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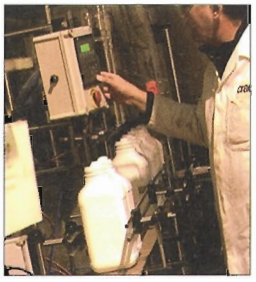

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Managing risk in pharmaceuti

Paul Woitach, managing partner of **Pharmaceutical Advisors**, offers a set of tools to help manage risk and improve lead-times in pharmaceutical outsourcing

Despite its scientific sophistication, the pharmaceuticals industry lags behind other industries in the maturity of its outsourcing practices. Several factors make pharmaceutical outsourcing more challenging than other industries. These include the regulations governing manufacture and approval, the capabilities and culture required to operate under cGMP, development timelines and product attrition.

In addition, the reliance on Small Pharma to be the industry pipeline means that development is often carried out in an outsourced environment, with limited resources and potentially limited perspective to anticipate, plan and manage effectively. The industry's failure to integrate the various aspects of R&D is well known and magnifies the challenge of successful outsourcing.

Companies small and large benefit from the structured frameworks used in other industries to manage risk and improve lead-times in working through CMOs.

To some, such 'frameworks' imply the bureaucracy that pharma companies of all sizes seek to avoid. Yet some structure is essential, given the complexity of pharmaceutical development, in order to maintain leverage, be flexible, agile and effective. It also helps sponsor companies to be better customers, which helps vendors to reduce cost and time, with better outcomes.

The framework for managing risk in outsourcing (Figure 1) is simple and involves understanding your true requirements, having a structured selection process and proactive execution. Whilst many of these principles seem obvious, the nature of the industry causes them to become 'lost in the cracks' between the functional worlds of medicinal chemists, process chemists, chemical engineers and the rest of the organisation that is focused on other sexier R&D activities like demonstrating efficacy. Hence we start with earth, wind and fire.

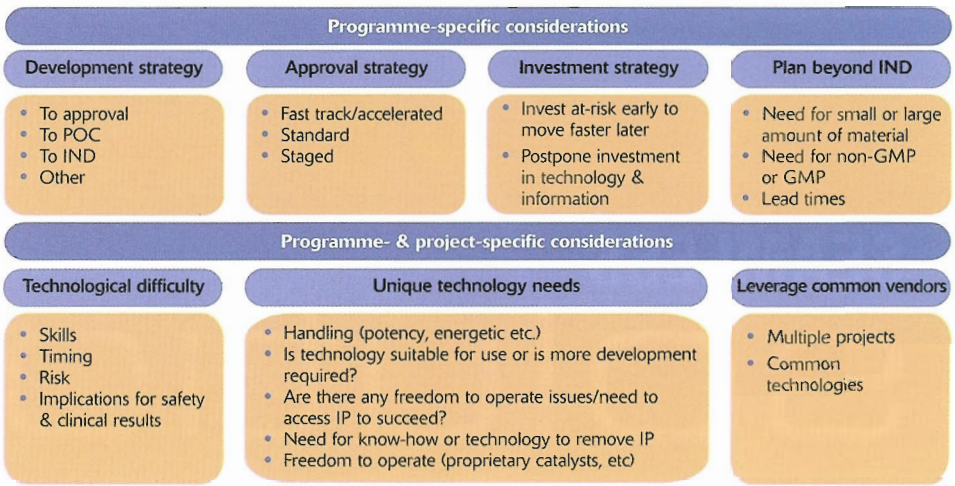

Figure 2 - Programme-specific considerations

Understanding your requirements

What does strategy have to do with a CMO making APIs? Sadly, many companies outsource with largely technical requirements in mind, considering only one of the three outputs of pharmaceutical outsourcing. These three are **material, technology** and **registration-enabling information**.

1. Understanding all your requirements

a. Strategic content
   i. Link to company strategy
   ii. Management support & awareness
   iii. Realistic expectations & appropriate internal resourcing

b. Integrated planning
   i. Integrated development plans
   ii. The right inputs to sourcing decisions

2. Selection

a. Well-planned sourcing & selection process
   i. Understanding of potential risks in a CMO relationship & strategies & tactics to mitigate these risks prospectively
   ii. Diligent CMO assessment & selection
   iii. Contract structure & negotiation which balances the rewards & leverage

3. Execution

a. Programme & relationship management
   i. Planning & maintenance of detailed project plans
   ii. Proactive & relentless relationship management
   iii. 'Partner-like' goodwill, mutual respect & professional interaction

Figure 1 - Framework for proactive management of outsourcing risk & timelines

Despite the appearance of being technically straightforward, an outsourcing programme often benefits from considering such diverse items as the final dosage form, any anticipated synthetic or formulation changes, the interim and preferred synthesis technology and drug product formulation, the expected need and timing for process development and optimisation, the required analytical technology, process safety and reaction engineering, cGMP needs and timing, the impact of changes on bioavailability or toxicology, the trade-off between speed and process learning, document and information needs and the ability to manage vendors and distance.

Many of these factors are not clear at the time that outsourcing decisions must be made and it does not make sense to invest to make them so. Understanding the implications of the alternatives, however, can fundamentally change the structure of an outsourcing business relationship.

But this is all tactical. Where is the link to strategy? Is it really needed? Often, outsourcing is planned with only project inputs being considered. Project requirements are the details of a project scope. Programme requirements, on the other hand, are applicable to all of the projects supporting a sponsor's given programme.

Corporate requirements affect all programmes. You may not be able to influence them but you need to know what they are. The broader programme or corporate considerations with significant implications are outlined in Figure 2. Depending on the combination of choices that apply, these can result in very different structure of the technical or business aspects of an outsourcing programme.

Where the strategy is to develop proof of concept, the sponsor is driven to make material to 'get into man'. The implications for outsourcing are that sponsors will typically have less concern over restarts, delay spending on process optimisation and scale-up tasks

al outsourcing

or formulation development, minimise their spend on analytical method validation and design stability programmes to allow discontinuation and cost recovery if clinical results are unfavourable.

On the other hand, if the strategy is to develop to commercial launch, the sponsor works to 'deliver the first pill sold', recognising the risk of clinical failure at any key investment decision point. The sponsor will typically try to minimise restarts and will be more willing to incur process development and validation costs earlier if these efforts reduce risk in the long term.

Sponsors may choose to accelerate scale-up and move to a commercial CMO earlier, if efficacy risks are overcome. In both cases, the basic goal of making material is the same, but the requirements, scope of work and list of possible vendors might be quite different.

Integrated planning across functions such as drug substance (DS)/API and drug product (DP)/dosage form is critical but is often ignored, because of the serial nature of the need for each in the clinic (the DS first for toxicology, then the DP for tests in man). Unfortunately, this view ignores the many interrelationships that need to be considered to make things happen in the right order, as shown in Figure 3.

The issue is best described by the paradox between DS and DP development. The DP cannot be finalised if the DS form is not finalised but the DS form cannot be finalised until the DP requirements are understood.

If the DP vendor is conducting salt selection work, the DS vendor then depends on the DP vendor to begin production! Timing for the finalisation of the DS form and the final DP must be linked and planned backwards and forwards, yet often these outsourcings are run separately and by separate people.

Sourcing & selection

Successful outsourcers define project-specific requirements in the context of programme and corporate requirements. Once project specific requirements are defined, the criteria for CMO selection can be established. Companies can conduct a business assessment screen first before investing in technical discussions.

A list of high-level CMO selection criteria includes both business and technical considerations. The former include the candidate's business strategy and strength, its financial health and stability, any conflicts of interest and its response to a RFP - including the attitude of the legal department and its negotiating style.

Technical considerations range from capacity and scale to overcall capability, a project-specific technical assessment, quality, experience, proprietary technology and tech transfer, regulatory history, location, cost and others. Each factor should be considered with project-appropriate weighting, because their relative importance can vary from one project to another. Figure 4 shows the detailed elements of the sourcing and selection process.

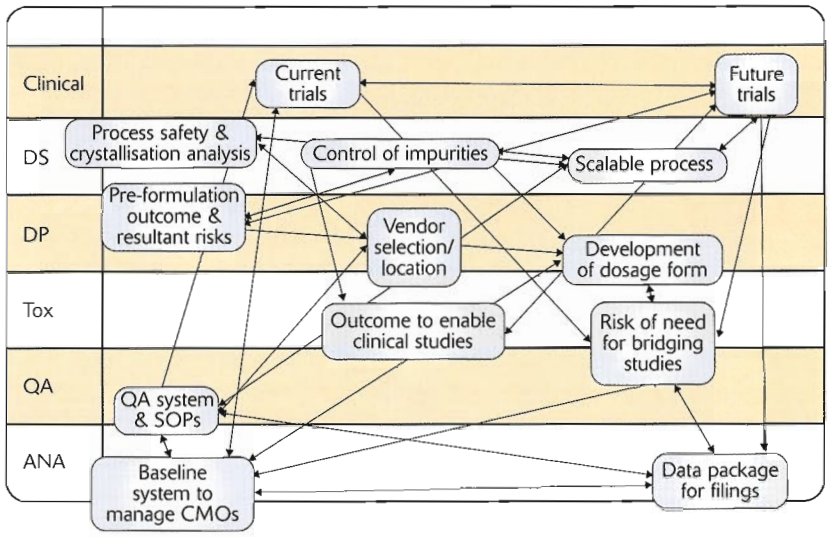

Figure 3 - Interrelationships over time in pharmaceutical development

In selecting and executing, successful outsourcers understand that sponsor and vendor share the responsibility for success. Vendors need to understand the required scope and assess *their* risk.

If they are uncomfortable with the perceived risk, they will insert 'go/no-go' steps. They also need well defined technical and business scope. Hastily written technical information packages ultimately cost sponsors money and time, and can reduce their vendor choices in the future.

In screening companies, a common pitfall that we have observed occurs where sponsors fail to put vendor capabilities in the broader context. Yes, the vendor can scale up on time but...will the way they scale up be easily transferable to another facility, or are they best at scaling up for their equipment or favouring the use of their technology?

To what stage can the CMO support your needs and should you care? What are the other future tech transfer implications for you, or your future partner? Fewer tech transfers can be better, but a transfer within the same company to a different facility is still a tech transfer.

The best vendors rarely have much flexibility. Before you put timelines in front of vendors, build in time for CMO selection, scheduling lead times for when problems occur and iterations for to-be-demonstrated technology. The only certainty is that things will go wrong. Successful companies understand where there is leverage and where a CMO's situation can affect them. To do that, sponsors need to consider their future development plans.

Contract structure & negotiation

The contract structure can be a critical determinant of the balance of leverage with a CMO. Negotiation is relationship management, not just a formality. The behaviour demonstrated during negotiation of challenging issues is a good indication of how the other party will behave when things go wrong.

Successful negotiation often depends on a clear understanding of each organisation's situation and needs, shared objectives and consistent messages from one organisation to the other across all points of contact. Goodwill and trust are critical to productivity in inter-organisational relationships. Contentious negotiations not contained by either party can impact the project team members' perceptions of the other party going forward.

Contract structure becomes a common source of conflict and delay as the project progresses where sponsors failed to anticipate future needs. A frequent example of this is where contracts established to support early development and supply cover activities through to the delivery of the first GMP lot(s), yet fail to address future clinical supply cost.

Contract manufacturing is a very challenging and often lumpy business, so sponsors should expect CMOs to seek short-run profit maximisation. Future issues can be avoided if the sponsor proactively anticipates its needs and builds them into contractual terms, for example:

- The rights to process and analytical methods and technology
- Provision for future supply and/or additional projects
- The separation of development from commercial contracts to simplify earlier contracts
- Pricing incentives for the achievement of higher yields and, in turn, lower unit pricing
- The right to all IP and know-how required to produce the product
- The right to transfer the production technology to other sites for manufacture
- Payment obligations triggered by the acceptance of deliverables (reports, QA release, etc.)
- Fixed pricing on each segment of the project as its scope becomes well defined (i.e. both parties are motivated to complete the work in a timely fashion)

- Terms which delineate the obligations of the parties in communication and interactions, including arbitration

Quality agreement

The quality agreement describes certain roles and responsibilities of the sponsor and the CMO, typically covering the right to audit, product release, change control, other notifications and interactions, investigations, etc.

Successful companies approach quality agreements in a phase-appropriate fashion, considering that CMOs have many clients. They recognise that, regardless of the phase, inadequate attention to detail can transfer risk to the sponsor in situations where the CMO is still within its rights.

Examples we have seen of inadequate specificity include the CMO changing raw material suppliers, changing the impurity profile, unclear timing of investigations resulting in a fix costing €530,000, changes to metabolic conditions and raw materials, altering a fermentation and inadequate documentation to support filings, resulting in re-work.

In each case, the CMO was operating within its agreement. Lack of site- and product-specific post-run data checklists often results in sponsors not getting the data they need, increased cost and delay of back and forth to get it right. Indeed not knowing where you need to be specific can result in big costs later.

Managing costs & timing

The risk of surprise should decrease as a project progresses. Hence, successful companies set a step beyond which cost increases cannot be passed on, except for unforeseen and unavoidable technical issues. To manage this it is important to be specific about the scope change order process to then make sure that you are not paying for avoidable errors or for deviation investigation and reports.

On-time can be far more important than speed. Successful companies sometimes employ concessions or incentives for on-time delivery. Pay for early delivery only if you realise a benefit. The opportunity cost of capacity is high for busy vendors. Successful companies insert provisions to avoid learning that they have been bumped in exchange for 'best efforts' to catch up in a later slot and without penalty.

At the same time, sponsors should expect that CMOs will seek to reduce their risk in the event of non-delivery and also reduce their risk in the event of sponsor cancellation. Penalty fees on both sides are common.

Best practice, however, is to avoid forcing a CMO to pay fees and to identify a win-win which can gain back time. If something fails, it is usually faster to recoup at a contractor than to start over with someone else.

Managing execution & the relationship

Sponsors who have been successful in managing and executing apply specificity with realistic expectations, adequate internal resources, proactive management and metrics and a sound quality agreement. They also do not expect that CMOs will be critical and help them avoid mistakes.

CMOs are service businesses that focus on doing what customers ask. How many vendors want to build a reputation for showing up their clients? Will they stop you from making process changes that affect impurity profiles?

I.	Outsourcing strategy
•	Corporate requirements
•	Programme requirements
II.	Integrated development planning
•	Clinical
•	Drug substance
•	Drug product
•	Drug safety
III.	Programme requirements
•	Development considerations
•	Clinical considerations
•	Commercial considerations
•	Regulatory & filing strategy
IV.	Project requirements
•	Confirm understanding of requirements
•	Establish selection criteria
V.	Vendor identification
•	Long list
•	Pre-screen/initial screen – paper screen
VI.	Initial screening
•	Short list 4-10
•	Request for information on capability areas of interest
•	Phone screen 4-10
VII.	Request for proposal (RFP)
•	Candidates for RFP
•	Finalise RFP
•	Send out RFP
VIII.	Selection & screen
•	Execute CDA
•	Issue RFP & QA draft
•	Share desired terms & conditions and QA or critical quality issues list
•	Assemble & analyse responses
•	Phone interviews
•	Summarise ratings against criteria
•	Narrow down to top 2-3 potential suppliers
IX.	Final selection
•	Remote/paper quality audit
•	Initial site/technical visit
•	Detailed business evaluation
•	Tech transfer package
•	Criteria for quality audit
•	Preliminary negotiation
X.	Final negotiations & initial contracting
•	Contingency plans
•	Identify potential issues related to quality agreement
•	Finalise workscope document
•	Finalise price
•	Confirm and get to know project team
•	Full QA audit & QA sign-off
•	QA sign-off
•	PO/final sign-off
XI.	Kick-off/Initiate tech transfer

Figure 4 - Sourcing & selection process

Adequate internal resources facilitate better planning and executing, thus facilitating more on-site involvement early in the relationship. The more time on-site up front, the less time fixing things later.

Sponsors should not make assumptions about the CMO's motivation to deliver. The key issue is when things go wrong, will you get all that is required to meet your timeline? Successful companies realise that they are one of many clients and strive to understand how their demands change as *they* progress, consider the impact on the vendor and strive to be a good client.

CMOs do not have unlimited surge capacity and their ability to add FTEs is limited. Sponsors with problems often assume that raw materials will be available when required, that there will be no significant technological hurdles or unplanned experimental failures, that CMOs have resources, capacity and schedule availability to meet all needs exactly when required.

One of the largest bottlenecks in working with CMOs is caused by sponsors underestimating the analytical rigour required to complete an NDA or other filing. Successful sponsors consider the relevant issues related to these factors even when planning early stage supplies. As things change, they make new expectations clear and 'inspect what they expect'. In doing so, they keep metrics simple.

Summary

Our experience is that the successful outsourcing programmes in both large and virtual companies are built on a simple framework This framework allows them to understand all their relevant requirement by first understanding which are, in fact relevant. They do that by putting things in the context of company strategies and functionally integrated drug development plans.

They then execute a well thought out sourcing and selection process that considers risks and the balance between CMOs and sponsors. That positions them to execute the programme effectively and proactively and manage the relationship with the CMO relentlessly for mutual success.

They recognise that risks need to be anticipated to be mitigated, strive to know what they do not know by tapping functional groups or the right consulting teams that help them to do that. They move forward with realistic expectations and appropriate internal resources. They recognise that their CMO is not a 'partner' but exercises 'partner-like' goodwill, mutual respect and professional interaction.

Ultimately, the ability to manage risk and improve lead-times in working through CMOs can be accomplished by sponsor companies of any size with the discipline of the right framework and appropriate internal and expert resources and execution.

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