Towards Equitable Risk Relationships

Views on Risk Sharing in Sponsor-CMO Contracts

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As our case is new, we must think and act anew. - Abraham Lincoln

For more than a quarter century, I have been negotiating and living with contracts involving all types of sponsors, from the world's largest pharmaceutical companies to biotechnology start-ups and entrepreneurs working out of their homes. Risk sharing in these relationships is currently a popular topic in blogs, trade magazines and conferences that serve our industry. This paper is a contribution which I hope many will find helpful. I have found that equitable risk sharing can lead to the kind of long term relationship that benefits both parties. My perspective is that of a leading CRO/CMO which provides niche, high value manufacturing for clinical trials and low volume commercial products, as well as premium drug lead development services. In my experience, the most satisfactory contracts are those which bind the parties in a "joined at the hip" relationship.

The Past Did Not Prepare Us For The Present

When I started out, there was a comfortable orderliness to the industry. Blockbusters on the market were providing a generous return on investment (ROI), and new drugs with exceptional promise seemed to be steadily flowing through the development pipeline. The resistance by third party payers was in its infancy. The IP and liability challenges faced by big pharma in those days were really just bumps in the wide, smooth highway. Although only non-core activities were outsourced, there was ample opportunity for high quality service providers, and sufficient funds to pay for these services.

I mention the "good old days" only to emphasize the drastic change that we have witnessed. Worse, the rapid change came without a road map for the future. For big pharma, the uncertainty about the best path forward, combined with an overpowering sense of urgency for aggressive action, were in my opinion two of the factors which led our industry to embark upon a massive outsourcing of development and manufacturing services to China and India. A rationale for the continued escalation of offshore outsourcing has been that it will provide access to extremely large drug markets. I hope so. Many of us fear, however, that western big pharma may not enjoy full access to these markets, after having transferred expertise, funded the creation of a large drug development and manufacturing infrastructure, but simply created competitors of the future.

The New Paradigm

Movement of business to offshore suppliers has profoundly affected the North American CRO/CMO service sector. Those of us who have persevered are stronger because we have become even more focused on delivering value and building relationships. Circumstances have changed our customers too. Developing new drugs today is an order of magnitude more difficult, more expensive, and more uncertain, and the ROI for success is dwindling. Sponsors need us and we need them more than ever, and it makes sense that this interdependence should involve

a deepening sense of commitment by both of the parties to a project and to each other. Risk sharing is an essential part of this paradigm shift.

Companies like Dalton have survived because of our understanding that we can accept only measured risk of appropriate size. Dalton is predominately a project based business; in our business model, we don't have capital to put at risk and wait for a highly uncertain return at the end of a 10- to 15-year product development cycle that we do not control. We don't have a steady cash flow from product sales, and therefore must generate regular revenue from projects on a 'cost plus' basis. When we assume contractual risk, what we are looking for is an alignment of risk by both parties, and an appropriate distribution of risk according to the capacity of each in the spirit of fairness.

Our business model does not always align with that of the sponsor. What I notice in some larger sponsors is the view that outsourcing is seen primarily as an exercise in risk transfer - the initial proposed contract is often asymmetrical. This is the antithesis of the concept of a community in which sponsors and vendors can jointly prosper in the new paradigm.

In the matter of how risk should be shared between sponsors and CMOs, the industry is still learning. A consequence is that there is not a large body of best practices precedent to draw upon, nor is there a large body of case law governing contractual relationships. Another area of the CMO/sponsor relationship management that will be of great benefit is the development of legal expertise which specializes in writing contracts that would balance risk sharing relationships. In the meantime, we are seeing the slow evolution of a beneficial risk sharing culture, advancing on a contract by contract, clause by clause basis.

Tales from the Trenches

By outlining some cases which my company has encountered over the years, I hope to share my perspective with those who negotiate with small to mid-size CMOs, and if possible to benefit the entire community. In my own case, I benefited from reviewing past experiences and lessons learned when writing this article. The examples are not about what I did right or what others did wrong, they are about the realities encountered when trying to enumerate and mitigate contractual risk. Although the stories are based on true situations, I have adjusted some of the details to respect confidentiality.

1. Specifications. This should be straightforward, and it is the cornerstone of clarifying deliverables. A manufacturing contract often contains a standard list of specifications and Dalton releases product batches to our sponsors after ensuring that they meet the agreed upon specifications. An early clinical phase project comes to mind in which we learned from our sponsor (who did some of the product testing in house), that a full scale batch did not meet the specification for impurities. Preliminary scale batches had gone well. What happened? With an un-validated process, there were numerous possibilities to be investigated – analytical methods, raw material supplies, manufacturing process parameters etc. The problem could be tracked down, but such investigations are time consuming and therefore expensive. The question was, "Who pays?". Contractual language needs to include ownership for the cost of these investigations. A thorough and complete investigation is a regulatory requirement if the product advances, and therefore the funding of such is a critical element not to be overlooked.

2. Sponsor's Raw Material Supplier. Dalton was negotiating a contract for a synthetic manufacturing process scale up. The sponsor had done all the early development at small scale and had already identified a vendor for a key intermediate. In setting up the project the sponsor had obtained a quote and time line from this vendor, which was then integrated into the delivery schedule and contract for the final product. However, when Dalton ordered the intermediate, the vendor informed us that they would not honour the time line because it had been based on past smaller orders from the sponsor. When informed of the problem, the sponsor felt that managing the supply of raw materials was our issue, and that we must bear responsibility for any delay in the clinical trial. While we did not disavow our responsibility we had counted on the sponsor's prior experience in supply chain management for their material to meet their timelines. Dalton explored alternative vendors for the intermediate, none of which were able to meet the timeline and/or specifications. So in order to salvage the time line Dalton decided to synthesize the intermediate internally.

While we count on our sponsor's expertise, ultimately we are expected to transcend their knowledge in order to take their product to the next level of development. This can extend into the supply chain before we even have the contract to supply. The lesson for us here was that the contract must be very clear on which party is responsible for which elements of the supply chain as this is crucial to meet delivery commitments.

3. Raw Materials Inventory. In contract negotiations, a sponsor wanted to impose severe penalties for failure to meet ongoing product delivery over a three year period. To put things into perspective, the value of the projected annual product sales for Dalton was in the low six figures. The penalties were in the low seven figures. This requirement to have penalties for delays was to be independent of raw material supply issues.

Because a few of the key raw materials were single source vendors, several complications arose. We did not have the option of tying the vendors to delivery contracts with penalties that would cover our potential seven figure risk, as the value of the raw material to the vendors was less than five figures. The only way for us to guarantee that we would meet that delivery clause was to have raw material inventory that would cover the three year period. One of the main considerations in deciding whether to accept the sponsor's condition therefore became the expiry dates for the stockpiled raw materials. What made the conversation particularly interesting was that one of the vendors was making a raw material specifically for the sponsor prior to our involvement in the project. This vendor had no other customers for this raw material and the sponsor had not studied the stability of the material.

The solution in this case was for the sponsor to pay for the raw materials covering the three year period in advance. While the sponsor agreed to assume this aspect of raw material risk to timelines, there was still a penalty for late delivery for any reason except force majeure.

4. Contract Quantity Underproduction or Overproduction. We contracted to produce a specified amount, 1 kg, of product using an un-validated, multi-step process. We knew that the sponsor needed at least 700g. At the end of the run, we wound up with 800g. The sponsor accepted the material, but refused to pay the full contract amount because of the 200g 'shortage'. On the one hand, this is reasonable; what if we had produced 1200 g and given it all to them? Would they have paid us more? What we do now is stipulate in the contracts that we are paid full price for +10% or -10% of the agreed quantity.

Another approach that shifts the risk to the sponsor is used by many suppliers. The sponsor pays for a manufacturing campaign, rather than a set quantity, and whatever is produced

is considered fulfillment of the contract. In our experience, sponsors do not prefer this arrangement of risk sharing. However, depending on our assessment of the manufacturing process risk, we might favour this approach over the former.

5. Valuable API Liability. The proposed contract was a straightforward sterile fill of an API for about $75,000. The problem was that the sponsor expected us to accept the risk for the value of the API they provided, which was $500,000. Yes, we have insurance to cover accidental loss of the API in a failed run, but we obviously didn't want to use our insurance and shoulder the deductible for such a small contract value. We declined the contract under this risk sharing arrangement. In other cases of this general type, we would consider securing specific risk insurance and include the fee in the quote, or placing a cap on the API liability in the contract.

6. Penalty for Missing Contractual Deadline. Like the example above, this one is a risk potentially mitigated by insurance. A contract under negotiation involved the supply of clinical product for a trial to start on a fixed date. The main risk involved third party raw material supply, since the GMP manufacturing presented no special challenge. The sponsor wanted the contract to contain a penalty of $1,000,000 for failure to meet the deadline. The value of the contract business to Dalton was, however, only about $50,000. We did not accept the project. This case had an interesting post script. Failure to meet the deadline would have indeed caused a serious financial setback to their development program, but where did the $1,000,000 penalty come from? I later learned that this was the amount of their insurance deductible. Since then, I have found that this isn't the only sponsor who tries to cover their insurance deductible by shifting the risk to their vendors. I wonder if the insurance industry is aware that coverage for drug development programs has this form of hedging. Should we be negotiating risk insurance per contract as part of the quote in these instances as well?

7. Regulatory Jurisdiction for Global Product. The contract was for sterile fill of a product for worldwide distribution. The problem was defining the regulatory requirements within the Master Service Agreement. The sponsor was unable to commit to which countries the product would be sold in, and attempted to capture all scenarios at once. As the CMO, however, we are obligated to know which standards apply when manufacturing the products. Ideally we would review the requirements for each of the countries in which the product is to be launched, and ensure that our production process and testing regime meets the standards of each jurisdiction as they launch. The risk we needed to manage was related to the expansion of contracted sales including a new regulatory jurisdiction or compendia standard some time after the original launch and related contract negotiation and pricing. The pitfalls go beyond test method requirements of the new jurisdiction. For historical, political, or ideological reasons, some countries have very specific stipulations regarding production facilities that are not universal. For example, until recently Brazil did not allow any human product to be made in a site that makes any veterinary products.

8. Power Supply and Insurance. The power supply in our part of North America is exceptionally reliable. A decade ago, we were confident that we were managing the risk of power loss adequately with a combination of warning systems and insurance. But then, with no climate conditions or other circumstances that might have predicted a problem, there was a catastrophic failure of power across the entire eastern seaboard of the US and Canada during a GMP production run. This outage lasted for days. After the system was on line again, we had unannounced outages for weeks after the main event. We lost not only the product from this run, but also the raw material, which was extremely expensive. Since we did not have contractual language covering this scenario, the sponsor insisted that it was our risk to bear and we ended up absorbing the losses.

We were insured for losses due to power failure, but what I didn't know was that the power interruption insurance only covered power failure if the disruption occurs within 300 metres (~1000 ft) of the building, e.g. collision of a truck with a power line pole near the property. A wide area outage, which is what happened, was not covered. (To our knowledge very few insurance claims were paid from this event.) That year, to complement our Uninterruptible Power Supply (UPS), we installed a large scale back-up power generator that automatically takes over in the case of a power failure and is capable of providing power to the entire facility.

9. Specialized Equipment Acquisition. A situation that has occurred more than a few times is the selection of Dalton to do specialized process development and manufacturing, even though we did not have the necessary specialized equipment. We have moved forward through arrangements in which the sponsor was financially involved in the equipment purchase, installation, and validation. This creates some complications. For example, if the sponsor wants to own the new equipment in our facility, who is responsible for maintenance when it is not being used? Many do not realize how expensive, and at times unpredictable, maintenance costs can be. Since the equipment takes up valuable space in our facility, what is a reasonable fee for equipment storage? Should there be a hiatus in the production requirements of the sponsor as sometime happens, we could be storing the equipment for two years or more. What is a fair cost to the sponsor for this service? In the risk management of sponsor capital purchases for project specific equipment, Dalton may be given the right to use the equipment for other customers on the condition that the original sponsor retains manufacturing priority and receives a portion of contract revenues to offset the original cost of the equipment and ongoing maintenance and storage.

In some cases we have chosen to make the entire investment ourselves, accepting the risk that long term production volume would justify the expense and also allowing Dalton to use the equipment for other customers. Sometimes the outcome of this risk acceptance was very favourable; sometimes it was otherwise.

David and Goliath

Dalton may be viewed as a "David" whose sponsors and whose competition are often very large organizations. In reality we are neither too small nor too big, but just the right size for most of the development programs that find their way to us. What I want to share here are a few observations from my perspective about the realities introduced by large differences in company size. We should not, and I do not, associate large size with villainy, and small size with virtue. The size differential between two entities just means that they will have different businesses, different perspectives, and different roles to play in our industry. In fact, the paradigm is shifting to an understanding that the best choice of a supplier should not be made purely on size. Instead, it is better seen as a decision based on fit. The perfect fit is related to culture and would be expected to change with the stage of development of a product.

There are great differences between manufacturing in Phase I/II compared to Phase III yet, there is a common belief related to CMO size that continues to hurt inexperienced sponsors. Early stage sponsors with promising leads will often demand to know whether a smaller CMO will be able to produce the large quantities required for future Phase III trials and commercial production. What they are trying to do is reduce their downstream risk of lost time if they have to shift to a large CMO as they advance from Phase II to Phase III. What they should be focussing on is getting to Phase II as fast as possible following the maxim of "fail early, fail fast". This requires a high level of flexibility on the part of the CMO. In early stage contracts that Dalton has

had, we have seen work plans change ten or more times as new information about the product emerged.

In our experience, contract negotiations with sponsors that are orders of magnitude larger than ourselves involve some peculiar challenges. Two of these are described below.

(a) Negotiating One Step Removed. In contract negotiations and project execution involving large pharma, we generally deal with some type of "supplier relations" function. They represent, *inter alia*, the corporate business group, the corporate legal department, and the corporate drug development group. The supplier relations group is often not in a position to share the corporate perspective with us, because they don't have the broad picture or the authority. Very often they have a mandate to include certain clauses, but the rationale behind them is not known, and even though the context is inappropriate, there is no movement to change. Negotiations can seem interminable, because each victory of compromise is "subject to head office legal approval", which may not be granted. If approval is given, we often have to wait a long time. In some cases more than a year has been spent negotiating contract terms. We have had instances in which legal costs incurred in redrafting contracts can exceed the profit from a project.

(b) Large Sponsor "Entitlement". I am pleased to see a decline in the use of leverage on the part of large sponsors, which is a basic assumption that if a service provider wishes to do business with them, they should carry all of the liability when things do not go right. We insist on an escalation process to manage any disputes ultimately ending in arbitration. The liability bias in contracts against CMOs may be on the way out, but it is not gone. In negotiations not that long ago, a clause thrust on the table covered indemnification of the sponsor in the event of an unspecific change in IP relating to the product. Why would a service provider be expected to indemnify a sponsor against an adverse IP outcome for a drug candidate whose IP it does not own? Because of size, the large sponsor has a different view of litigation risk than the small vendor. The legal department of a large global pharmaceutical company is equipped and experienced at handling ongoing mid-size or major lawsuits. For the small CMO, the cost of a single lawsuit can be ruinous. If the actions of a large sponsor financially ruin a CMO and thereby eliminate it from the marketplace, neither the sponsor nor the industry will benefit in the long term.

An Irrevocable Union - The Better Way

In my experience, the most satisfying business relationships have been ones in which the contract has irrevocably bound, typically for a five year period, my company and the sponsor. We were joined at the hip, or, put another way, we couldn't fire them, and they couldn't fire us. Of course there have been challenges and misunderstandings, but it is amazing what can be done to work collaboratively and advance a project to success when there is an additional contractual bond.

I have selected three examples of actual joined at the hip relationships to show how we have worked through difficult situations together.

Example 1. The contract was for sterile fill of an API into vials. The runs proceeded normally, but then a critical parameter of product stability in the vials began to drift out of specification. We immediately began an investigation, but came up against questions which, for a number of reasons, valid at that time, could not be answered. What we negotiated was shared

cost for a new fill, with the understanding that further fills would be done at Dalton. It was a way of sharing the consequences of this misfortune, advancing the program, and sharing the long term benefits when ultimately successful.

Example 2. We were contracted to carry out bio-analytical testing for a sponsor. As the project evolved the number of samples that we were required to test increased to the point that we needed another analytical instrument. The sponsor paid for the instrument and recouped the capital cost through a reduction in price of the testing we performed. The "discount" applied to all samples run on that instrument for a fixed time period. Their samples also had priority. They gained the extra testing they needed faster and for less money, and we acquired a new instrument. Overall, we all benefited using this creative approach for managing capital expenses. Incidentally, this approach was also applied to production equipment.

Example 3. Dalton's chemists developed a patentable route to an intermediate which was critical to the manufacture of an important API for a drug soon to come off patent. The drug was a low volume, high value product and the dosage form was a solid dose. Dalton had aspired to add larger scale solid dose manufacturing capability as we moved to commercial product supply. We had several possible partners interested in taking the technology that we had developed to commercial production. One potential partner was willing to invest in expanding Dalton's infrastructure and license the patent for the production of API. In return for the investment, Dalton reduced the price for the manufacturing to equal the partner's costs plus a nominal but defined margin. Also, a percentage of the transfer price for the product went to pay down the capital investment. Where Dalton benefited by sharing risk was in a profit sharing arrangement on the sponsor's sales. Overall, both companies gained from the arrangement - the sponsor with lower costs up front, and Dalton with added manufacturing capability, a commercial supply agreement, and a share of some of the upside on final product sales. Let me emphasize that developing business relationships of the type just described requires a tremendous amount of trust on both sides.

Aiming for Attitude - "First Seek to Understand, then be Understood"

Beyond being a provider who tries to be fair, I strive constantly for an attitude of genuine interest in helping a sponsor be successful, and I insist that my staff does the same. This extends to the pre-contract stage. For example, what I have sometimes found in dealing with biotech start-ups is that management doesn't fully understand how product development can be advanced through creative financing options, such as project based financing. In cases like this I endeavor to assist them in seeing what is available, and if possible introduce them to venture capitalists or 'angel investors' who might be interested in their product or platform.

In the negotiation stage, I aim to see proposals on both sides of the table from the point of view of the sponsor. This is not an easy discipline to practice, but in most cases it can really speed the discussions along. Once a contract has been signed, our attitude must be one of caring and nurturing mutual trust. We see ourselves as an extension of our sponsor. Obviously, the ideal sponsor is one with a similar disposition and perspective. A win-win attitude is not a naive sentiment. It is the gate that leads to a kind of environment in which we all can survive and prosper. Let us work together to foster a culture that rewards creativity, encourages generosity, and engenders optimism and hope.

The trouble with our times is that the future is not what it used to be.

- Paul Valery, 1871-1945

About the Author

Upon graduation from a Masters in Chemistry program, my professor Dr. Doug Butler and I identified the need for the supply of complex chemical entities for research purposes. As a result, we founded the Dalton Pharma Services business. The business model continued to evolve and expand over the last 27 years eventually focusing on supporting leading pharmaceutical companies in their drug discovery, development and manufacturing programs. Utilizing our unique customer relationship management strategy, our goal is to provide high quality, innovative scientific services in a timely fashion that meet our global customers' objectives. We have successfully collaborated with industrial customers, academia and researchers from around the world advancing new drugs towards commercialization.

About Dalton Pharma Services

Dalton Pharma Services supplies chemistry, analytical and formulation development services to the biotechnology and pharmaceutical industries with a focus on chemistry, medicinal chemistry and pharmaceutical dosage form manufacturing. It's modern, Health Canada approved facilities in Toronto, Canada, offer cGMP manufacturing of sterile aseptic liquids and solid dosage forms to its customers at any stage of the regulatory process (Phase I, II, III or commercial). Dalton conducts sterile fills in vials or syringes, either aseptically or terminally sterilized. Dalton also produces cGMP active pharmaceutical ingredients at gram to kilogram scales. Founded in 1986, Dalton brings more than 25 years of experience to every customer project, at virtually any stage. Dalton Discovers, Develops and Manufactures.

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