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Outsourcing Molecular Biology Tasks: A Valuable Business Tool for Accelerating Bioprocessing R&D

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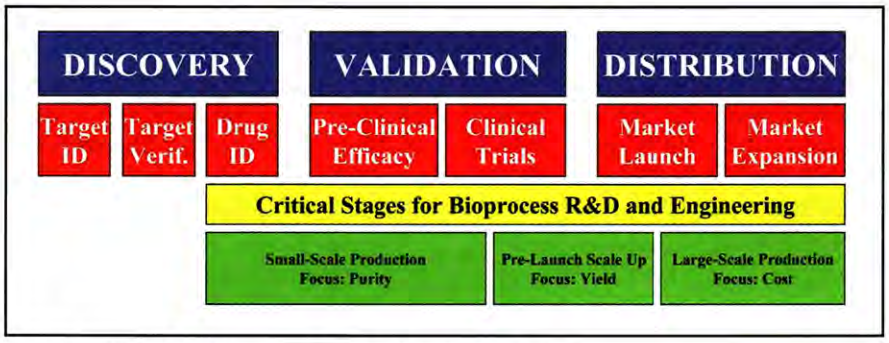

Figure 1. Role of BioProcessing in Drug Commercialization

A significant percentage of new pharmaceutical commercialization activities now focus on biological-based therapeutics. This increasing demand for biologicals necessitates the continued expansion and technological improvement of bioprocessing activities. As Figure 1 illustrates, bioprocessing plays a critical role throughout the entire drug commercialization process. Bioprocessing researchers and engineers must provide access to: 1) biologicals for drug discovery research, 2) substantial amounts of purified drugs for pre-clinical and clinical validation studies, and 3) improved reagents and production methods for large-scale drug distribution.

Bioprocessing executives face an evolving series of business challenges that are influenced by the size, age, competitive landscape, and funding status of their companies. Throughout the lifecycle of a biotech company's products, bioprocessing executives are charged with the responsibility of:

- Ensuring bio-functionality
- Improving yield
- Improving purity
- Decreasing production costs
- Decreasing production time

This multi-faceted responsibility requires bioprocessing leaders to make strategic choices using complex, multi-dimensional decision matrices. These leaders must identify and assess the most efficient and cost-effective systems for 1) guaranteeing access to drug candidates, 2) meeting market demand, and 3) progressively lowering production costs. Unlike some biotech managers who can operate within a fairly limited and vertical framework, bioprocessing leaders must strategically position their attention and influence horizontally across the whole organization, effectively spanning the entire drug commercialization process.

Drug Commercialization Dynamics

Biological-based drug commercialization is a long, arduous process riddled with economic and technological challenges. Successful drug commercialization is fueled by investments. These funds can be obtained either from government grants, institutional investors, loans, or internal finances generated by corporate revenues. No matter the source, all commercialization activities require that a corporate leader convince a fund manager to invest in a specific business opportunity.

These fundamental business dynamics are true for biotech start-ups, mature biotech companies, and even large pharmaceutical companies. Whether it be a start-up CEO "pitching" to investors or a "big pharma" vice president reporting to a budget committee, drug commercialization requires that business leaders compete for limited financial resources. In order to support the success of their company, bioprocessing executives must always look for ways to equip corporate leaders to obtain funds and rapidly convert them into significant financial gains.

During the early stages of drug commercialization, corporate development is driven by technology validation activities. At this stage, initial funding is

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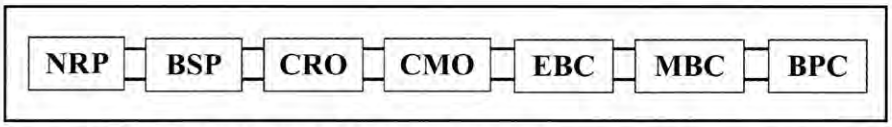

Figure 2. Biotech Supply Chain. NRP: non-profit research partner; BSP: biotechnique service provider; CRO: contract research organization; CMO: contract manufacturing organization; EBC: emerging biotech company; MBC: mature biotech company; BPC: big pharma company.

based upon a drug candidate's market potential as well as the leadership team's predicted ability to achieve technology validation milestones. Because time and financial resources are frequently limited during this stage, achieving technology milestones requires a focus on rapid drug candidate production followed by efficiently executed validation studies.

Once a drug candidate has successfully passed all technology validation milestones, funding sources will invest in preparing for large-scale distribution. During the market launch phase, corporate leaders must focus on dramatically increasing drug production yields while maintaining bioefficacy. After the product is launched — and if the market responds positively — investor metrics shift from revenue generation to profit-based indices.

The economics of drug commercialization can be condensed into two financial goals: 1) growing revenues by gaining significant market share and 2) improving profitability by lowering costs. Bioprocessing leaders serve as a critical linkage between drug discovery and drug distribution. This critical positioning within the corporate structure grants bioprocessing executives the opportunity and corresponding responsibility to identify strategies for improving corporate value.

Maturing Biotech Business Solutions

Because the biotechnology industry is rapidly maturing, biotech executives now have access to many of the business models that previously created significant value for the manufacturing and computer industries. Strategic alliances and outsourcing relationships represent two of the more successful business practices for driving rapid corporate growth and profitability. Within the pharmaceutical-based biotech market sector, outsourcing is becoming more widely employed as a tool to grow and protect equity value prior to a strategic venture or company merger.

Many industry experts have predicted a dramatic shift from the more traditional FIPCO model (fully-integrated pharmaceutical company) to the more efficient VIPCO model (virtually-integrated pharmaceutical company). Alex To, head of the biotechnology research group for Credit Suisse First Boston, said, "Instead of conglomerates that can do it all from genetic research to product marketing, the biotech industry is now a matrix of supply chain relationships along the drug discovery process, with increasing reliance on technology alliances and partnerships." One interpretation of this supply chain structure is illustrated in Figure 2.

Bioprocessing Business Strategies

This supply chain infrastructure creates powerful opportunities for today's biotech companies to adapt to the rapidly changing, highly competitive biotech market space. By establishing strategic alliances and/or outsourcing relationships, biotech companies can pursue new market opportunities with significantly reduced investments in time and money. This adaptability is particularly important when considering the dynamic nature of the biotech industry. New discoveries frequently lead to products that displace old technologies. New market opportunities discovered and established by emerging biotech companies can be overtaken by established companies with larger financial reserves.

Successfully navigating this competitive biotech landscape requires a frequent assessment of market opportunities, competitive forces, and strategic positioning. All corporate activities must align with the two primary financial goals of drug commercialization: 1) growing revenues by gaining significant market share and 2) improving profitability by lowering costs. The strategies best employed for achieving these financial goals depend largely upon the biotech company's strategic focus, available resources, and product pipeline. Innovative bioprocessing leadership can help create a business strategy that simultaneously explores new market opportunities and improves gross margins.

Developing a strong business strategy requires that a company's leadership have a thorough understanding of their organization's core competencies in the context of drug discovery, drug validation, and drug distribution. Core competencies include: 1) proprietary technologies, 2) trade secret processes, and 3) scientific expertise. The leadership team must also know the structure and cost of their company's entire existing infrastructure (facilities, tools, and talent). Infrastructure costs are defined as:

- Facilities: real estate, labs, utilities, telecommunications and database systems
- Tools: equipment, computers, software, reagents (shipping and storage costs)
- Talent: salaries, health insurance, retirement benefits, recruiting, training

Having assessed core competencies and infrastructure parameters, the company leadership can determine at any point in time if their overall corporate profile continues to align with the current business model. It is entirely possible that the dynamic state of the biotech market may have positioned the company to seize a new market opportunity. The major question remaining is how the company should approach this new opportunity.

Restructure or Outsource?

Biotech executives can improve corporate performance either by restructuring the company, by forming strategic alliances, or by outsourcing non-core activities. The overall goals for exercising any one or more of these business strategies include: 1) cutting costs, 2) boosting efficiencies, 3) paring away non-core functions, and 4) focusing on speed and increasing value.[1] Because the metrics for pursuing a strategic alliance are far more complicated than those associated with restructuring or outsourcing, they will not be discussed in the context of this article.

Corporate restructuring can consist of three major activities: 1) refocusing, 2) reorganizing, and/or 3) rebuilding. All three of these restructuring activities can yield variable expenditures and financial returns. Refocusing a biotech business model may lead to short-term cost reductions as non-core assets are released, but may in turn require substantial resources to build the infrastructure for the new focus area. Although corporate reorganization activities can yield more efficient management structures, the reorganization process can lead to short-term productivity losses while new management systems are established.

Choosing to outsource non-core activities, however, allows companies to acquire valuable business services without the up-front capital expenditures or the productivity downtime associated with the corporate restructuring process. Outsourcing non-core activities can also grant organizations access to: 1) top-level professionals, 2) state-of-the-art technologies, and 3) industry-defined best practices.[2,3]

According to the Michael F. Corbett and Associates consulting firm, outsourcing can be employed to obtain tactical, strategic, or transformational objectives. Tactical objectives are associated with short-term projects that have immediate and measurable outcomes. Strategic objectives, however, are associated with long-term increases in productivity as well as substantial decreases in overhead. Transformational outsourcing is associated with fundamentally altering a company's business model.[4-6]

Table 1. Pricing Trends for Biotechnique Services. Historical prices were obtained from the journals *Science* and *Biotechniques*. Prices represent the average of advertisers' fees over a one-year period. In order to compensate for artificially low prices advertised by new companies employing loss-based, low-cost marketing strategies, prices that were significantly lower than the norm and did not persist over a nine-month period were discarded.

	1994	1999	2002	% Change
Oligo Synthesis (price per bp)	$2.50	$0.75	$0.45	-555%
DNA Sequencing (price per run)	$400.00	$30.00	$11.50	-3480%
Peptide Synthesis (price per aa)	$24.50	$14.50	$14.00	-175%
Polyclonal Antibody (price per inoc.)	$2,000.00	$1,150.00	$850.00	-235%

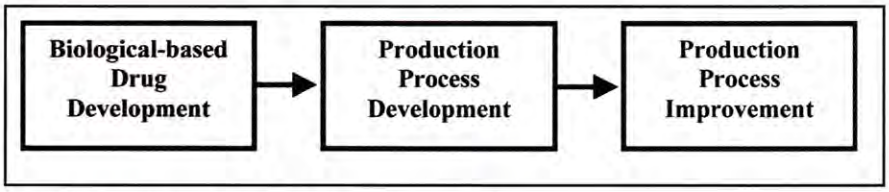

Figure 3. Fundamental Roles for Bioprocessing R&D

Tactical Outsourcing

Tactical outsourcing can significantly improve project completion rates. Because the drug commercialization pathway is composed of numerous, diverse, and staged bioprocessing activities, the possibility that short-term inefficiencies could arise within a specific activity area is very high. Tactical outsourcing can alleviate these inefficiencies by compensating for fluctuations in personnel and equipment productivity.

Strategic Outsourcing

Strategic outsourcing is focused on improving a company's long-term efficiency and effectiveness. Outsourcing can increase a biotech company's overall efficiency by reducing the levels of wasted effort associated with performing bioprocessing activities. This efficiency results from the fact that the outsource provider assumes the overhead and management costs associated with performing the specific bioprocessing function. Because the outsource provider is only rewarded if the contracted service is executed properly, the customers are guaranteed the effective completion of their desired bioprocessing activities.[7]

Transformational Outsourcing

Transformational outsourcing can empower biotech companies to expand their core competencies into new market sectors. This form of outsourcing is particularly valuable for companies that own a powerful and proprietary bioprocessing system. Rather than attempt to build a FIPCO, the bioprocessing company can outsource drug commercialization activities that reside upstream and downstream of their core technology. Thus, transformational outsourcing may turn their company into a VIPCO.

Outsourced bioprocessing can also provide substantial risk mitigation ben-

Figure 4. Molecular Biology Service Trends: Biotechnique outsource conversion occurs through a series of predictable steps.

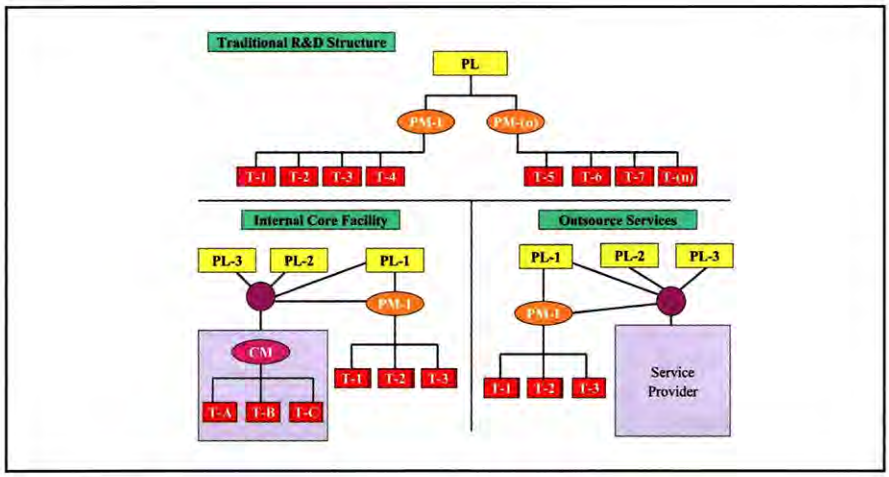

Figure 5. R&D Managment Structures. PL: Project Leader; PM: Project Manager; T: Technician; CM: Core Facility Manager.

efits at the tactical, strategic, and transformational levels. As honest and experienced molecular biologists will readily attest, nothing is "certain" when working with biological systems. Predicted biological outcomes are not guaranteed when performing bioprocessing R&D activities (e.g., the expression of a desired recombinant protein may unexpectedly produce lethal effects in an expression host). Many biotech service providers only charge their customers a one-third to one-half up-front project initiation fee. When compared to performing novel bioprocessing activities in-house, outsourcing significantly mitigates a company's financial risk.

Outsourcing Bioprocessing R&D

As introduced earlier, bioprocessing leaders are responsible for ensuring the bio-functionality, improving the yield, improving the purity, decreasing the production costs, and decreasing the production times for generating biological-based therapeutics. One strategy for managing these responsibilities is depicted in Figure 3.

Bioprocessing executives must carefully choose the organizational structures and business solutions that best enable them to manage the R&D process. As the number and maturity of R&D outsourcing opportunities expands, bioprocessing leaders are becoming more willing to compare the status and effectiveness of their company's historical R&D structure with the advertised strengths of R&D service providers. Figure 2 previously introduced the existence of three R&D outsourcing entities: non-profit research partners (NRP), biotechnique service providers (BSP), and contract research organizations (CRO).

As Figure 4 illustrates, biotechniques employed in R&D activities follow a natural progression toward becoming an outsource service. Once researchers begin to accept and use a specific biotechnique, it becomes economically feasible for commercial providers to develop and market reagents and kits to perform that technique. As the theory behind the technique becomes commonly understood and the need for faster performance grows, automated equipment is developed and sold, allowing a technician to perform the procedure even faster. With the availability of this automated equipment, outsourcing services such as university/industry-based core facilities and for-profit companies emerge.

Improving bioprocessing R&D productivity can be accomplished either by restructuring internal research groups or by pursuing outsourcing relationships. Figure 5 illustrates several business models for managing R&D activities. Both the Traditional R&D model and the Internal Core model have significant overhead, management, and inefficiency costs associated with them.

Internal core facilities can offer significant process and efficiency improvements over traditional R&D models. The overall productivity of R&D core facilities, however, is gated by the magnitude of internal orders. Fluctuations in order volume and staffing can dramatically hinder the effectiveness of internal core facilities.

Cost and Time Improvements

Outsource R&D service providers can provide dramatic improvements in cost, quality, and turnaround time due to competitive pressures and larger order volumes. Project quality and turnaround time are frequently influenced by error rates. R&D service providers achieve lower error rates because they have a single focus, established best practices, cutting-edge methodologies, and state-of-the-art equipment.

As more companies embrace outsourcing R&D activities, specific biotechniques are exposed to free-market forces. The ensuing competition leads to lower prices, higher quality, and faster production times. Table 1 clearly illustrates how the prices for biotechnique services have dramatically dropped since 1994. These improve-

Table 2. Molecular Biology Service Providers

	Clone Acquisition								Gene Modifications		Gene Construction															Protein Production Services				Virus Production Services		
	Library Construction Services				Library Screening Services		Pre-made libraries				Protein Expression vectors					sRNA vectors	Gene therapy vectors					Complex Transgenes									
	Genomic			cDNA	Genomic		Genomic		cDNA														Gene targeting constructs									
	(1) BAC Clone	(2) Plasmid	(3) Lambda	(4) Plasmid	(5)		(6) Plasmid	(7) Lambda	(8) Plasmid		(9) Site-directed mutagenesis	(10) de novo gene synthesis	(11) Bacteria	(12) Fungi	(13) Baculovirus	(14) Mammalian cell culture	(15) other	(16)	(17) Retrovectors	(18) Lentivectors	(19) Ad vectors	(20) AAV vectors	(21) Herpes vector	(22) Tissue-specific expression vectors	(23) conventional knock-out	(24) conditional knock-out	(25) knock-in	(26) Bacteria	(27) Fungi	(28) Baculovirus	(29) Mammalian cell culture	(30) other	(31) Retrovectors	(32) Lentivectors	(33) AAV vectors
Althea Technologies, Inc. www.altheatech.com Year of inception: 1998									✔																						
AppTec Laboratory Services www.apptecls.com Year of inception: 1982																															
ATG Laboratories, Inc. www.atglabsinc.com Year of inception: 1994							×	×	×		×	×	✔		✔	×															
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GenScript Corporation www.genscript.com Year of inception: 2001											×	✔						✔										×	×	×			
Nature Technology Corporation www.natx.com Year of inception: 1997	×	×	×	×							×	×	×				×		✔	×		×		×				×			✔	×	×

× = service provided
✔ = area of expertise

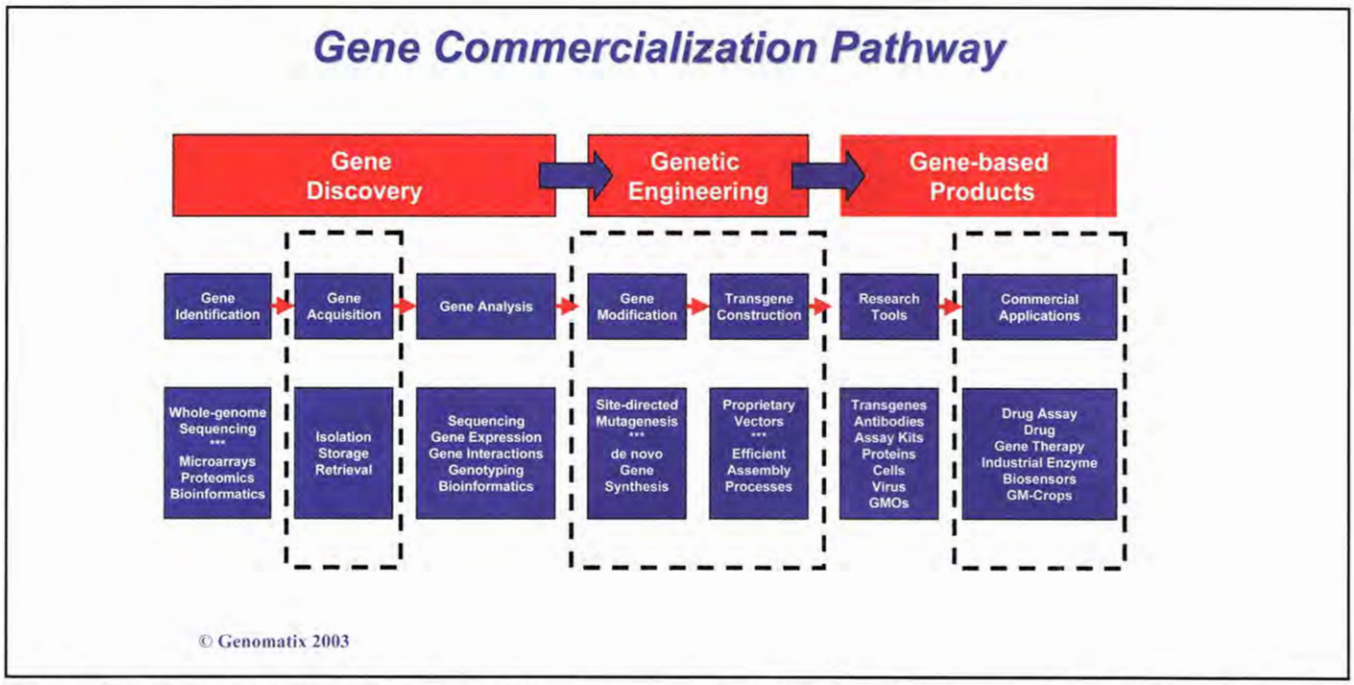

Figure 6. Gene Commercialization. This figure illustrates the process and underlying biotechniques associated with commercializing gene-based products.

ments in price and turnaround time ultimately accelerate all R&D activities.

Outsourced Gene Commercialization

Biological-based therapeutics can be separated into four major classes: recombinant proteins, nucleic acid polymers, viral gene therapy systems, or cells and tissues. Developing any of these therapeutic classes first requires that researchers acquire the genetic material that encodes a biological-based pharmaceutical. These DNA molecules must then be retrofitted for bioprocessing activities. Figure 6 illustrates the pathway by which genes are converted into commercial products.

As introduced before, the research goals of bioprocessing scientists are to: 1) ensure the bio-functionality, 2) improve the yield, 3) improve the purity, 4) decrease the production costs, and 5) decrease the production times for biologicals. Researchers can employ numerous molecular biology techniques when striving to fulfill these goals. Strategies for achieving these goals include, but are not limited to:

- Changing the codon structure of a gene to correlate with the expression host's preferred codon usage (codon optimization)
- Producing synthetic DNA molecules (de novo gene synthesis)
- Altering the genomic structure of expression hosts to include enzymes and co-factors needed to generate recombinant proteins harboring the appropriate post-translational modifications (gene insertion)
- Ablating genes from expression hosts that encode biological entities that prevent the efficient isolation of specific biological-based therapeutics (transient gene deletion: siRNA; stable deletion: gene knock-out)
- Developing DNA cloning vectors that facilitate the rapid construction of transgenes required to produce recombinant proteins, virus, and cells

Molecular Biology Services

Over the past twenty years, a network of service providers has grown that can perform nearly all of the molecular biology strategies defined above. The boxed regions in Figure 6 highlight those areas where molecular biology services can provide significant value for bioprocessing researchers. These services include 1) clone acquisition, 2) gene modifications, 3) gene construction, 4) protein production, and 5) virus production. Table 2 provides a listing of established molecular biology service providers and their areas of core expertise.

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