



Increasing R&D Productivity: Effectively Implementing Biopharma's Strategy

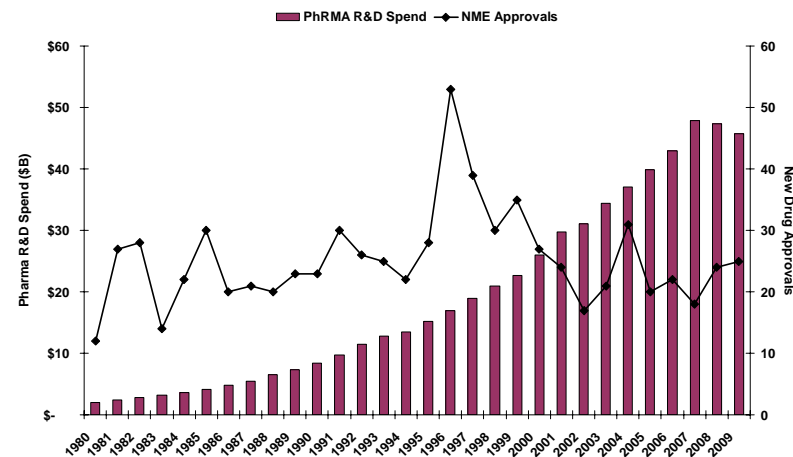
Productivity in the biopharmaceutical industry (biopharma), which can be defined as the number of new molecular entities (NMEs) approved each year, has faltered over the past two decades despite increasing investment in new drug R&D, driving comprehensive changes in the industry's strategy. Expected revenue growth from new therapeutics and markets is insufficient to replace an estimated \$74 billion in sales at risk from patent expiration by 2012. The global recession has caused generics competition to surge in biopharma's core markets, and healthcare reform and drug reimbursement pressures portend price compression. The increased importance of comparative effectiveness in FDA reviews further reduces the chances of success of even efficacious, safe new therapeutics. In response to these increasing pressures, the industry as a whole has embarked on a tripartite strategy: access innovation through external partnerships, pursue rare and under-treated diseases, and target emerging markets as a significant source of revenue¹. With all players pursuing a

seemingly uniform approach, the trajectory of each biopharma will be determined by how it executes its externalization strategy through its network of external partners.

Current Status and Recent Gains

Biopharma's productivity has remained relatively constant over the past decade, despite enormous escalations in R&D expenditures, as shown in Figure 1.

Figure 1. Pharmaceutical R&D Spend and NMEs by Year

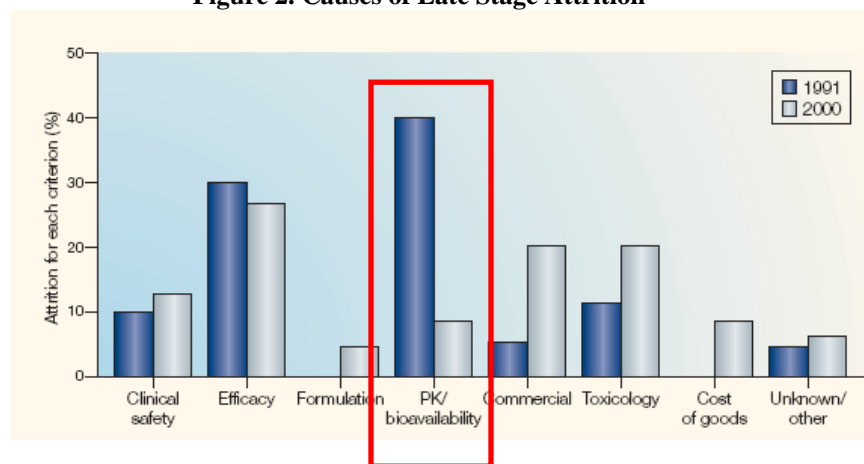


Source: PhRMA, FDA CDER

It has been argued persuasively that the major, and most costly, losses in productivity occur in Phase II²⁻³. Reducing attrition throughout the lengthy development cycle is the most effective and economic means to increase the number of NME approvals from the very large number of molecules that enter early

development². However, the causes of the costly attrition in clinical trials have changed over time, as shown in Figure 2, and it is instructive to examine the causes of the attrition as well as how the industry adjusted to combat it.

Figure 2. Causes of Late Stage Attrition



Source: Kola and Landis, 2004.

Until approximately 1980, the discovery, lead selection and lead optimization (LO/LS) efforts, and the proof-of-concept (POC) studies relied on *in vivo* testing, with comparatively little use of *in vitro* assays⁴. The advent of powerful platform technologies, such as high throughput screening (HTS) and combinatorial chemistry, which promised to yield a very much greater number of development candidates than were available previously, coupled with the general desire to limit experimentation on animals, led to a drastic increase in reliance on *in vitro* assays in discovery and LO/LS. The inadequate

drug-like properties of the lead candidates produced by the new development engine, especially as compared to those generated in earlier decades, was not appreciated until large clinical failure rates due to unsuitable pharmacokinetics (PK) became apparent in late 1980's and early 1990's. The industry recognized the importance of selecting development candidates with drug-like properties⁵, and through concerted efforts that are implemented at the discovery stage and thereafter⁶⁻⁸, the failure rates directly attributable to unacceptable PK/ADME properties have been reduced substantially⁹⁻¹¹ (Figure 2).

Furthermore, it has been recognized widely that other properties of the drug candidates can have a substantial influence on the eventual clinical and commercial success, on the cost of development, and on the cost of goods. Specifically, the evaluation and optimization of the solid state properties of drug candidates has been integrated into the discovery and candidate nomination stages¹²⁻¹⁴.

Reducing attrition from causes that are identifiable in pre-clinical development is projected to be the key to attaining the desired improvements in overall productivity and efficiency. The successful adjustment illustrated herein is a testament to the scientific teams and the vast base of development knowledge that has been accumulated by the industry, and each biopharma organization in particular. For each biopharma, one of the key predictors of the successful implementation of its strategy to improve productivity will be the preservation and the continued utilization of the internal development acumen, and its translation to the new business model.

Creation of the External Team: Theory

A part of biopharma's strategy to achieve greater innovative productivity is the assembly of a network of external discovery/development teams that mirror the internal teams. As it executes its plan, it must ensure that the network is structured appropriately so that the advances biopharma has made in minimization of clinical attrition and product development are not reversed by sub-optimal components in the newly created network. Put differently, the new network can not achieve the desired productivity gains if it is allowed to "re-discover" the old mistakes.

The teams within large biopharma firms that are responsible for creating the external network must clearly understand what makes an effective partnership. It is not merely the external partners' capabilities that will lead to a productive relationship. Rather, the capabilities are the minimum requirement, and they must be accompanied by mutually compatible work processes. For example, a potential external partner may have a technology platform for generation of leads for a specific target of interest to a biopharma. During the pre-partnership due diligence process, the depth and breadth of the external partner's capabilities are assessed, and the value of the technology platform may be verified. The team at the external organization appears also to be scientifically sound and the culture, or way of working, is aligned with that of the biopharma. The discussion then progresses to the negotiation of the mutually agreeable terms.

Creation of the External Team: Some Practical Hurdles

The industry has recognized that the most effective method of cost reduction is the improvement in the quality of assets that are progressed into the clinical trials. However, the overall investment in the pre-clinical development of the drug candidates has not increased commensurately with the increase in the costs of the clinical phases. In fact, the massive reorganization of the pharmaceutical industry has focused on the discovery and the pre-clinical development organizations. The net effect has been the de-centralization these activities, such that data inputs upon which development decisions are based come from multiple sources, including many over which biopharma has no direct control. These include licensors of intellectual property/technology, contract research organizations (CROs), contract manufacturing organizations (CMOs), consultants, equipment vendors, and other contributors.

The outcome of the efforts to improve productivity may well rest on the ability to coordinate the various contributing organizations, to align the business and scientific processes to the unified overall standard of quality, and to integrate the information flow for optimal assessment of developability/translatability of each NME program.

Therefore, what appears to be a straightforward partnering process in theory, in practice is rife with challenges. First, the team charged to establish the partnership is composed of individuals from business development, scientific, and finance teams, all of whom have different training, experience, and

agendas. They are necessarily at odds, all trying to deliver productivity, but viewing the problem from different perspectives and with different time tables.

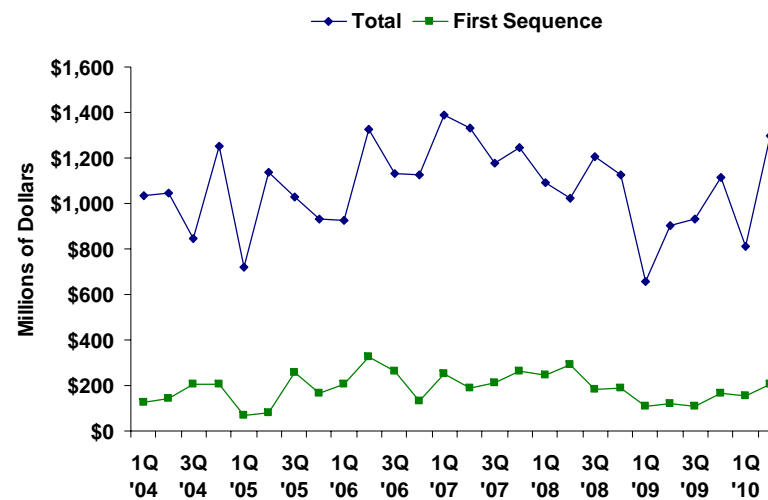
Acquisition of technology is an example of an area in which the apparent perfect synergy between a small innovator company and a large biopharma fails to materialize. Anecdotes from large pharma operational management all cite cases of weak due diligence in licensing deals, resulting in the need to repeat entire pre-clinical programs or to jettison the programs completely. Evidence of biotechs failing to meet expectations is demonstrated by the lack of a productivity increase despite acquisitions over the past 10 – 20 years. Furthermore, in practice, collaboration with and oversight of the external partners has proven difficult, in part due to the lack of training and experience with such external/internal partnerships.

External Alliances: Limitations in the Current Economic Climate

Biopharma’s external R&D alliances can be characterized by their developmental stage and type of organization. From 2000 to 2010, mid-to-late stage deals have increased from 29% of alliances to a projected 60% in 2010, as biopharma attempts to halt its revenue decline by acquiring advanced clinical candidates¹⁵. In addition to late-stage deals, biopharma continues to seek partnerships with venture capital (VC) backed biotechs, as well as with academic organizations and contract research organizations. Irrespective of the development stage or type of organization, biopharma must be diligent in assessing the strengths of these organizations before forging an alliance.

Acquisition or partnership with a large pharma has been a desirable exit strategy for emerging biotechnology companies for many years. Over the last decade, 80% of emerging biotech companies’ drugs that were approved had been partnered with a large biopharma, and of those, 22% had been forged in early development while the majority were later stage deals¹⁵. The biotechs rely on investors, typically VCs, to provide sufficient capital for to the development of assets of value to biopharma. In 2009 in particular, the financing by VCs decreased substantially due to the global recession (Figure 3) and many funds focused on supporting the companies in their existing portfolios, since the time to exit necessarily increased.

Figure 3. Venture Capital Investment in Biotechnology

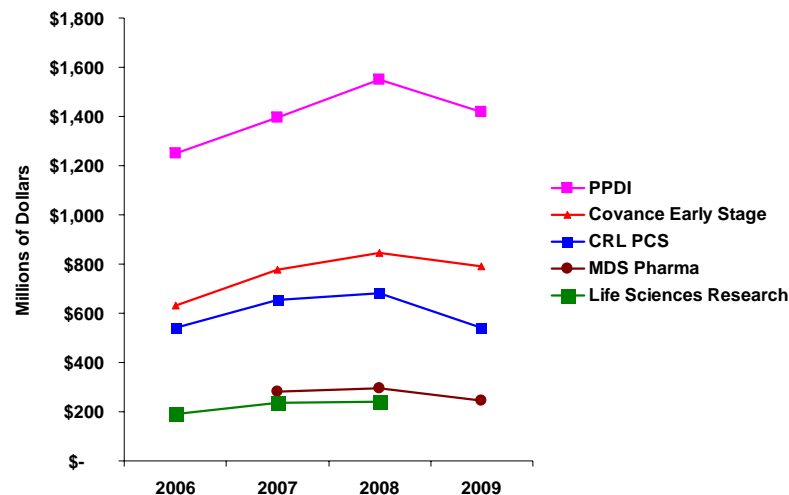


Source: PriceWaterHouseCoopers/NVCA MoneyTree Report

Moreover, biopharma has been favoring late-stage acquisitions. The combination of these factors has led to a decline in investment in the biotechs in early development, and these groups have been forced to reduce their spending. The spending reduction has affected the activities considered by the biotechs to be “wants” but not “needs”, and specifically the de-risking of pre-clinical candidates. In fact, of great concern is the potential disconnect in outlook between the biotechs and the biopharma on the value of de-risking candidates and the pre-nomination due diligence, and the systematic evaluation of developability. The molecules that compose biopharma’s 2008-2010 external early stage pipeline cannot be de-risked as assiduously as the drug candidates had been in previous years because the resources are significantly diminished.

Most emerging biotechs focus exclusively on building value through their proprietary technology, and so they use CROs extensively for necessary and complimentary R&D. As displayed in Figure 4, CRO revenue from early stage services has fallen significantly during the recession, and the outlook for 2010 and 2011 is also expected to be lower than it was earlier in the decade. This observation is not surprising, given that resources are predominantly being directed toward late stage deals¹⁶⁻¹⁷. The number of products in the biopharma pipeline already has fallen off, and may continue to do so as biopharma disinvests in early-stage development, both internally and in external alliances, and as emerging biotechs fail to secure funding for their early stage assets¹⁸.

Figure 4. Early Stage CRO Revenue Down 6-20% in 2009



Source: Company financial statements

Academic institutions are increasingly entering alliances that bring them funding to support basic research, simultaneously allowing biopharma to access cutting edge technologies at the earliest stages of discovery. Many academic-industry partnerships include scientists at the pinnacle of their disciplines, but this advantage is offset by their lack of practical drug development experience and lack of understanding of the drug development process. For example, many academicians often fail to appreciate the extent of the medicinal chemistry efforts required to develop a molecule that is appropriate to advance into preclinical studies. This results in programs that need considerably more resources to yield a de-risked candidate than had been anticipated, to overcome the physicochemical and pharmaceutical liabilities of the original

lead through expert medicinal chemistry and formulation development efforts.

CROs also are striking alliances, becoming an essential piece of biopharma's network. Over the past two decades, the CRO industry has grown significantly, providing capabilities at all stages of discovery and development. As biopharma forges these alliances, their operational team must have a solid understanding of how each CRO operates so that the CRO's capabilities can be integrated effectively into the network. Productive alliances maximize the strengths of each contributor and are functions of the fundamental differences in business models among the contributors.

The Search for the Ideal External Partner(s)

The failure of an external partner to meet expectations of a biopharma development team is a common occurrence. The members of the biopharma teams are typically very strong scientists and managers within their company, but they do not have experience in selecting and partnering with external organizations. Is it safe to assume that if the team selects a CRO that appears to have the required capabilities, that the partnership will be productive? Not necessarily. Much depends on the experience of the biopharma team in selection of the most appropriate CRO and its appreciation of the different CRO business models, which represent unique value propositions, resources, processes, and profit formulae. When this understanding is coupled with the teams' scientific and managerial skills, the likelihood of an effective partnership is greatly increased.

When a biopharma, a biotech company, or an academic group evaluates prospective collaborators, for example a CRO, it is likely that the project needs have been identified and the evaluation centers on the assessment of the CRO's value proposition: can the CRO meet their needs effectively, efficiently, conveniently, and on time. The initial discussions are focused on what needs to be done and seeing if the capabilities of the CRO appear to meet those needs. When the CRO demonstrates that it has the technical resources (trained people, intellectual property and/or proprietary know-how, equipment, facilities, etc.), the discussions typically move into how the work is going to get done through the CRO's established processes. When the capabilities and processes seem to fill the need for the biopharma or biotech, then the discussion moves to the proposal stage, and the specific terms are established, specifying the time to deliver the work, the pricing, and other details. At this point, the biopharma/biotech can theoretically assess the value proposition put forth by the various CROs, from which it has solicited proposals. The proposals are scrutinized by the technical team and by procurement but the viewpoints of these departments differ. The scientific team knows the technical needs and they are able to quickly assess the competence and potential of the various CROs. Procurement, on the other hand, must achieve the best pricing, and while it is understood that the technical needs must be met, procurement must control cash outlays in the short term. So the team must strike a balance and try to obtain the requisite capabilities for the lowest price, thus obtaining what they hope will yield the greatest value.

Realities of the External Collaborator Selection Process: The Business Model is Critical

To make an informed choice of the most appropriate external partners, the team must understand the two distinct, complimentary, but not interchangeable CRO business models, Solution CROs and Process CROs¹⁹. Both types of CROs are needed for biopharma to increase its productivity via its externalization strategy.

Solution Business Model

Solution CROs are organizations that provide customized solutions to unstructured problems, utilizing resources to diagnose and solve the problems expertly. Examples of Solution CROs include R&D organizations and consulting groups. The value a Solution CRO brings to its partner is its resources, intellectual capital, and most significantly, its people. Solution CROs have experts from different disciplines who have strong problem-solving skills, the ability to integrate data from various sources, identify key issues, and to develop a solution to the problem. Although each particular problem is unique, these experts know the analyses required, understand the implications of the findings, and have the resources to perform the requisite investigation. Their work is hypothesis-driven, requiring experimentation and interpretation of the results. Recognition of problems and knowing how to trouble-shoot is a necessary part of developing a productive solution. The fees for Solution CROs are almost always fee-for-service. Because the solutions they generate are applicable in subsequent parts of drug development, Solution CROs generate

high value and their teams command premium prices. Since each project and approach is unique, their fees will differ depending on project, stage of product development, and among different Solution CROs.

Process Business Model

Process CROs are organizations that work in standardized ways, fine-tuning their processes to deliver valuable products and services. Examples of Process CROs include drug product manufacturers and central laboratories services. Their strength is to create and implement processes that can replicate high quality services or products. Thus, the bulk of their value arises from their processes and equipment, and the efficiency of the processes are volume dependent. Process CROs do not depend nearly as much on their people as Solution CROs do because their service or product is predictable and uses set protocols ranging from staff training to product shipping. Their staff requires fewer experts than a Solution CRO, since the work is process driven. However, they must have experts on hand to trouble-shoot problems that will arise in a small percentage of cases. Because of the predictable nature of their work, Process CROs are able to deliver their product or service with a fixed price that is set in advance and determined by the market, and for this reason, the pricing between Process CROs tends to be relatively uniform.

It is crucial to outsource programs to the appropriate providers. A Solution CRO is unlikely to be as efficient and cost-effective in execution of a high volume sample analysis as a Process CRO. Conversely, Process CROs are unlikely to be as

effective or to offer an equal quality outcome in the design and execution of customized projects. There are many anecdotes of instances where a CRO failed to meet expectations, causing unnecessary slippage in timelines, increases to the budget, and significant unanticipated oversight by their biopharma partner, because the commoditized studies were unsuitable for a particular project.

Differentiation between Potential Partners

So how is a biopharma to assess if an organization is a Solution or Process CRO, particularly if it is positioning itself as a “one-stop shop?” One approach is to use the desired outcome of the work as the starting point. Once the biopharma’s operational team establishes the nature of the work, the critical attributes may become clear. The work may be well-defined and easily repeated, making it amenable to a Process CRO, or it may be hypothesis driven, requiring experimentation and, therefore, suited for a Solution CRO. During the capabilities discussion, the operational team typically assesses how a CRO intends to handle specific types of problems that invariably arise. A Process CRO will have processes to solve problems, while a Solution CRO will try to determine the mechanism causing the problems, propose a hypothesis and test it. These two approaches to problem solving are very different, and thus the outcomes will also be different.

Another way to differentiate between the different types is to evaluate the pricing structure. It is unlikely that a Solution CRO will have competitive rates for process-driven services. However, Process CROs will often propose to provide

development work that requires experimentation at a discount, in order to capture all aspects of a program. The operational team needs to conduct particularly thorough due diligence in these cases, since the Process CRO typically does not have the right people on its staff to do the developmental work that requires experimentation, and the outcomes are likely to be sub-optimal. Deficiencies that are built into such sub-standard developmental work become greatly amplified once the product is transformed into a routine process, whether it is manufacturing or routine testing. Another way of evaluating if a “one-stop shop” can effectively provide both Solution and Process-driven services is to determine the customer retention rates by new program placement. This is not the same as customer retention. Once a biotech begins using a CRO for work on a single program, they are leery of changing CRO providers since it is a red flag to the regulatory agencies and potential acquirers. Therefore, if not satisfied with the service, a biotech will complete the program once committed to a particular service organization, but this biotech is unlikely to return for subsequent drug development programs.

Evaluation of the development pathway makes it immediately obvious where Solution CROs and Process CROs should be used. In early development, there is great uncertainty and many moving parts as the program is put together. Experts are required who will be able to synthesize the data from many areas to construct a workable solution in a reasonable timeframe, and although the costs appear to be high, the solution is dependable and brings tremendous value to downstream events. As the program moves into mid and later development, most processes are established, so the Process

CRO provides high quality, acceptable turnaround time, and the best price.

Leveraging a Solution CRO in Early Development: Reducing Biopharma's Strategy to Practice

Biopharma is assembling its externalization network to access the discoveries and research advances in academia and biotech companies, and it also seeks to leverage the best practices from CROs. Biopharma recognizes that the interface between late discovery and early development is critical to ensure that de-risked, drug-like molecules are advanced into the clinic, and that molecules with unsuitable properties are eliminated before scarce resources are expended on their development^{2, 13-14, 20}.

Biopharma has reorganized its internal teams so that the pharmaceuticals and biopharmaceuticals groups interface closely with the medicinal chemistry and pharmacology groups. Since some of the same people are charged with creating external groups to mirror their internal groups, does it make sense for them to work with a CRO that does all the tests but is not able to integrate the information (a Process CRO)? Or does it make sense for to collaborate with an external group that has the same integrated, experienced functions that are able to respond to new data and make informed decisions (a Solution CRO) in support of the internal teams? Late discovery and early development require experimentation and integration of interdependent disciplines. None of it can be reduced to a single process, since every molecule has its unique chemical, pharmaceutical, and business attributes.

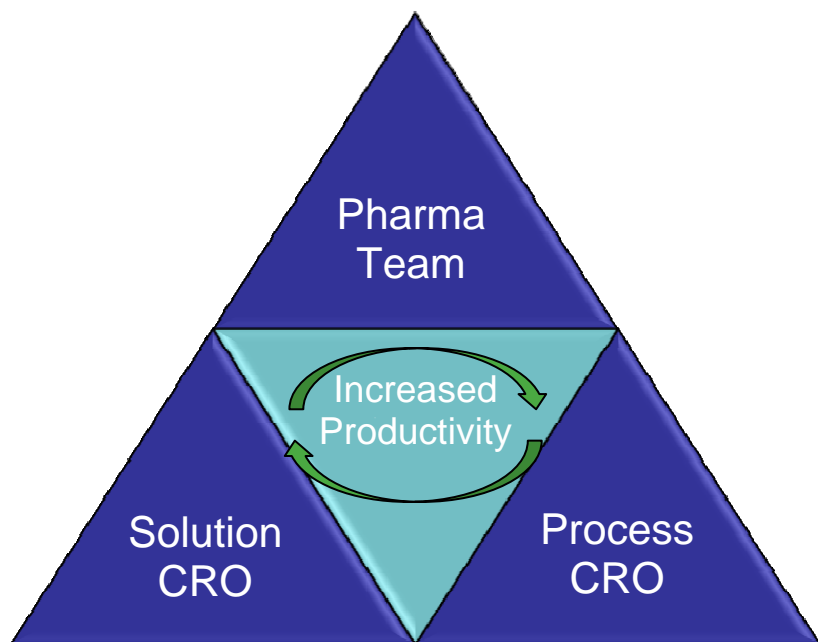
For example, properties that must be characterized in late discovery/early development include solubility, stability, physical form, metabolites, absorption and PK profiles, and of course, none of these can be evaluated without the corresponding analytical and bioanalytical methods. These properties must be assessed in an integrated fashion for the compounds that are coming through biopharma's pipeline, whether their origin is an external biotech partner or from the biopharma company itself. Despite the universally accepted importance of suitable physicochemical properties as a major determinant of development cost and clinical success, there is an industry-wide trend toward development of drug candidates with progressively poorer aqueous solubility than ever before²¹⁻²². In the aggregate, the drug candidates progressed into Phase 1 clinical trials are trending toward larger molecular weights and higher lipophilicity, and the compounds currently in development tend to exhibit even worse properties, with the overwhelming majority projected to be in the problematic BCS²³⁻²⁴ classes II and IV.

These molecules will likely require enabling formulations for commercialization, and even then, they may have limitations. A Solution CRO must be used in the candidate nomination and early development timeframe to develop the methods and processes that will become routine. At that point, it is logical that a Process CRO is used to manufacture API and drug product and perform the non-clinical and early clinical evaluation.

Biopharma's externalization strategy holds great potential to leverage resources that could be effective in reducing costs and

yield greater productivity. Knowledge of the ways to work with those resources is key; the operational teams will benefit from understanding the different types of business models that will facilitate these interactions (Figure 5.)

Figure 5. Optimal Use of Partners can Increase Productivity



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