ZenBio Inc.

Observations on Trends in Outsourcing to Preclinical CROs

Introduction

Outsourced research services for pharmaceutical discovery and development have emerged as a viable and reliable model for bringing new drugs to market. With the typical investment of more than $800 million in development costs for each new drug, a well-coordinated partnership with contract research organizations (CROs) and other third party providers (TPPs) can deliver results that beat the conventional discovery and development research model in both time and expense.[1]

This document examines the current state of drug discovery and development research outsourcing, where the pharma/biotech industry is headed and the factors driving the shift, it also outlines some key areas to consider when developing relationships with outsourced research providers. Through a thorough understanding of how outsourcing functions best, you can guarantee positive and profitable experiences using outside research providers.

Current Situation

The prevailing biopharmaceutical discovery and development platform has remained largely unchanged for nearly 40 years. Emphasis on internal, centralized control of research and development demands a proportionately large investment of resources. It is unfortunately more the rule than the exception that drug discovery efforts require enormous investments of money and time, and far too often generate no usable return.

The inefficiency of operating a traditional in-house drug discovery and development program has proven to be costly with marginal results. Subsequently, investment capital for drug development that has been generally scarce in recent years, and in some sections of the market, it has virtually evaporated. This shift has resulted in a growing number of pharmaceutical and biotechnology companies laying off R&D professionals to cut costs. What we are witnessing is the twilight of the old-model drug development platform. Overall, the post World War II industrial approach of very large, bureaucratically structured organizations performing all functions internally has been shown not to produce sufficient return on investment—nor to produce it quickly enough to be viable in today's global economy.

Disadvantages of fixed R&D costs and costs to ramp-up with new infrastructure

The expense of maintaining real estate, physical plant, and full-time employees to pursue drug development under the old platform can be crippling. Indeed, in the case, of the large pharmaceutical manufacturer, Pfizer, the company had to demolish a large research campus in Ann Arbor, Michigan that it had recently constructed and subsequently abandoned, only to reduce property tax liability on the vacant space.[2] The old development platform burns money—regardless of whether or not any results are generated, and under current global economic conditions, it is not a sustainable business model.

Gloucester Pharmaceuticals Incorporated, the company that developed Istodax®, embodies a new, improved and successful outsourcing model. In the past, many investing companies in the pharmaceutical industry looked to support CROs that could develop an array of products and could work together with other CROs. However, judging by the $640 million purchase of Gloucester Pharmaceuticals by Celgene Corp. in 2010, the CRO industry clearly demonstrated the ability to support two different types of investment models.[3] Martin Vogelbaum, the investor who founded Gloucester Pharmaceuticals as well as one of the partners of Rho Ventures, "sees [Gloucester Pharmaceuticals] as a model for future biotech start-ups."[4]

The Istodax® example reinforces the singular drug development model because the product demonstrated the potential for high effectiveness and high feasibility of production in the early stages of development. Although investing in CROs poses some uncertainty, using a conservative approach to support established CROs with promising products can be highly lucrative.

Lack of flexibility

For a large company to change course it can mean abandoning expensive real estate and equipment, and also terminating employees. Often, instead of terminating employees for failed projects, many companies have the tendency to shift these employees onto projects where they may have less expertise or desire to work. This tendency is usually detrimental to the remaining projects and may lead to further problems. Additional hidden costs from changing focus can result from opportunity losses from not pursuing promising leads.

Problems in speed to market

An abundance of promising drug development projects take too long and are too costly for one division of a company to perform, so they do not generate results. Consequently, such projects are abandoned without achieving desired objectives. Additionally, with routine reorganization and subsequent changes in focus, project slowdowns are inevitable, adding more time and expense to the remaining projects.

In-house expertise to carry out projects effectively

Delegating duties and spreading in-house R&D employees too thin may lead to inefficiency due to lack of specialization. Bringing in specialized expertise for specific projects is no longer cost effective. The hiring of qualified personnel requires the Human Resources department to spend large amounts of time and money hiring new employees proficient in the required task that may not be required after the completion of a project.

Current infrastructure doesn't support build-out or expansion for new programs

Many new projects may be limited if a company focuses on jobs that are now considered routine, even if they once contributed to the company's initial expansion and success. Failure to plan in both the long- and short-term may also contribute to excessively strained or limited resources. Inadequate space and equipment requires a company to spend time and money to obtain sufficient capital.

In a large bureaucratic project management structure, too often the emphasis is not on actual completion of the project but in avoiding blame for any perceived delays during steps in the process. This can result in a tendency to "toss the project into the next cubicle", wherein it becomes someone else's responsibility. Companies' priorities and directives commonly change, resulting in frequent shifting of focus, acquiring new expertise, personnel and resources to make these changes. These factors can have devastating effects on budgets, time lines and more importantly, morale. We also must keep in mind mergers and acquisitions, because there are tremendous real costs regarding integration of new personnel and programs, re-evaluation of project portfolios, and budget cuts, due to global changes in the corporate structure.

Trend toward outsourcing

Market research in May 2010 indicated that approximately 25 percent of all biopharmaceutical drug development is outsourced, and UBS Global Healthcare found that this percentage represents an overall CRO market size of roughly $20+ billion, which will grow at an annual rate of roughly 15%.[5] Prevailing market forces—decreased capacity, growing workload, and scarce capital—will increase levels of outsourcing throughout all aspects of biopharmaceutical R&D during the next decade. In short, the development of new products will shift from R&D to O&D (Outsource and Development).

The Shift from Tactical Outsourcing to Strategic Outsourcing

Early outsourcing efforts were marked by an emphasis on tactics and execution. Research projects were typically awarded in pieces, on a project-by-project basis, usually to the lowest bidder in competitive rounds. Monitoring of procedures and results was inconsistent if it existed at all; the CRO was often viewed as a "black box" where a project was put into one end and a result came out the other, without much knowledge of what went on within the process. Furthermore, the relationship between the research client company and the CRO was somewhat adversarial, with a clear distinction between the client as the superior and the CRO as the subordinate. Sponsor companies have typically outsourced on an ad hoc, per-project basis, due mainly to the lack of sufficient in-house personnel to perform a particular function. Sponsors have also historically engaged multiple service providers, who typically focus on niche service offerings.

Under the old model, sponsors solicited bids from multiple providers, and then went with the low bidder. Medium and large sized sponsor organizations may have relationships with dozens of contract service providers. Managing the resources and logistics for so many unrelated components requires a substantial commitment of resources; in which case the sponsor

ultimately micromanages many outside suppliers, which hardly differs from managing employees. Planning and governance of the relationships generally falls to middle managers who are often unsatisfied with their level of communication with top management. A disconnect that can waste time, money, and become particularly troublesome during critical decision periods.[6]

In transactional outsourcing, the service providers are generally not engaged in the project until development plans and protocols have been unilaterally approved by the sponsor organization. According to Alan Morgan of the CRO firm *ICON*, the "relationship between pharma companies and CROs has evolved from being very transactional in nature, through a process of preferred provider relationship, to one of closer strategic collaboration."[7] Surveys and case studies conducted by the Tufts Center for the Study of Drug Development (CSDD) have confirmed Mr. Morgan's statement finding that risk sharing between the CRO and sponsor is gaining prominence in contracts and that CROs are developing a more comprehensive knowledge of their clients' desires.[8]

Strategic outsourcing emphasizes forming long-term partnerships in which the sponsor and the CRO work together on multiple aspects of many projects and where both companies have substantial knowledge of each other's operations. With up-to-date knowledge of the CRO's activities, the sponsor can correct its research path, if necessary, while minimizing the time and expense of shifting focus.

Principal Drivers for Outsourcing Research Functions

Operational

Having the ability to quickly bring in scientific capabilities and efficiently allocate expertise can be crucial during important points in a project. By leveraging the CRO's resources, such as equipment, space, time and personnel, the sponsor company will receive more benefit than the typical in-house hiring of additional personnel. If the sponsor company only needs an increase in personnel for a brief period of time, instead of hiring an employee that can cost $80,000+ per year, it can contact a CRO and contract numerous workers for a specific time period for a more reasonable cost.

Economic

Many sponsors are under tight cost constraints, so they turn to CROs when they need more resources. After the CRO and sponsor company decide on a contract price, the responsibility of managing internal costs falls to the CRO. As a result, the sponsor can more accurately predict its overhead and payroll.

For example, the sponsor company and CRO agree upon a price for an assignment, but in the process, the CRO encounters unforeseen additional expenses. As the CRO, it must decide whether to decrease costs of other aspects of the project, or pass along the price increase to the sponsor company. This allows the CRO to independently function as a cost-saver, without stressing the sponsor company. If the sponsor company were to not contract with a CRO, the price increases may be more pronounced and harmful to the project budget.

Scientific

Many preclinical CRO's can fill areas where the sponsor organization may be lacking and the sponsor may see economic benefit of not developing in house expertise for limited projects. Instead of the sponsor company spending a substantial amount of time and money looking for equipment that may only be used once or twice, they can save time and money by contracting with a CRO. Additionally, contracting with a preclinical CRO allows the sponsor company to assess the feasibility of a project before it reaches the clinical stage.

For example, a company may require a piece of equipment for a very specific test, but instead of paying hundreds of thousands of dollars for that equipment, the sponsor company can find a CRO with that equipment and will subsequently only have to pay the cost of running the experiment. Furthermore, if these test results are not what the sponsor company expected or desired, the company can alter the path of the project without having to worry about reselling the piece of equipment

Components to Consider When Selecting an Outsourcing Partner

Proper due diligence

Building relationships with your CRO partner is paramount to having clear and constant channels of communication. Recognize that there is no perfect formula or one design that fits all. Take into account the CRO's reputation and customer service track record. Additionally, consulting with past and current clients of the CRO is great for obtaining testimonials or recommendations.

Manage expectations

Outsourcing can reduce time and expense on a portion of the project, but it does not guarantee successful outcomes. Before picking an outsourcing partner the sponsor company should consider realistic results and areas with exceptionally high possibilities for delay or failure.

Personnel turnover

Although long-term personnel turnover is present in any job field, examine the short-term turnover and try to gauge turnover rates. A project leader change in mid-project can be particularly detrimental for a sponsor company, especially if the project requires particular job skills.

Point person

This is the person that you will be dealing with as the project advances. Having only one point person ensures the clearest possible lines of communication between the CRO and the sponsor company. High personnel turnover and frequent changes of the point person should raise red flags for the sponsor company.

Capacity

Before choosing a CRO, consider your prospect's capacity for taking new or expanding upon existing projects. Ensure that the CRO has the trained personnel and required space for the desired project. Last-minute overloading of the CRO with work may delay the R&D process even further, possibly to the point of a standstill. Conversely, before a CRO bids on and potentially wins the sponsor company's project, ensure that the CRO is not already working at maximum capacity.

Deliverables

Clearly outline what you want to see at the end of the study before entering into a contract with a CRO. Listing your goals beforehand will encourage transparent communication and minimize communication breakdown between the sponsor company and point person within the CRO.

Nimble/Responsive

A CRO should be focused on the projects of its customers and able to adapt relatively quickly to changing parameters. Specifically, the CRO should have a positive history of identifying and resolving issues and possible setbacks. A sponsor company should have the ability to customize their project, but also should give the CRO a reasonable amount of time to course-correct.

Area of expertise

A CRO should have focus, qualification, and confidence in the field it claims. A good indication of expertise includes employees who have contributed scientific research in the company's field. Additionally, a CRO that focuses on one portion of the development process, such as pre-clinical, will be more efficient at producing results compared to a CRO of the same size that claims to be proficient in both pre-clinical and clinical activities.

Key Considerations When Developing the Contract

Scope of work and format

The client should consider the scale to which it wants the CRO to perform services or create products. Likewise, the CRO should consider the feasibility of the client's desires and should supply honest responses about providing said services and/or products. To avoid pitfalls and develop a trusting relationship with the CRO, a sponsor company should be as forthcoming as possible with its ideas, goals, and timeline. Greater transparency and communication between both parties will minimize costly misunderstandings and subsequent mistakes.

Experimental design

When assigning roles to the CRO, the design of the experiment(s) should be straightforward and require minimal upkeep by the sponsor company. The idea of the CRO is to remove the burden of additional and possibly routine activities for the sponsor company, while maximizing return on investment. Take into consideration the time, manpower, and money required for each portion of the experiment.

Do you need a pilot study?

Before embarking on large or complex projects, a smaller scale pilot study may be beneficial to determine the feasibility of the larger endeavor. Such pilot studies can mitigate concerns that may arise once the sponsor company has committed to running the project on a larger scale.

Contact person

An effective contact person should have previous leadership experience, be accustomed to complex projects and be able to course-correct as necessary. In addition, this person should be able to maintain composure and level headedness even if he/she must explain a setback or delay to the sponsor company. Furthermore, this person should be honest and willing to tell the sponsor company the realistic status of the project, even if it is not favorable. Finally, this contact person should be eager to stay on top of the progress of the project and be willing to provide regular status updates.[9]

Cost

Make sure you fully understand any costs that you may need to explicitly outline in the contract. Are there specific costs for which you would place a ceiling and are there other costs that can be more flexible?

Deliverable parameters:

Determine how you will analyze the project's success or failure. Are there results that should be guaranteed while other results may be more open ended? Before beginning a project, the sponsor company and CRO should agree upon a reasonable timeline with aggressive, yet attainable deadlines.

Without research and planning, choosing a CRO can be a stressful and risky investment, but the right CRO can help a client avoid caveats and other common pitfalls that sap money, resources, and time.

Look at the outsourcing cycle

Knowledge of the outsourcing cycle is paramount for understanding the planning and decision-making processes that foster the client-CRO relationship.

1. *Company review and selection*: Choose a CRO company that has the capacity and capability to deliver solutions. Refer to "Components to Consider When Selecting an Outsourcing Partner" for criteria to consider.

2. *Experimental design*: Refer to "Experimental design" under the "What to Consider When Developing the Contract" header as a starting point. Every experiment will have a different design, and choosing the optimal design can be the difference between success and failure of a project.

3. *Detailed project consultations*: Discussing the project guidelines and goals beforehand will help to determine feasibility and resources required, as well as identify potential snags before they occur. This consultation builds the foundation of the client-CRO relationship.

4. *Protocol control*: After discussing the proposed project with the CRO and the signing of the contract, the CRO will begin performing its assigned tasks. Often the CRO will follow established in-house protocols or develop new standard operating procedures (SOPs) appropriate for the project. To ensure project integrity, the CRO must consult with the sponsor regarding alterations and changes beforehand.

5. *Site quality/Site audits*: Although a proper-fitting CRO should demonstrate value to its clients without frequent micromanaging, a client should take particular note when the CRO takes steps to separate itself from the competition. For example, Good Laboratory Practices (GLP) certification displays that the CRO meets "the minimal standards for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by FDA or EPA."[10] Although certification is commonplace in the United States, other countries, both developed and developing, may hold their laboratories to different minimum standards.

6. *Contract and favorable pricing*: A contract between the client and CRO ensures maximum transparency between the services desired by the client and the services that can be performed by the CRO. With the booming growth and creation of new CROs over the last decade, a client must be careful when selecting the lowest bidder. Often times, these new CROs will undercut the established competition but will then disappear within a year because they are unable to cover fixed costs. Although efficient spending is important, working with an established CRO that has been around for 10+ years demonstrates its commitment to low, yet sustainable prices as well as high quality services.

7. *Reporting and assistance with data interpretation*: After the CRO performs the services outlined in the contract, it should be able to convey its results using reasonable and upfront methods of communication.

8. *Product / Reagent selection and control*: Choosing high quality products and reagents help to ensure continuity between tests and accurate results. In an effort to undercut the competition, some CROs may use inferior products and reagents, which could later void the results in a project and end up costing the client significantly more money when it switches CROs or pays for new product.

9. *Customized research solutions developed for specific applications*: A reputable and established CRO should have the ability and resources to customize its services and products to the need of a client. Although a client may have an idea of a scientific process or procedure, CROs may have a more efficient and effective method for producing results or creating a product.

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