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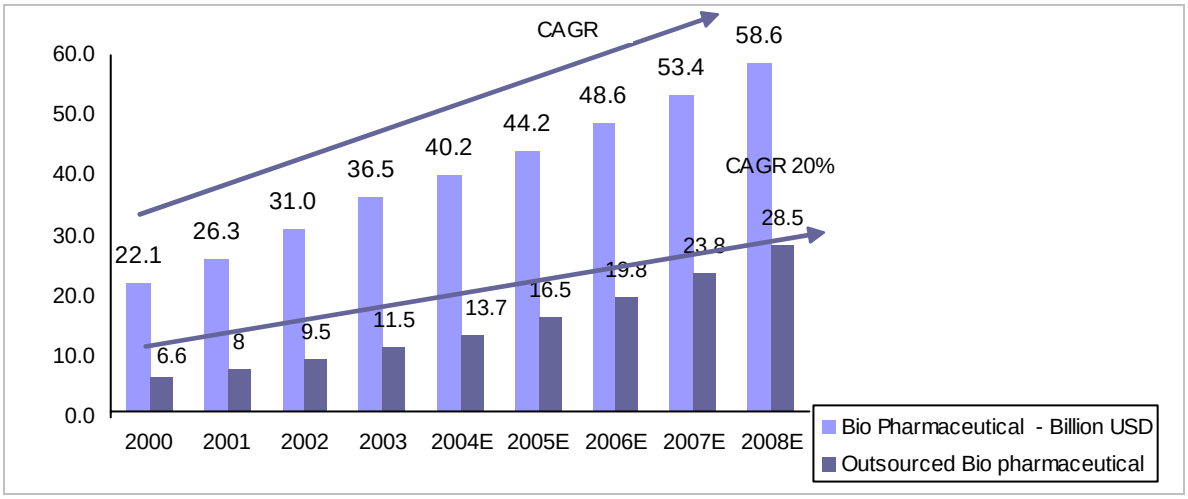
Biopharmaceutical Outsourcing – Moving to Centerstage

Biopharmaceuticals[1] is the most upcoming segment of the pharmaceutical industry due to the evolution of biotechnology. This has resulted in highly efficacious products that aim at providing cures for life-threatening, difficult ailments, which have been difficult (well nigh impossible!) to treat. This industry is keeping its nose to the grindstone to reach the pinnacle. Certain factors, like increasing costs, complex regulatory issues, high prices, tremendous competition, etc., are forcing companies to improve their operational efficiency and productivity. Outsourcing has become a strategic imperative for companies in their quest to improve their efficiency and productivity.

Figure 1: Outsourcing in Biopharmaceutical Market (USD billion) – (2000-2008)

According to Figure 1 the biopharmaceutical market is forecasted to growth at a CAGR of 10 percent reaching USD 58.6 billion in 2008 from USD 36.5 billion in 2003. Outsourcing in this sector, however, has been increasing at a rate of 20 percent per annum. The coming years will witness an increasing proportion of biopharmaceutical activities being outsourced



Source: BBC, Inc. IMS Health & EVS Analysis

[1] Biopharmaceuticals refers to any products/agents that are produced using biological processes, organisms, or products for the purpose of pharmaceutical consumption.

Outsourcing or Offshoring – Does It Really Matter?

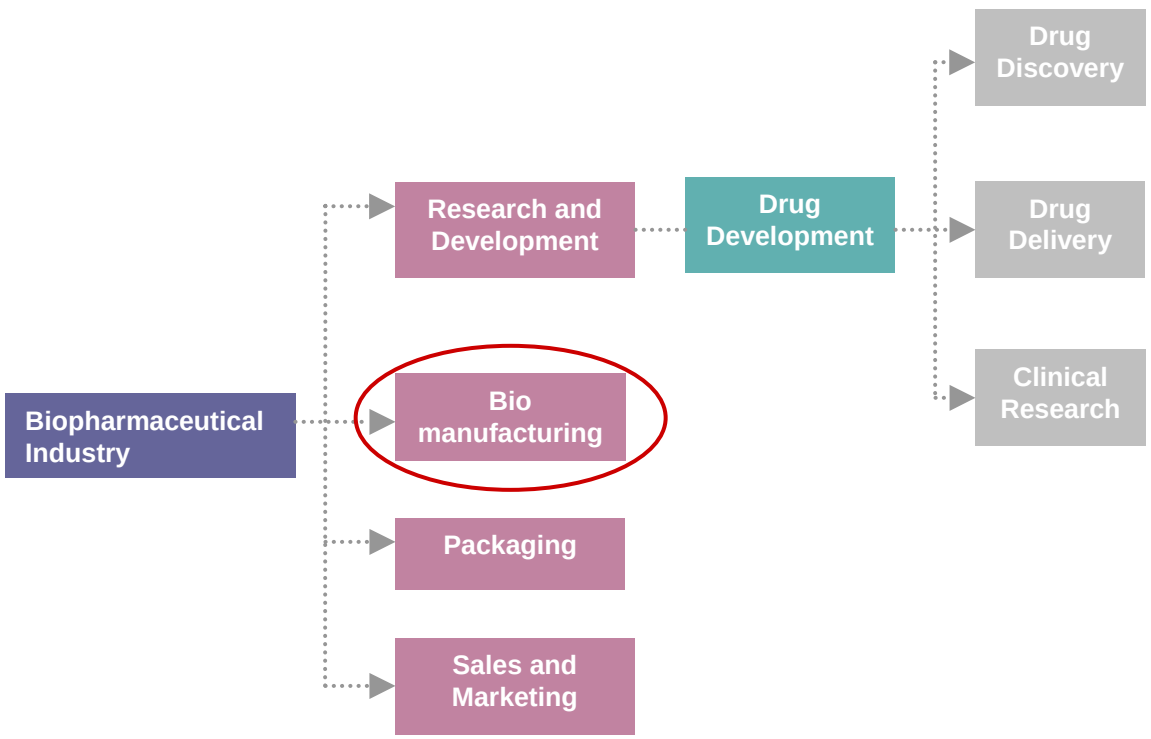
The conventional idea of offshoring processes to low-cost Asian countries is not the only way out for biopharmaceutical outsourcing. Outsourcing in biopharmaceuticals has crossed the Rubicon as far as cost reduction is concerned. Companies now have a vision that goes beyond cost cutting. In fact, the majority of the top service providers, like Boehringer Ingelheim, Lonza Custom Manufacturing, etc., are based in the United States. However, there are emerging opportunities in Asian countries, which is driving offshoring of biopharmaceuticals to these destinations. Biocon in Bangalore, India, has announced that it will manufacture Bristol-Myers Squibb's (New York, NY, USA) recombinant insulin product. In the area of clinical trials, the Biopharmaceutical Manufacturing Technology Center (Singapore), a part of the Bio processing Technology Institute, has opened a pilot-scale facility to produce materials through Phase II clinical trials.

Panorama of Outsourced Segments in Biopharmaceuticals

Outsourcing in this industry began in the 1980s with manufacturing and gained momentum in the next decade to include areas such as R&D, clinical trials, marketing, sales, and packaging. The rules of the game in outsourcing in this domain are similar to those of the other industries; as in the above-mentioned segments, the degree of outsourcing differs on a case-to case basis, as companies are cautious about abdicating full control of their prime functions. For example, they may keep all R&D to themselves and outsource the entire manufacturing process and 50 percent of their sales operations.

Exhibit 1 captures the major segments in which activities are outsourced in the biopharmaceutical industry.

Exhibit 1 – Outsourcing in the Biopharmaceutical Industry



Source: Evalueserve analysis

There are several steps in the drug discovery and development cycle that can be outsourced, right from lead and target identification and analysis, through devising the delivery mode to early- and late-phase clinical trials.

The most commonly outsourced R&D activities include bioavailability and bioequivalence studies, analytical/bioanalytical activities, clinical trials, clinical trial monitoring and management, biostatistics, licensing, regulatory affairs related to clinical research, and many more.

Contract biopharmaceutical manufacturing represents the most attractive segment in biopharmaceutical outsourcing. It includes various expression and fermentation technologies (to produce cell cultures, proteins, antibodies and enzymes), and transgenic animal production. According to the Second Annual Survey (2003) of the Biopharmaceutical Manufacturing Capacity (BioPlan Associates, Rockville, MD, USA), 35 percent of biopharmaceutical companies were expected to outsource their activities in 2004, which would rise to 47 percent by 2008. Clearly, by 2008, approximately half the biopharmaceutical companies will be riding the outsourcing bandwagon. The following figure shows the market size of the various activities outsourced within bio manufacturing. Microbial fermentation is the forerunner, with 46 percent of the market share, and is a relatively standardized and mature technique. Mammalian cell culture technique, which is a relatively new technique, comes a close second with 33 percent of the market, and is a high-growth area.

Other than R&D and manufacturing, companies also outsource activities such as primary, secondary and sterile packaging of biopharmaceuticals. Some firms also employ a contract sales force with ample marketing muscle for some of their products.

Table 1 summarizes the wide range of activities outsourced in the major biopharmaceutical segments.

Table 1: Outsourced Activities in Various Biopharmaceutical Segments

AREA	EXAMPLES OF OUTSOURCED ACTIVITIES
Drug discovery	• Lead identification • Target identification • Analysis (analytical/ bio analytical) – Chromatographic analysis – Microbiological analysis – Biochemistry – Biocompatibility – Bio molecule analysis – Stability studies – Dissolution testing – Drug compatibility – Solubility study – Hygroscopicity – Filter validation – Analytical method validation

AREA	EXAMPLES OF OUTSOURCED ACTIVITIES
Clinical Research	• Preclinical development • Clinical trial design and development • Phase I to Phase IV clinical studies • Clinical trial management • Clinical trial monitoring • Bioequivalence • Bioavailability • Pharmacovigilance • Pharmacogenomics • Regulatory affairs • Biostatistics • Licensing
Bio manufacturing	• API manufacturing • Bulk manufacturing of formulations • Cell cultures • Antibody production • Cell-line development • Protein production • Fermentation • Expression technologies • Transgenic animal production
Packaging	• Primary packaging • Secondary packaging • Sterile packaging

Source: Compiled by Evalueserve

Outsourcing – to Maximize Internal Efficiency and Capacity

The high cost of building a bio-manufacturing facility (ranging anywhere between USD300-USD900 million to build, equip, validate and get the facility approved) is seemingly the hinge pin in outsourcing. More so, if it takes a minimum four to five years for a facility to become operational,[2] a lot of companies prefer not to make this huge capital investment.

However, cost cutting is not the only imperative for outsourcing. It is a strategic option, which is being exercised by many companies to augment their efficiency and expertise. It also provides an opportunity to partner companies, to establish and foster long-term, strategic relationships, thereby making them more proficient and better prepared to match their capabilities and offerings in tune with market and demand dynamics.

In addition, outsourcing allows these companies to shift their focus from non-core activities, concentrating and expanding their core competencies. For example, Genentech has outsourced the manufacturing of Rituxan (rituximab) to Lonza, so that Genentech can concentrate on expanding its own competency.[3]

Another major reason for companies to outsource is to reduce their time-to-market, with lower fixed costs. Eli Lilly had outsourced the development and manufacture of Activated Protein C (APC) to the Lonza Group, announcing that it was to facilitate the launch of the product in the market at a relatively cheaper development and manufacturing cost.[4]

[2] Source: Contract Services Europe, Feb/March 2005
[3] Source: Nature Biotechnology, 2004
[4] Source: HighTech Business Decisions, Press release

The Big Leap from the Early 2000s to 2005 – the First and Second- tier Participants

With a large number of biopharmaceutical drugs being tested (with expectations of being approved), contract-manufacturing organizations have been busy making significant investments to upgrade and expand their manufacturing facilities, to get a larger share of the growing biopharmaceutical outsourcing market.

The biopharmaceutical industry was facing a major shortage of manufacturing capacity up until 2001. However, with the prospect of bio manufacturing supplies outpacing worldwide demand by 2005-2011[5], the industry is metamorphosing into a completely new shape. The reason for such estimates is the capacity expansion undertaken by most tier-one and tier-two contract manufacturers in the last few years, as well as the ones being planned in the near future. For instance, Boehringer Ingelheim, the largest CMO in the world, nearly doubled its capacity with the setting up of its new facility in Biberach, Germany, in September 2003 – it later inaugurated another plant at its existing facility in Vienna, Austria.[6] Similarly, Lonza Biologics, the second- best CMO in terms of reactor volume, increased its capacity fourfold at its facility in Portsmouth, New Hampshire (USA), to include three 20,000-liter bioreactors that became operational in 2004. Building facilities is considered beneficial by the players as a means of producing quality products, and also to make profits by entering the huge global market.

Some companies have adopted the organic route of mergers/acquisitions to add capacity. Cangene acquired Chesapeake Biological Laboratories (CBL) in February 2001, to utilize its 71,000-square-foot manufacturing facility in Baltimore.[7]

The focus of some CMOs has also been to add capacities at locations that offer cost-competitive quality production with cheaper labor and lower land, construction and maintenance costs. One of such expansions was undertaken by Lonza, which entered the Asian market in August 2005 through a joint venture agreement with Singapore's Bio*One Capital. The purpose of this expansion was to establish a contract-manufacturing organization in Singapore, to capitalize on Singapore's existing strengths in process development and clinical manufacturing of biopharmaceuticals, as well as the country's capabilities in GMP[8] manufacturing of bulk actives for global pharmaceutical companies.[9]

Similarly, Celltrion (Incheon, South Korea) plans to set up and operate the largest bio manufacturing facility in Asia - and one of the largest in the world - by 2006. Bristol-Myers Squibb (New York, NY, USA) has entered into an agreement with Biocon, India for commercial manufacturing of its recombinant insulin.

Another route taken to reach newer markets has been by entering marketing collaborations with other companies that are already present in the market, as in the case of Cangene. Its marketing collaboration with BioGeneriX AG of Mannheim, Germany, from Oct 2003 has given it significant access to the European market, especially through the sales force of BioGeneriX' parent company, which is one of the largest generic drug companies in Europe.[10]

Strategic collaborations and agreements are also being undertaken by CMOs to acquire expertise in a new area or add products to their discovery pipeline. Laureate Pharma entered into a manufacturing agreement with Discovery Laboratories Inc. in January 2004, wherein it will provide manufacturing services that support Discovery Laboratories' product requirements.[11] It has also expanded its technical expertise, while bringing additional value to customers by entering into collaboration with EMD Chemicals Inc. in March 2005, which will enable Laureate Pharma to utilize EMD's expertise in packing and testing large-scale ion exchange chromatography columns.[12]

In order to strengthen its pipeline in the upcoming area of biopharmaceuticals, Lonza Biologics entered into an agreement with Y's Therapeutics, a privately held biopharmaceutical company, to collaborate with Y's

[5] Source: In-pharmatechnologist, 2004
[6] Source: Boehringer Ingelheim: Press release April 2005
[7] Source: Contract Pharma, 2001
[8] GMP: Good Manufacturing Practices
[9] Source: Lonza Biologics: Press release August 2005
[10] Source: Cangene Corporation, Press Release October 2003
[11] Source: Laureate Pharma: Press release January 2004
[12] Source: Laureate Pharma: Press release March 2005

Therapeutics on the cell-line construction and production of a humanized monoclonal antibody for the YSCMA program in April 2004

Apart from the CMOs, large pharmaceutical companies have spread out their biopharmaceutical manufacturing and research arms to carry out R&D and sales functions. These include GlaxoSmithKline (GSK) Biopharmaceuticals, founded in 2000 by GSK; and Abbott Bioresearch Centre (ABC), founded in 1989. This has resulted in their optimising their capacities, supporting their internal processes, and catering to the external client. For instance, ABC contributes its process development and manufacturing expertise to Abott's biologics projects and to partner companies such as the Cambridge Antibody Technology Group PLC, Eisai C., Ltd., and the Genzyme Transgenics Corporation.[13]

In the words of Jeff Leiden, M.D. Ph.D., President and COO. of Abott Pharmaceuticals and its Chief Scientific Officer, "ABC increases our strength in key therapeutic areas and builds our scientific capability. It also greatly expands Abbott's position as a global pharmaceutical player in terms of international commercial infrastructure."

Table 2: List of Key Service Providers

COMPANY	LOCATION	SPECIALIZATIONS AND CAPABILITIES	SERVICES OFFERED
Boehringer Ingelheim Biopharmaceuticals	Vienna and Biberach, Germany	• Specializes in mammalian cell culture technology, native and recombinant micro organisms and yeast	Offers entire process chain from early development to marketing, including large- scale manufacturing, filling, and global registration.
	Vienna	• Manufactures therapeutically active protein, plasmid DNA and single-chain antibodies • Two 6000- liter fermenter for biopharmaceutical production	
Lonza Biologics	Slough	• 4,800-liter fermentation capacity • Plans to expand clinical-scale mammalian cell culture manufacturing capacity	• Mammalian cell culture for producing monoclonal antibodies and recombinant proteins • Microbial capacity for manufacturing antibody fragments, recombinant vaccines and some other recombinant proteins • Entire process from development to marketing including full scale manufacturing and analytical services
	Portsmouth	• Three 20,000 Liter reactors	
	Lonza in Visp	• Facility for manufacture of parenteral grade biopharmaceuticals from microbes • Plans to expand with additional 15 metre square fermentation capacity • Plans to spend SFr14 million (USD 11 million) to expand its clinical-scale mammalian cell culture manufacturing capacity at its Slough, UK, production facility, which is slated to come online in the fourth quarter of 2006	
GlaxoSmithKline Biopharmaceuticals	United States	• Capacity of 5,000 liter scale bioreactor • Specializes in mammalian cell culture	• Development and manufacture of proteins and mammalian cell derived proteins for clinical trials and market • Preparation of bulk products • Analytical and regulatory services
	United Kingdom	• Capacity of 1000 Liter to develop animal derived purification process	
Laureate Pharma	Princeton, New Jersey	• Facility of 57,000 square feet • Bioreactors from 20 to 2,500 Liter size	Range of services from process development to finishing/ labeling/packaging
Abbott Bioresearch Centre	Worcester, USA	• 6,000 liter fermentation capacity for products requiring microbial and cell culture technologies	Develops and manufactures biopharmaceutical and therapeutic products

[13] Source: Abbott .com

COMPANY	LOCATION	SPECIALIZATIONS AND CAPABILITIES	SERVICES OFFERED
Cangene	Canada	• 25,000 square feet biopharmaceutical facility • Fermentation and downstream processing capacity up to the 2100 liter working volume	• Development services • Bulk product manufacturing • Finished product manufacturing
Dow Pharmaceutical Contract Manufacturing Services	San Diego	• Computer-controlled microbial fermenters up to 1,500 liter scale	• High-expression vector development • Analytical method development • Process development and scale-up • CGMP manufacturing
Sandoz	Schaftenau, Austria	• 3,000 liter and at 13,000 liter fermentation scale for mammalian culture • Microbial fermentation at scales of 3,000 liter, 13,000 liter and 40,000 liter	Cell culture services: • Media optimization • Refining cell growth condition • Process optimization • Fermentation development Recombinant microbial services: • Development and production • Analytical and regulatory
Celltrion	South San Francisco	• 1000 liter fermentation bioreactor • Plans of expansion with 50,000-liter microbial manufacturing facility in 2006.	• Feasibility and optimization studies • Cell culture, harvesting, purification and downstream processing services • CGMP compliant facility
Biocon	Bangalore, India	• 120,000 liter fermentation capacity	R&D services by Syngene

Source: Company websites

The Building Boom – Current Outlook

Historically, pharmaceutical companies have always opted to keep bio manufacturing 'in-house' due to personnel, production schedule, intellectual property (IP), regulatory and quality concerns. However, this strategy has been only successful in the case of larger established companies such as Amgen and Genentech. Today, biopharmaceutical companies are taking their first cautious steps towards outsourcing, because it has been proven that the benefits outweigh the risks and the wariness associated with the process of outsourcing. This trend is likely to gain momentum in the future. The industry is witnessing a rapid proliferation (and a concomitant surge in revenues) of small to midsized Contract Bio Manufacturing Organizations (CBMOs). Many firms have now turned to CBMOs for clinical or commercial production of their products, which has resulted in their increasing reliance on CBMOs.

The CBMOs have also been making substantial investments in downstream activities, to improve their expression systems and decrease the yield loss. For example, Abbott Bioresearch Center has multiple suites, with a fermentation capacity of up to 6,000-liters (mammalian and microbial). The Abgenix facility includes four 2,000-liter and two 12,000-liter bioreactors (mammalian).[14] This has resulted in a reduction in their manufacturing costs, increasing their value to the bio pharmaceutical companies that rely on them[15].

Additionally, the technological advancement in the industry is likely to bring down costs, thereby increasing the number of companies outsourcing their activities. One such advance is the increasing use and popularity of disposable, single-use bio manufacturing systems, which have the potential to maximize returns on investments in manufacturing facilities. Disposable apparatus are less expensive, when compared to conventional equipment. For instance, a disposable bag costs around USD 20000 per year, in comparison to stainless steel vessels that cost around USD 40000 per year on the 20 liter bioreactor scale.[16] The use of these single-use equipment has resulted in the reduction of some steps, such as cleaning, validation, etc., and consequently, the elimination of much of the documentation work and the risk associated with insufficient

[14] Source: Nature biotechnology, 2004
[15] Source: Contract Services Europe, Feb/March 2005
[16] Source: Contract Services Europe, Feb/March 2005

cleaning. The advent of these equipment has resulted in a faster changeover, simultaneous manufacturing of many products, and the absence of cross contamination.

SMOs are management service companies, which organize and manage the clinical trials. The need for this middle tier of organization emerged due to some challenges faced by Clinical Research market like widespread trials at multiple sites, fragmented CRO market, and the speed required for the process etc. In 2002, only 4 companies captured the SMO market but now 33 companies are in the rat race resulting in high growth and expansion. [17] It was estimated in 2004 that the growth rate of this middle tier of organization would be 43 percent in the next few years.[18]

Challenges Abound

These advances in technology seem to have changed the face of the industry, which has a come long way. There has been a sea change in the industry, in which, apart from there being multiple positive factors, challenges also abound.

Upstream processes, which are generally development- and engineering-related, are driven by technology development and are moving at a high pace. On the other hand, downstream processes like purification, refining, etc., are not able to catch up due to process bottlenecks. The challenges faced by downstream processes are many – efficacy, quality and safety are the key words of a product; added to this are the high costs and cGMP requirements of a bio manufacturing facility, stringent regulatory authorities that approve a process, the technology crunch etc. The logical conclusion seems to be that upstream and downstream processes should be integrated to overcome these challenges.[19]

A downturn in opportunities and soaring competition could be the future for small and mid-sized service providers. The financial status of large biopharmaceutical companies could facilitate the acquisition of smaller biopharmaceutical firms. This could result in processes to remain in-house due to the capabilities of large companies. If any process were outsourced, top vendors would be preferred. Hence, the whole gamut of processes outsourced to smaller service providers may dwindle. This could result in a cutback in opportunities and a rise in competition, keeping in mind the fact that the top eight service providers dominated 60 percent of the market in 2004.[20]

What's in Pipeline?

The increase in biotechnology products may result in an increasingly outsourced manufacturing market. Many new biotechnology products are in the pipeline at different stages of development and is estimated that approximately 240 new biotechnology medicines would reach the market by 2007.[21] Out of these, some blockbusters are also expected. This could see demand for bio manufacturing outpacing the supply, resulting in companies preferring to outsource their manufacturing processes.

The proliferation in patent expirations may lead to increase in outsourcing. It is estimated that by 2006, biologics patents worth USD 10 billion will expire.[22] The companies will be under pressure to focus more on their core competencies to develop newer products and also to outsource the manufacturing of the generic products to reduce costs. Moreover, a company would strategically view the outsourcing as a viable option, so as to manufacture the patented products also in a cost efficient manner.

Also, the biogeneric products require more trials compared to their counter part in the non-biotech sector to meet the safety issues and address the problems of bioequivalence. A slight variation in manufacturing process such as change in the culture media or growth conditions, can significantly impact the safety or the immunogenecity concerns of the product. This may lead to a requirement of new clinical trials to validate the process, which will be associated with high costs. With limited R&D facilities the generics firm may either seek partnerships or turn to outsourcing.

[17] Source: Contract Pharma
[18] Source: Outsourcing in Drug Development, Market Research 2004
[19] Source: International BioPharm 2005
[20] Source: International BioPharm, 2005
[21] Source: Businessweek online
[22] Source: ABN Amro Report

The process of developing guidelines in the field of bio generics will be slow since it is subjected to considerable legal interpretations on safety and technical concerns. In the US, there has been mounting pressure on regulators from the US Biotechnology Industry Organization (BIO), insisting that safety concerns to be addressed and debated before any guidelines for generic biologics were issued. Biopharmaceutical and biotech companies seem to be uniquely positioned to adopt outsourcing, both at home and offshore but to some extent the potential benefits will be overshadowed until the safety and technical concerns are satisfied. However, for the present, prepare to take a 'wait and see' approach, awaiting further developments in the industry in the years to come.

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