Don't Outsource Your Outsourcing

Advice for CEOs & senior management

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IF YOU ARE LIKE MOST OF MY CEO/senior management colleagues in small or emerging life sciences companies, every day is one where financing the company is on the agenda. Efficacy dominates the discussion, and so that aspect of development rightfully receives a significant portion of management's attention. Outsourcing has been seen as a solution to some organizational needs, but as the supply of outsourcing capability has expanded and matured, many managers have been lulled into a false belief that outsourcing has become easier and more straightforward. Chemical Manufacturing and Control (CMC) issues are increasingly driving development timelines. The interrelation of key drivers—increased potency, complexity of compound synthesis, proliferation of controlled release dosage forms, focus on safety, and the increased number of available contractors from all the corners of the earth—is actually making managing outsourcing more challenging in many ways.

Many of my senior manager colleagues do not think about these factors and, unfortunately, many fail to think about Drug Substance (DS) or Active Pharmaceutical Ingredient (API), Drug Product (DP), Safety and ADME and Clinical development concurrently. They prefer to stage things in line with the company's ability to pay for it OR the timing by which the output of those development streams are needed. While they correctly see these development streams as often having different vendor types, coordinated by different individuals within their organizations, these streams are in fact tied together early in the process in critical ways. Companies that do not consider all four in parallel when beginning any one of them face a significant chance of catastrophic delay or disruption in their clinical development programs.

The objective of this article is to provide insights for senior managers who are planning on outsourcing but have not run an entire development program with a significant reliance on outsourced work in the past. This area has become too critical for someone to learn "on the job." Though a combination of real-life "Don't Let this Happen to You" examples, along with some practical tips and checklists, the reader will hopefully be able to avoid ending up on the Darwin Awards List for Drug Development.

Outsourcing entire work steams like Chemical Development or Formulation Development is the best choice for many companies, but it requires resources and expertise with experience in running individual programs and running overall development in an outsourced environment. It also requires technically experienced staff in vendor management and contracting to truly anticipate and manage the leverage points and incentives in the relationship that can make or break timelines and budgets.

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"We hired a CMC person from XYZ Pharma and we're all going to be OK when we get to that. . ."

"We don't need to worry about what's needed to scale it up to commercial because we'll be licensing this out anyway. Our partner will handle that. . ."

"We don't need to think about investing in formulation work now; we know what we're going into man with. . ."

"They are going to give us GLP material, it will be fine for now. . ."

"We want GMP material with all the analytical data for our filing – we know someone who will be writing that CMC section for us. . ."

"We're waiting until we get some efficacy data before ramping up that investment. . ."

If you firmly believe ANY of the above statements, you will likely recognize a tangible benefit by reading further. If you quickly begin bashing your forehead on the desk when you read those statements, you are ahead of the game and this article may add some insights to your own expertise to help friends, colleagues, CEOs and boards avoid common pitfalls that can result in significant cost or time lost.

In addition, this article is written with the understanding that the challenge of managing cash burn and moving forward is a huge one and that everyone would do everything earlier *if they could* but that's just not the reality of drug development in any sized company today. PLANNING, however, is not costly and helps you better decide when to accelerate or reduce investment while managing development risk. Re-work and scope expansion are two of the biggest cost drivers and "timeline-busters" in outsourcing and, armed with that knowledge, the informed leader can better navigate through the challenging waters.

There are five key Concepts to keep in mind to help avoid the "I outsourced my outsourcing" trap.

1. Plan Backwards from commercial Launch – even if you intend to license out
2. Take an Integrated View Early across DS, DP, Safety, ADME and Clinical
3. Always Think Tech Transfer and Quality Agreements
4. Empower the vendor and your team by Structuring and Managing the Ongoing Relationship
5. Have Enough of the Key Outsourcing Management Skills in house

Plan Backwards from Commercial Launch

In making the decision to move a compound into development, all of the following are typically considered by the management team:

- Biological Profile
- Market Positioning and Rationale
- Competitive Situation
- Pharmacokinetics/Pharmacodynamic Summary and Issues ADME)
- Safety Information and Issues
- Physiochemical Differences
- Drug Substance Technology and Issues
- Physical Pharmacy and Dosage Form Issues
- Bulk Supply Status and Issues
- Intellectual Property Status and Issues

As your team plans outsourcing strategies and builds relationships, they will need to anticipate needs such as development of DS Technology and Manufacturing, Analytical Technology and Testing and, at the appropriate time, aligning Sourcing Strategies with Commercial Manufacturing Strategies

For DS, that means considering short-term and long-term issues relative to

- Final Form
- Synthesis Technology - Interim and Preferred Bond-Forming Route
- Analytical Technology
- Process Development and Optimization
- Process Safety and Reaction Engineering
- cGMP Manufacturing
- QA/QC
- Documents - Regulatory, Technology Transfer
- Sourcing Strategies

For DP, that means considering

- Preferred Salt, polymorph, solvate, including what and when
- Dosage Form Demands / requirements of DS
- Demonstration of Manufacturability including robustness/Scalability of Process
- Reproducibility for Bulk Form and Quality

It also means thinking about Analytical Technology for both DS and DP for

- Raw Materials
- Intermediates and In-Process Controls
- Finished Goods

Do you have a single person or team reviewing the business and technical requirements of all your outsourcing initiatives? While the focus of contract vendors can enable faster execution in many areas, lead-times and timelines can still be quite different in an outsourced environment, especially when it comes to incorporating analytical activities across multiple facilities. Contracting lead-times and scheduling lead times need to be considered.

Company M was making terrific progress moving towards the clinic but had to delay because one vendor developing an analytical method needed for salt selection was being selected independently of the vendor doing the salt selection work and timing was not integrated into their plans. Ordinarily the delay would have been about six weeks. However, because the delay was not considered in the original timeline between the company and its chemistry vendor, the new timeline was one that the chemistry vendor could no longer meet due to prior commitments, further delaying critical production of GMP material.

Your team should plan to look at the entire development program and technical processes early on in your planning process to decide if multiple activities within a program can be sourced to single vendors: can DS and DP (or Analytical and DS) go to the same place? Can calibration activities be consolidated to have on-site by one vendor rather than offsite to multiple vendors? As a client, you will face numerous opportunities for the other side to have more leverage than you would allow in most any other kind of transaction. The cost of that leverage to you gets greater as you progress in development. Any opportunities you can identify to gain leverage should be explored.

That said, do remember to always think in terms of mutual benefits—it's not necessarily a partnership, but win-lose will not create value in the long term. Keep it in terms of a "win-win situation"—despite my editor's dislike of that term—and you can still manage leverage. Weaker vendors will often agree to anything, but that doesn't mean your company will benefit from the relationship. You want to manage the vendor's assumptions about you.

Make sure your people do not limit your choices to only one or two possible vendors as you move through the Request for Proposal (RFP) process. You do not want to find out after you have started the RFP process that you have "Facility Risk," where the supply of facilities capable of handling—or willing to work with—your product are few. Being aware of that prospect early on—even in initial due diligence if you are acquiring—is critical to maximizing the value.

One company found out late in the game that their unique capacity needs could be met by a small number of vendors at commercial scale, all of whom required significant capital investment to do the work. Had this company "outsourced their outsourcing," they might have been facing tens of millions of dollars in capital investment at a vendor facility to handle their highly potent and toxic compound. The company, however, realized that the vendors were all looking at the worst case and had not spent the time to understand their process and develop an appropriate design to manage containment. The company took control of its destiny and developed its own design alternatives. As a result, the company gained significant leverage and control of the technical requirements discussion, saving millions and gaining a much better understanding of its process.

As your team begins to gather data on the DS/API chemistry, they should develop a registration strategy for what to file as the starting material, etc. Rather than being a regulatory exercise for making certain that the proper information is presented to the FDA, this is a technical and business strategy that is complimentary with the sourcing strategy for intermediates. For example, your company might choose to start production at step four in the synthesis and intermediates leading up to this step might be sourced from vendors. In this scenario, only strict optimization, process validation and rigorous analytical control *from this point forward* would be required.

Sound like boring, low value stuff? In fact, decisions made as you move from here can affect licensing value based on the sort of flexibility you provide a potential licensing partner around filing and sourcing. Smart companies create a great deal of value and flexibility by paying close attention to their API registration strategy early on in the process.

Looking from late-stage development and commercialization back into your early decisions will help you decide whether the speed of Phase I supply, which may result in costlier and slower scale-up and process development effort later, is more important to your overall program or whether some investment in analytics and development earlier best serves your overall plans. The best timing for such analysis is ultimately a function of your development timelines and strategy. The good news is that doing this right does not represent a major effort. Rather, ensuring that informed commercial scale-up perspective is a part of your early development and outsourcing planning can help you narrow down a number of these issues and better manage your risks.

Clearly these are difficult decisions to make with the many unknowns of the development process; attrition of the compound is a still high probability at this stage. Hence conventional wisdom avoids large investment until more unknowns are resolved. *Thinking* about them early on, however, will allow you and your team to begin to structure and quantify the cost and benefit of the alternatives, as well as to build your outsourcing capability and development agility. Good companies also invest the time to learn from the data gathered for failed compounds, improving their overall ability to manage development in an outsourced environment.

Take an Integrated View Early Across DS, DP, Safety, ADME and Clinical

Successful outsourcers integrate their DS and DP outsourcing planning early to align the information needs of the two streams, rather than simply working back from when a final dosage form will be required. For example, some early outsourced preformulation work on characterization and salt selection can bring focus to outsourced drug substance work and save time and cost. Giving early visibility of critical Drug Substance information to the Drug Product vendor or the person planning that activity helps provide critical feedback to the development plans and Drug Substance vendor in selection of routes and the need for technology for scale-up. Similarly the Drug Product planner will be able to better understand and plan yet-to-be-seen bioavailability and other challenges that will need to be addressed in finalizing the dosage form. Failure to do so can lead to delay and can damage your relationship with your vendors as it would put you in a position of having to come back with scope changes and /or demands that they might view as unrealistic. In addition, aligning information needs early helps ensure efficient, timely and professional assembly of filings as well.

There are significant implications beyond DS & DP as well. In reviewing toxicology data from an in-licensed compound, personnel at Company A identified a cardio-tox effect that they worried could kill the program. This was to be the compound's first time going into man. As their tox experience was not in this area, we helped them see that the effect was related to the species (dog) and that successful completion of certain tests would allow them to go into man in 18 months. This was certainly a disappointing delay, but it could have been far worse. We also conducted a brief review of the chemical structure and immediately identified the presence of polymorph issues. Hence, there was a good chance that they would have needed to repeat 18 months of tox work, had they done that work prior to resolving the polymorph issue. So rather than lose nearly $500,000 and nine months, they were able to move forward after appropriate polymorph studies and resolution of the issue. In this case, integration between DS and DP activities not only would have created problems within each of those streams; it would have affected the clinical timeline as well, placing supply squarely on the critical path.

This situation is common, despite the technical brilliance in place at most sponsor companies. All crystalline compounds have the possibility of solid state changes. Company X postponed polymorph studies, racing to the clinic to enable fundraising efforts and expecting to be able to complete polymorph analysis as if it were a tick-box needed for filing.

Polymorphic forms identified during subsequent analysis resulted in significant preclinical re-work, time and expense. Investors were not happy when the delays and squandered regulatory capital contributed to a subsequent "down round" of financing.

DP vendors typically conduct polymorph analysis to support salt selection that can drive what DS vendors should make and scale-up. There is not typically a connection between the two unless you make the link. In an arms-length RFP process, don't expect chemistry vendors to challenge your thinking for you. As service businesses, they can be very good at doing what you ask them to do but they often do not have enough awareness of the rest of your activities to help you anticipate how one area can affect another. You can't outsource the integration of your overall plans to your individual vendors.

Company T was forced to delay going into man, having to repeat stability studies because of changes in the impurity profile after process changes were made. Changing synthetic routes to improve the manufacturability of a process can change the impurity profile enough to send any company back to the drawing board. In this case, the chemistry vendor was doing just what it was asked to do, but Company T had not effectively done its own integration to anticipate what might happen to other parts of its development plan.

Always Think Tech Transfer And Quality Agreements

Company N was relying on the scale-up capability of its vendor but did not consider the ability of that vendor to scale up processes that were easy to transfer to another facility. The vendor was excellent at producing GMP material fast and inexpensively but its scale-up capabilities were skewed towards its own equipment. When it came time to transfer the process to a larger vendor, the process required significant process development work—with the risk of late-stage changes to impurity profiles! Your longer-term strategy needs to be factored into early clinical supply vendor selection.

Two keys to success in working with contract vendors are Technology Transfer and Project Management. If you don't do a good job with the tech transfer, there's a good chance you will have significant issues with the rest of the outsourced program, so at that point, scheduling and project management become moot!

Develop the Tech Transfer package early for comparison against the contractor's capabilities. If you are not certain whether you will do something in-house or will outsource it, the package can be useful as part of the decision process as well. In any case, you will want your team to have it completed prior to contractor selection or when comparing contractors.

Such a package is critical for knowing what to ask of a contractor in an audit or technical visit, and to make sure questions are at right level of detail. It also helps you to avoid scope changes later. Critical elements of the Technology Transfer Package for Chemistry include:

- Technology
- Raw material specs & vendors
- Unit opps as practiced
- Mass balances as complete as possible
- At a min, calorimetry for safety
- General safety and environmental
- Analytical requirements
- Proposed specs for API

The Tech Transfer Package is important for you to communicate credibility to vendors, assuring them that you are sending them something that is reproducible. Your ability to obtain a favorable price and good service is a function of how you can show the vendors that you are reducing *their* risk as well. If a vendor signs a contract without seeing a quality Tech Transfer Package, chances are it will put more *if*s and *then*s into their proposal, along with more cost. Vendors receiving "cocktail napkin" technical packages have to build in extra cost because of the uncertainty you are putting in front of them. One chemistry vendor builds in as much as a 25% price premium to cover the additional work required with companies that demonstrate lack of understanding through their technical information packages.

"I just need material to put into a rat, fast!" will send up red flags of later issues that you will pay for sooner *and* later. Often vendors receive processes that are not feasible and reproducible as they would like them to be so they then build in "fat"—that you pay for! In that case, the vendor will build Go/No-Go steps and milestones in and risk-manage from their side. As a result, your price goes way up and your deliverables go way down. If you come from a larger company or are operating within one, the issue is the same one as with tech transfer in house where someone "throws #$% over the wall."

Company Y found that the impurity profile for its compound had changed enough to create a similar problem as Company T. The root cause could be traced back to the vendor changing suppliers for a raw material that could have been avoided through better upfront management of the relationship and the quality agreement. Company Y had outsourced their outsourcing and was now paying a price that they did not anticipate.

The first time you or your team outsources a project, that vendor will not as yet have a good, clear understanding of what you want and how you need to do things, so you or your team would be well served to "hold their hand." If you believe that people in general want to do a good job, your chances of things going right are a lot higher if you conduct business in person, as opposed to fax or e-mail. Never forget that *much more time and cost is wasted in fixing what went wrong than in getting on planes at the beginning.*

Company C spent nearly four additional, unplanned months of phone calls and e-mails trying to transfer a process with sub-par documentation to a vendor. The problem was solved in just a few hours when the chemists were put together to observe each other in their respective labs. Company C lacked the perspective on what the vendor needed to know to transfer the process in. Though Company C was working with a well-established vendor, the vendor's experience was not enough to overcome the lack of information on the process. As a discovery-based company, Company C was struggling to provide what it ultimately did provide.

Hence successful outsourcing is not something to delegate to someone as a task to look after from time to time. Make sure that the people you have interfacing with your vendors can travel immediately if need be and can do so often. *This is a must for a virtual company* and not a role for someone whose personal responsibilities will keep him from traveling at a moment's notice. Distance should not, in most cases, be a barrier. If the vendor is working with your proprietary dosage form technology (and hence will need closer monitoring), you may want to consider a vendor that is more local.

As you structure RFPs and contracts, you should build appropriate estimates for failures and explore how you can make use of that material in agreements.

The Quality Agreement is not only something that the agency looks for; it can serve as a critical core of the relationship with your vendors. Company H found that it had not clearly defined how deviations and investigations would be communicated between the vendor and the sponsor. The company started to see unexplained variation that cost more than $750,000 to isolate and identify and nearly risked their ability to supply the product. Certain metabolic conditions (low dO_2) and raw material changes resulted in changes to the composition in fermentation runs. The vendor was operating within the established agreement it had with Company H. Company H had acquired the compound from a virtual company that had outsourced its outsourcing.

Company I had a similar problem with a vendor during process development, when inadequate documentation resulted in rework to prepare the development report for filing—yet the vendor had delivered on the specs set out in the RFP!

Spend the time and effort in developing your quality agreement to suit your business and your strategy. It is wise to put this in front of vendors early in the discussion process, as it often takes time to work back and forth on the document. There is one caution on issuing the Quality Agreement too early, as you should avoid having the vendors build in additional and unneeded quality and cost that is not phase appropriate for your stage of development. Specify (and don't compromise) on what you need. Explain that you need GMP, but leave some flexibility on HOW the vendor achieves it to be cost effective. In addition, have your team think about how the Quality Agreement will change for supply agreements and development agreements

When you conduct a Quality Audit, don't limit it to quality issues alone. Have your team look for all issues—operational, organizational, etc. It is usually well worth the expense of sending an operational team member or consultant along with the person who will conduct the audit.

Enable the Vendor and Your Team By Structuring and Managing the Ongoing Relationship

Manage with Metrics and keep it simple! Clearly cost and "on-time against milestones" are major metrics. There may be key parameters in the Quality Agreement worth measuring as well. An unseen driver of cost and delay and consumption of scarce internal resources is the number of times documents must go back in forth. It's typical that a vendor does not deliver everything that's expected, so agree on site-specific and product-specific checklists. For example, the amount of time wasted going back forth to get data and info that was not provided at the end of the run is usually significant. Agree on what and how long after completion of the run.

Don't assume that pride of workmanship will be a motivator to help the vendor achieve goals. You need to think about the other guy's internal metrics and ensure they are aligned with yours. Always ask, "Are they motivated to achieve our goals?" It's ultimately going to affect money, time and deliverables.

At the same time, don't forget to be a good client as well. As company P moved forward in development and added functional skills, its information requirements with its vendors changed and personnel were frustrated with continual scope changes and delays. In fact, the delays and cost overruns were largely self-imposed and could have been avoided by better requirements definition early on. There was nothing complex or challenging about the company's technology, but they were learning all about the difference between early and late development at their own expense!

Despite those editorial objections, keep a "win-win situation" in mind at all times and be a good customer. Contractors hate scope change as much as sponsors do. Many projects look very different at the middle or the end than at the beginning. Indeed, problem escalation and disputes are often are a function of inadequate scope definition or tech transfer at the beginning. You and your team can avoid much of it – as long as you treat it in "win-win" terms. You will also need to allow for idiosyncrasies of contractors. The more standardization you force, the more everything becomes an exception process and the more frustrated everyone becomes. You need to balance good process, controls and flexibility for the best development outcome.

As you progress through development, you will need compound and development information from contractors, so consider your filing and Pre-Approval Inspection needs early on and establish a documentation system for all contractors. Specify what you want and the way you want it documented (beyond just batch tickets); in this way, you will build a development report as you go and, at the same time, you'll appear more professional to contractors and regulatory staff.

Consider establishing complementary project managers on your side and on your vendor's side. The goal is that all information will flow between those two individuals except for people on the team, i.e. you do not want to impede scientist-to-scientist interaction. What you want is the ability to quickly and efficiently track, document and manage scope change and information flow. You should reward project managers for on-time and on-budget performance and insist on both sides rewarding their project managers this way. You can also establish hard and fast rules for change order process and how it works for both sides.

Have Enough of the Key Outsourcing Management Skills in house

In trying to manage effectively in an outsourcing environment with limited internal resources, senior managers need to keep several things in mind. Speed is obviously not important; it does not buy you anything relative to your overall development timeline. *On time* can be more important if you've planned well. If you need speed as well, you may need to create the appropriate incentives. Remember: there's also an internal cost component as well as an outsourcing one. If you haven't planned backwards, just being on time can extract a cost premium—for both sponsor and vendor.

Ease of doing business can encompass many variables but is best confined to the question "Can you work with my systems or do I have to adjust for your systems?" The implications on internal resources required can be significant. Regardless, there are still significant resources required to lead and manage the process.

Seeking vendors with flexibility can actually increase your internal resource consumption. Don't expect the best vendors to have excess slack to accommodate weakness on your side.

Company S assumed that the DP vendor it had worked with in the past would be able formulate an in-licensed compound into a much smaller dose for a new indication. Not being expert in formulation, Company S did not appreciate the need for specialized skills to achieve content uniformity at such a small dosage and assumed that their long-time vendor could do the work. Unfortunately, the vendor was not capable of doing the work in time to meet the clinical timeline. Having "Outsourced their Outsourcing," Company S was forced to use a dosage form that was more costly and more difficult to manage in the clinic to meet the timeline. Company S failed to have the formulation expertise in house to plan and manage the activities of its formulation vendor.

Effectively outsourcing any aspect of drug development is no small effort and wise companies seek to understand the internal resource requirements and dedicate an appropriate level of FTEs and expertise to be in control of the process. That can be a person or a significant fraction of an FTE for a work stream in a small company, or many FTEs in a large one, outsourcing multiple functions.

Wise senior managers avoid the "I Outsourced My Outsourcing" trap by planning backwards with the right expertise on their team and by doing so before it becomes too late to fix it. ■