determine the root cause; effectively contain the problem; apply corrections; and issue corrective and preventive actions that drive significant sustainable continuous improvement.

QUALITY AGREEMENT

A robust quality agreement must include guidance and rules of engagement associated with the critical quality systems. The quality agreement must define specific roles and responsibilities of each organisation and identify shared responsibilities.

Finally, the quality agreement must define formal governance expectations for the working team, the management team and management with executive responsibility. These keys will drive continuous improvements and accountability to a predetermined and agreed-upon scorecard that measures the success of the partnership.

Using the keys described above along with comparative analysis will greatly affect the CM selection process by uncovering issues prior to entering a contractual partnership. It is important to know specifically what constitutes a great fit in a strategic contract manufacturing partnership. CM's are not "one size fits all" and pharmaceutical manufacturers must invest adequate time in the selection process. By doing so, the reward is an exponential return on the initial investment that will lead to the long-term successes associated with a highly effective collaborative team.

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