

Industry Developments in
U.S. Biopharmaceutical Contract Services

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INTRODUCTION

In 2008, BioCrossroads released a report, *Biopharma Discovery and Development Contract Services – Indiana Market Opportunities and Funding Options, an analysis of the pharmaceutical and biotech development and manufacturing sector*, that researched and highlighted the trend of pharmaceutical and biotechnology companies increasing utilization of third party contract service providers (CSPs) as strategic partners for outsourced services necessary to bring a product to market. Outsourcing was utilized to combat the high costs and long lead times of product development and to manage scientific and business risks. In particular, the report focused on Indiana's leadership in the sector and the potential for new opportunities and growth. With more than 8,000 workers and 40 companies working in the CSP sector, Indiana is a national center for biopharma development and manufacturing. The state is one of only a few areas in the United States with a concentration of companies that excel in specialized and sophisticated drug development services such as contract research, contract manufacturing, and logistics.

What was a new trend in 2007-2008 is now an industry standard and the emergence of fully integrated pharmaceutical networks (FIPNETs) have changed the landscape of pharmaceutical product development. This market trend and analysis addendum to the 2008 report discusses challenges in the industry due to the downturn in the economy, the impact of healthcare reform, and other influences that are impacting the biopharma contract service sector and anticipated market trends in 2010.

I. 2009 – A CHALLENGING YEAR FOR CONTRACT SERVICE PROVIDERS

Over the past decade, contract service providers to the pharmaceutical industry such as clinical research organizations (CROs) and contract manufacturing organizations (CMOs), benefited from a trend of increased outsourcing by pharmaceutical companies. However, 2009 was a challenging year for this sector. While pressure for outsourcing continues to increase, uncertainty over healthcare reform and tighter spending controls have created significant headwinds for a sector that had been growing revenue consistently in the double-digits. For the period ending September 30, 2009, four of the five largest CROs by market capitalization had year-to-date revenue declines ranging from one to sixteen percent.

The following market developments led to lower growth and in some cases, losses, for several major CROs and CMOs in 2009:

Uncertainty led to clinical trial cancellations and delays – During 2009, several large CROs reported Phase II and Phase III clinical trial cancellations and delays. While attrition and portfolio prioritization led to some of these cancellations, uncertainty caused by the potential impact of healthcare reform on pharmaceutical companies' ability to be reimbursed for new products also contributed to the termination of projects. In addition, while smaller biotechnology companies provide modest revenue for large CROs, the inability of many small biotech companies to obtain additional equity financing in the current bleak capital markets resulted in a decline in clinical trial work and exacerbated the revenue declines of many CROs.

Pharmaceutical companies continued a shift towards strategic partnerships with CSPs – The upcoming expiration of patents across the industry, coupled with pricing pressure from public and private payers, continue to push pharmaceutical companies to establish strategic relationships with contract service providers. An asset transfer by a pharmaceutical company to a CSP, coupled with a long-term service contract, has formed the basis for several strategic partnerships. In 2009, Covance acquired Merck's Gene Expression Labs for \$145 million. As part of the transaction, Merck transferred the facility's employees to Covance and signed a five-year contract to provide genomic analysis services. Covance and Eli Lilly and Company formed a similar type of strategic partnership in 2008 when Covance acquired Lilly's toxicology and pre-clinical facility in Greenfield, Indiana, and entered into a ten-year contract to provide such services to Lilly. PPD and Merck completed a similar transaction in 2008. At Baird's Health Care Conference in September 2009, ICON plc's management reported that "clients are increasingly engaging CROs at a more strategic level as indicated by the level of client management engagement, willingness to share drug pipeline intentions, and deepening reliance on CRO scientific and therapeutic expertise."

Contract manufacturing organizations also continue to establish innovative strategic partnerships with pharmaceutical companies. For example, in late 2009 Eli Lilly and Company announced the sale of its Tippecanoe Laboratories manufacturing facility to a Germany-based multinational holding company, Evonik Industries AG. The manufacturing site, located in Lafayette, Indiana, will remain in operation with a focus on producing active pharmaceutical ingredients (API) and specialty chemical and animal health products. The former Lilly employees at this facility are now employed by Evonik.

Such a shift from a "transactional" relationship to a "strategic" partnership benefits both the pharmaceutical company and the CSP. In the examples described above, the pharmaceutical company reduces its operating expense and headcount associated with these activities, while benefiting from additional operational flexibility. The employees transferred from the pharmaceutical company to the CSP bring knowledge of the pharmaceutical company's policies and procedures and incorporate that knowledge into their new role as a service provider. In addition, the employees benefit from the CSP's use of the facility to serve multiple clients. In

summary, the CSP gains a long term revenue stream and experienced employees that can operate a facility more efficiently by serving multiple pharmaceutical clients.

Utilization of late-phase clinical trial services increased – As noted above, several CROs were adversely affected by the postponement or cancellation of clinical trials in 2009. However, the trend of pharmaceutical companies spending significant amounts of money on late stage services (Phase II – Phase IV clinical trials) should be on the rise as companies seek to accelerate the commercialization of drug candidates to compensate for upcoming patent expirations and conduct post-marketing trials as required by the FDA.

The pharmaceutical industry continued to disaggregate – In 2009, pharmaceutical companies continued the trend of reducing the size and scope of their operations with the intent of becoming more efficient and effective to address significant external pressures from customers, competitors and shareholders. In general, companies have moved towards a more flexible business model by partnering with specialized service providers to perform drug development activities, closing facilities in connection with functional outsourcing, and selling or spinning-off non-core assets. Companies have utilized different strategies as they move toward a future where businesses must be more flexible to address these external pressures:

Partnering with specialized service providers – In 2008 and 2009, Eli Lilly and Company further implemented its fully integrated pharmaceutical network (FIPNET) strategy by transferring existing research and manufacturing facilities, and the employees working there, to contract service providers and, in turn, signing long-term service contracts. Through this strategy, Lilly has reduced its headcount by over 1,000 employees, but still has access to those employees' skills and expertise through service contracts with the CRO and CMO, respectively.

Facility closures coupled with functional outsourcing – Many pharmaceutical companies have closed manufacturing facilities over the past few years, but AstraZeneca has disclosed a strategic decision to eventually exit manufacturing its own products entirely. In 2008, the company closed manufacturing facilities in Spain, Belgium and Sweden, resulting in the elimination of 1,400 positions. In November 2009, AstraZeneca disclosed that it will outsource the manufacture of all APIs and is currently evaluating bids for these manufacturing services. As reported on the in-Pharma Technologist.com website, "Although sourcing...APIs from Asia is an established cost cutting move, to date, none of Astra's Big Pharma peers have proposed such a complete implementation of this strategy."

Sale or spinoff of non-core assets – In 2008, Bristol Myers-Squibb (BMS) performed a review of its business lines and elected to sell or spin-off products that were not core to its pharmaceutical business. BMS sold its Convatec business unit to a private equity firm and spun-off its nutraceutical unit, Mead Johnson, to shareholders.

II. 2010 – MARKET TRENDS

Industry changes will reduce the number of CSPs utilized by pharmaceutical companies – The Pfizer-Wyeth and Merck-Schering-Plough mergers continued a trend of consolidation among pharmaceutical companies as they face pricing pressure and pending patent expirations. *The Wall Street Journal* reported that the pharmaceutical industry reduced its headcount by 40,000 workers in 2009. Many analysts forecast that the pharmaceutical industry will continue to restructure and consolidate in 2010 as \$6.5 billion in revenues from existing products vanish when patents expire.

As the number of strategic partnerships between pharmaceutical companies and CSPs increases and the industry's need to improve productivity and increase speed to market continues, a reduced number of CSPs will be utilized by each pharmaceutical company. These trends, accompanied by a consolidation within the pharmaceutical industry itself, will lead to increased competition for a smaller number of large pharmaceutical clients. Based on the breadth of service offerings and worldwide scale, larger CROs are positioned to gain market share from this trend. However, smaller CROs will be able to compete by specializing in niche services such as recruiting clinical trial participants from underserved populations and specific countries, by providing insight into specific disease states and by providing better client service.

CROs will become increasingly important in the development of biomarkers - Due to pressure from public and private payers who want assurance that the products they reimburse lead to positive clinical outcomes, pharmaceutical companies are striving to find biomarkers that will allow them to identify biological targets, to better understand the mechanism of action for drug candidates and to stratify patients during clinical trials.

BioCrossroads believes that CROs will become increasingly important partners in the development of biomarkers that could be utilized as companion diagnostics to the therapeutic agents commercialized by their clients. A press release from Covance in late 2008 noted that “pharmaceutical companies are adopting biomarker strategies for the vast majority of new drug candidates, and it is predicted that within the next ten years biomarkers will be a standard aspect of drug development for any novel candidate.”

As pharmaceutical companies increase their utilization of CROs for biomarker services, CROs are gaining access to expertise via acquisition while also building these capabilities internally. Examples of Covance's strategy include its acquisition of a minority interest in Caprion Proteomics, which enable it to gain access to that company's proprietary proteomics discovery technology, CellCarta®. In addition, Covance has bolstered its internal capabilities by establishing its Biomarker Center of Excellence in Greenfield, Indiana, with the intent of focusing on biomarker testing and validation and leveraging the services that already reside at Greenfield, including in vivo preclinical safety and efficacy assessment, and a variety of sophisticated preclinical imaging modalities.

Mandated comparative effectiveness studies will begin to affect the pharmaceutical industry and its CSP partners – In 2009, the American Recovery and Reinvestment Act (ARRA) provided \$1.1 billion for comparative effectiveness research and established the Federal Coordinating Council for Comparative Effectiveness Research (FCCER). These funds are being distributed to the Health and Human Services agency, National Institutes of Health and Agency for Healthcare Research and Quality with the goal of “providing information that helps clinicians and patients choose which option fits an individual patient's needs and preferences.” Depending on whether or which final version of healthcare reform legislation is ultimately passed by Congress, these agencies may perform retrospective reviews of previously published literature and clinical trial results. In the future, these federal agencies – or a newly-created agency - may choose to perform their own independent clinical trials, similar to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study coordinated by The University of North Carolina at Chapel Hill and funded by the National Institute of Mental Health. These prospective clinical trials, which may be administered through the Centers for Education & Research on Therapeutics (CERTS) and research universities, could provide opportunities for CROs to support federal agencies with clinical trial design and execution in selected cases.

Regardless of the short-term impact of comparative effectiveness on CSPs, with the establishment of the FCCER and its significant funding, comparative effectiveness analysis will now be a critical component of the process by which pharmaceutical companies discover, develop and distribute their products to patients.

Healthcare reform will accelerate the development of generic biologics – Another impact of healthcare reform, at least as proposed at the time of this update, is the anticipated finalization of a regulatory pathway for generic biologic products (biosimilars). Eliminating regulatory uncertainty will allow domestic CMOs to prioritize this potentially significant market and determine how to approach potential customers. As soon as the U.S. Food and Drug Administration (FDA) finalizes the rules and regulations for the data package which must be filed by biosimilar manufacturers, CROs could benefit from the clinical testing required before

product launch. CMOs could gain a new, large market for their large molecule manufacturing services through these new FDA requirements for biologic products.

CONCLUSION

Despite a slower than expected year in 2009 for many CSPs, the underlying reasons for pharmaceutical and biotechnology companies to outsource selected activities to CROs and CMOs will continue for the foreseeable future. CSPs should continue to grow as the pharmaceutical industry disaggregates and moves towards a more flexible business model. Biomarker services and the need for larger clinical trials will provide opportunities for additional growth moving forward. However, with the consolidation of the pharmaceutical industry and the continued trend of strategic partnerships between CSPs and their clients, many companies in the sector will be faced with finding new revenue sources or merging with other providers in the sector.

III. INDIANA'S CONTRACT SERVICE SECTOR

Expansions

- AIT Laboratories established a CRO division, AIT BioScience, and invested in a new facility in Indianapolis.
- BioConvergence added a biorespository to its facility in Bloomington and expanded its services to include clinical sample management.
- BioStorage Technologies invested \$6 million to expand its operations in Indianapolis with plans to hire 125 new employees.
- Covance Laboratories announced that it would invest \$41 million and locate its company-wide Biomarker Center of Excellence in Greenfield.
- Elona Biotechnology established a new subsidiary, Zimmerman Biotechnologies, to produce generic biologic products.
- Schwarz Pharma Manufacturing, a unit of UCB, announced a \$12 million expansion of its Seymour manufacturing plant and distribution center.
- In Elkhart, Stanbio Life Sciences completed a GMP facility for pharmaceutical manufacturing services.
- Waterstone Pharmaceuticals received a \$12 million investment to expand contract manufacturing services in Indianapolis.

Other Developments

- In September 2009, Eli Lilly and Company (Lilly) announced a company-wide reorganization and restructuring aimed at lowering its cost structure and accelerating the development of new products. The plan targets \$1 billion in cost savings by the end of 2011 and accelerates Lilly's existing strategy of moving from a fully integrated pharmaceutical company to a fully integrated pharmaceutical "network" of internal capabilities and external companies partnering to discover and develop new therapies. As an integral part of this strategy, the plan establishes, within Lilly, a Development Center of Excellence charged with playing an increasingly significant role in accessing both internal and external capabilities to advance the development of priority projects identified by the company's newly formed business units in oncology, diabetes, existing markets, emerging markets and animal health.
- Lilly announced the sale of its Tippecanoe Laboratories manufacturing facility to Evonik Industries AG. The manufacturing site, located in Lafayette, Indiana, will remain in

operation with a focus on producing high-quality active pharmaceutical ingredients (API) and specialty chemical and animal health products.

- Enzon Pharmaceuticals announced that it entered into a definitive agreement to sell its specialty pharmaceutical business, including a manufacturing facility in Indianapolis, Indiana, to Sigma-Tau Pharmaceuticals, the U.S. subsidiary of an Italian pharmaceutical company.
- inVentiv Clinical Solutions announced it had acquired ParagonRx, a consulting company specializing in pharmaceutical risk management and optimizing medication use. The acquisition will enhance inVentiv's REMS service offerings and will be supported by the company's Indianapolis office.
- The Purdue University-based National Institute for Pharmaceutical Technology and Education (NIPTE) received a two year contract from the U.S. Food and Drug Administration (FDA) to ensure that FDA reviewers are kept up to date on pharmaceutical manufacturing and technology.
- Ivy Tech Community College developed a certificate program for workers in biotechnology manufacturing.

Source> InsideIndianaBusiness.com, Indianapolis Star, company websites

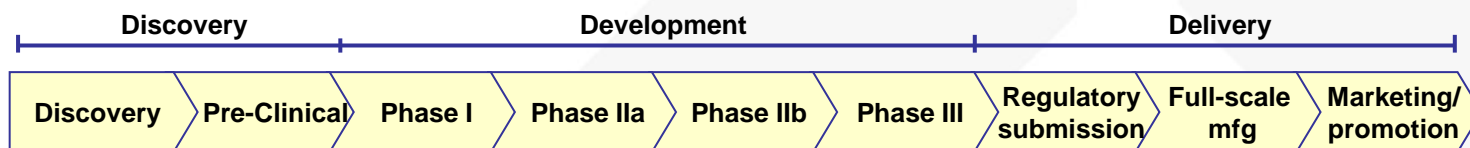
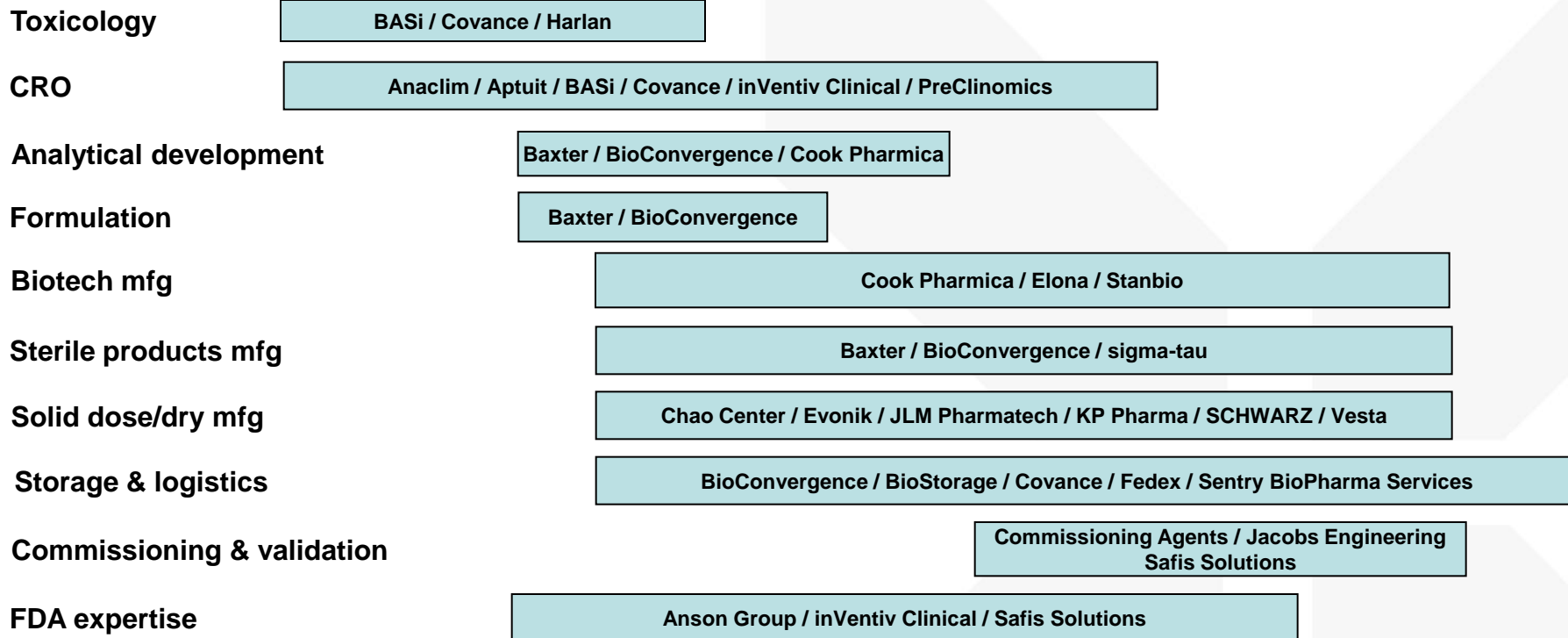
Biopharma Development and Manufacturing in Indiana

Company	Activity	Employees
AIT BioScience	CRO	5
AIT Laboratories	Toxicology	350
Aledo Consulting	Reimbursement Consulting	8
American Family Pharmacy	Contract Manufacturing	10
Anaclim	CRO	10
Anson Group	FDA Consulting	12
Aptuit	CRO	100
BASi	CRO	185
Baxter Biopharma Solutions	Contract Manufacturing	1,000
BioConvergence	Contract Development	43
BioStorage Technologies	Sample Management	50
Bristol Myers Nutritionals	Dry/Wet Products Manufacturing	700
Bristol Myers Pharma	Solid Dose Manufacturing	300
Chao Center for Contract Manufacturing	Contract Manufacturing	21
Commissioning Agents	Regulatory Compliance	140
Concentrics Research	CRO	30
Cook Pharmica	Contract Manufacturing	400
Covance Central Labs	CRO	1,200
Covance Laboratories	CRO	300
DCL	Specialty Lab	200
Elona Biotechnology	Contract Manufacturing	14
Evonik Industries	Contract Manufacturing	700

Company	Activity	Employees
G&S Research	Market Research	45
Harlan Laboratories	CRO/Research models	350
IN Institute for Biomedical Imaging	CRO	70
IU Vector Production Facility	Biotech Manufacturing	13
inVentiv Clinical Solutions	CRO	150
JLM Pharmatech	Contract Manufacturing	20
KP Pharma	Contract Manufacturing	25
Krauter Solutions	Storage and Logistics	15
Lilly—Clinton	Dry Products	200
Lilly—LTC North	Biotech Manufacturing	1,500
MD Logistics	Cold Storage	105
MicroWorks	Specialty Lab	10
Midwest Compliance Laboratories	Specialty Lab	5
MICR	CRO	18
Pharmakon Compounding	Contract Manufacturing	10
PreClinomics	CRO	15
Safis Solutions	FDA Consulting	20
SCHWARZ Pharma (UCB)	Contract Manufacturing	360
Sentry BioPharma Services	Storage and Logistics	30
sigma-tau	Contract Manufacturing	150
Stanbio Life Sciences	Contract Manufacturing	10
Vesta Pharmaceuticals	Contract Manufacturing	20

Total: 8,919

Indiana's contract service providers can take a molecule from the lab and move it through development to full-scale manufacturing



About BioCrossroads

BioCrossroads (www.biocrossroads.com) is Indiana's initiative to grow, advance and invest in the life sciences, a public-private collaboration that supports the region's existing research and corporate strengths while encouraging new business development. BioCrossroads provides money and support to life sciences businesses, launches new life sciences enterprises (Indiana Health Information Exchange, Fairbanks Institute for Healthy Communities, BioCrossroadsLINX, and Datalys Center), expands collaboration and partnerships among Indiana's life science institutions, promotes science education and markets Indiana's life sciences industry.

About BioCrossroadsLINX

BioCrossroadsLINX (www.biocrossroadslinx.com) is a non-profit organization, established by BioCrossroads to build upon Indiana's strengths in drug development and manufacturing through educational and workforce development programs and regional collaborations. BioCrossroadsLINX analyzes, organizes and publicizes Indiana's strength in biopharmaceutical development and manufacturing.

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