

## GLOBAL CONTRACT MANUFACTURING COMPANIES: PHARMACEUTICAL AND BIOTECHNOLOGY

Contract manufacturing is a strategic option for many companies

From big pharma to smaller specialty entities, contract manufacturing serves as a strategy for various industry players. Significant factors driving market growth include continued efforts to cut costs, outsourcing by pharma companies of non-core businesses, and an increasing amount of specialty and biotech firms that do not have in-house manufacturing capabilities. The contract pharma market will continue to rise as companies cut costs to offset problems regarding pharmaceutical productivity trends. Non-core businesses being outsourced include manufacturing and product/process optimization.

As manufacturing processes become more complex and regulatory requirements become more burdensome, pharmaceutical companies are developing longer-term, more beneficial strategic deals. This process often results in pharmaceutical companies dealing with fewer partners, but these providers need to be able to deliver a full-service offering to compete for business. For a pharmaceutical entity to strategically outsource, the company must reinvent this relationship via persistent discussions with its preferred partners on planning, common objectives, and the responsibility of operating more effectively versus key metrics.

During recent years pricing pressures have driven manufacturing contractors to form operations in emerging markets. Offshoring has resulted in companies establishing facilities in India, China, Singapore, South Korea, and more recently Malaysia. Significant investment continues to flow into Asia with many western CMOs expanding operations there, especially in China. As the marketplace becomes more price competitive, the option to outsource certain projects to lower-cost Asian regions – particularly for producing large-volume products – will become a valuable option. This trend should have a strong impact on the worldwide CMO arena.

## UBM CANON DATA PRODUCTS

828B Newtown-Yardley Road, Suite B  
Newtown, PA 18940  
United States  
Phone: +1.215.944.9800  
Fax: +1.215.867.0053  
Website: PharmaLive.com

**Stephen Corrick**  
*VP and Executive Director*  
UBM Canon Publishing  
steve.corrick@ubm.com

**Roger Burg**  
*VP, Operations*  
Publications Division  
roger.burg@ubm.com  
+1.310.445.4221

**Glenn Glasberg**  
*Circulation and Marketing Director*  
glenn.glasberg@ubm.com  
+1.215.944.9810

**Sandra Baker**  
*Data Products Manager*  
sandra.baker@ubm.com  
+1.215.944.9836

**Amanda Wells**  
*Assistant Marketing Manager*  
amanda.wells@ubm.com  
+1.215.944.9840

**Brandon Materazzi**  
*Marketing Assistant*  
brandon.materazzi@ubm.com  
+1.215.944.9809

**Andrew Humphreys**  
*Editor In Chief, Data Products*  
andrew.humphreys@ubm.com  
+1.215.944.9812

**Stefanie Fedder**  
*Manager, Data and Content*  
stefanie.fedder@ubm.com  
+1.215.944.9807

**Silvia Arriola**  
*Data Specialist*  
silvia.arriola@ubm.com  
+1.215.944.9803

**Diane Stroh**  
*Data Specialist*  
diane.stroh@ubm.com  
+1.215.944.9828

**Andrew Ellison**  
*Data Specialist*  
andrew.ellison@ubm.com  
+1.215.944.9826

**Rebecca Mayer**  
*Contributing editor*

**Kim Stannard**  
*Production assistant*

**UBM Ltd. Corporate Head Office**  
Ludgate House  
245 Blackfriars Road  
London, SE1 9UY, United Kingdom  
Phone: +44 (0) 20 7921 5000  
Website: ubm.com

**UBM Canon Headquarters**  
11444 W. Olympic Blvd.  
Los Angeles, CA 90064  
United States  
Phone: +1.310.445.4200  
Fax: +1.310.445.4299  
Website: ubmcanon.com

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Sandra.Baker@ubm.com or call: +1-215-944-9836

### EDITORIAL ADVISORS FOR SPECIAL REPORTS

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# GLOBAL CONTRACT MANUFACTURING COMPANIES: PHARMACEUTICAL AND BIOTECHNOLOGY

The worldwide contract pharma market could generate up to \$50 billion in annual revenue within the next five years. Between 2011 and the early part of the next decade, this market could more than double in value.

Active pharmaceutical ingredient (API) manufacturing constitutes the largest segment of the total market. Final dosage form manufacturing is forecasted to generate the quickest growth during upcoming years at a nearly double-digit rate.

Pharmaceutical companies are increasingly relying on contract manufacturing, research, and packaging services to fulfill many basic needs and specialized competencies. The companies endeavor to save costs and product development time while simultaneously being efficient and productive.

Various dynamics in the pharma arena are influencing companies' manufacturing and development strategies. Companies are increasingly positioning themselves to respond to needs and provide customers with efficient and simple solutions. Consumer demand is simple: they want less expensive, well-made drugs available when needed. Pharma contract research and manufacturing companies are scrambling to make this occur.

Elevated costs in R&D and drug formulation are propelling companies to seek measures to maximize their resources. These measures include companies outsourcing their functions to CROs and building new research and development sites in Asia.

Contract manufacturers can accommodate many sterile project types, from lyophilized and aseptic filling to a wide variety of vials, and pre-filled syringes to blow/fill/seal services. Some studies point toward the worldwide contract manufacturing organization (CMO) market growing at a rate of about 10% annually during the upcoming years.

John Lanza, National Biotech and Life Sciences leader of **McGladrey & Pullen LLP**, believes that the entire outsourcing model is growing at a significant pace within the life-sciences space. "Many of the large pharma companies are re-evaluating their supply chains due to recent events such as **Johnson & Johnson's** issues, the earthquake in Japan and access to resources in China," he says. "Life sciences companies are recognizing the overall economies of scale that outsourcing can provide and are seeing the economic advantage of decreasing their risk in supply and increasing quality assurance."

During the next decade, demand for

contract manufacturing services will continue to originate with developed market-based pharma players. As the largest market, the United States represents more than 40% of marketplace demand. Moving forward, pharma companies are expected to outsource growing amounts of manufacturing as companies concentrate on R&D and marketing activities. Additionally, industry experts project that growth in the biotech market will provide a strong opportunity for CMOs.

According to **Alkermes plc**, pharmaceutical contract manufacturing will emerge as a strategic option for many companies ranging from very large to smaller specialty pharma entities. Key factors driving growth include continued efforts to cut costs, outsourcing by pharma companies of what is considered non-core, as well as the increase in the large amount of specialty pharma and biotech companies that have no internal manufacturing capabilities.

"... What is certain is that this market will grow as companies are seeking to cut costs to offset in part the problems relating to pharma productivity trends," Alkermes reps say. "Growth will come from companies continuing to seek ways to cut costs and outsource what is considered 'non-core' – for many this is manufacturing and product/process optimization."

Cutting costs is widely believed to be the most common factor that leads companies to ink outsourcing deals. Other factors contributing to the trend in outsourcing manufacturing responsibilities include the need for specialization; ability to free up in-house resources for other projects; and improved flexibility in terms of supply chain, time lines, and regulatory management.

To overcome these issues and remain competitive in the marketplace while continuing to grow their businesses, leading pharma companies are turning to outsourcing as a viable strategy. Outsourcing enables pharma companies to reduce costs without sacrificing quality, according to Steve Goodman, VP of strategy for **VWR International LLC**.

In recent years the concept of outsourcing has made considerable inroads into manufacturing, primarily because manufacturing accounts for roughly one-

## Industry Environment

- Large pharma R&D restructuring
  - Reduction in internal R&D resources, generic competition, healthcare reform driving increased strategic outsourcing
- More stringent regulatory environment
  - Requires the use of service providers with strong intellectual capacity and high quality standards
- Globalization of R&D activities
  - Customers are seeking lower cost alternatives with the same quality standards they receive in the US
- Biotech funding environment
  - Availability of capital has stabilized



We believe market pressures will exert increasing trend toward outsourcing.

Source: AMRI



quarter of company costs. Manufacturing a drug places a large strain on a company's resources including time, money and manpower.

The time frame for developing a new medicine through product launch can take up to 15 years. The cost to research and develop a successful new molecule can exceed \$1 billion. With fewer potential blockbuster drugs entering the market in recent times, the industry's ability to grow and sustain relies on faster new drug development and cost containment.

Pharma manufacturing requires the use of advanced technology including cGMP synthesis and scale-up, impurity profiling and lyophilization, as well as stringent regulatory compliance such as good manufacturing practices.

When drugs gain regulatory approval, pharmaceutical companies need large quantities of product supplies for marketing and distribution. Projecting a company's manufacturing needs and procuring extensive capital requirements are large challenges. As a result, contract manufacturing has gained popularity.

By outsourcing such activities to CMOs, pharmaceutical companies are able to expedite research and development activities but still gain potential revenue. As the niche continues to develop based on growing necessity, contract manufacturing organizations are offering an extensive array of value-added services.

"Using contract manufacturing and outsourcing helps big pharmaceutical companies achieve corporate goals by saving tremendous resources that would otherwise be required for capital investment in facilities and equipment," states Vadim Klyushnichenko, Ph.D., VP of pre-clinical services and process development for **Paragon Bioservices** Inc. As a rule, contracted projects are completed faster and more efficiently since they are placed in specialized companies with experienced manufacturing personnel.

Dr. Klyushnichenko compares the role of contract development and manufacturing companies to a hospital emergency room. "People do not enjoy visiting hospitals for obvious reasons," he observes. "However, they go to emergency rooms for rapid professional medical help when they are in critical condition. The doctors in the ER provide immediate assistance and then refer the patients to a specialist at a later date."

Contract organizations provide similar

help for their clients when time, money or other resources are limited to expand their own laboratories or build a manufacturing facility. They look to CMOs, which are experienced in a particular area of drug development.

"Since contract-based projects are milestone-based and depend on the successful delivery of results, an unsuccessful project can be terminated early, while successful projects can be transferred to clinical and commercial manufacturing significantly faster than at a traditional pharmaceutical company," Dr. Klyushnichenko says. "So, the main advantages of contract manufacturing and outsourcing are rapid development of innovative drugs and faster launch of clinical and commercial manufacturing."

## GROWTH MARKETS

The global pharma contract manufacturing market has generated robust growth in recent years and the future of this segment holds great opportunities for the industry. Due to economic woes worldwide, several countries are seeking ways to minimize drug expenditures. Pharma and biotech companies have been charged with the difficult task of minimizing drug costs, which in turn has led them to evaluate opportunities for manufacturing outsourcing.

On a larger scale, the global pharmaceutical industry has been wrestling with the increasingly competitive generics market, declining R&D productivity, growing governmental pressure to reduce drug prices and declining patent life spans.

The United States is the leading pharma contract manufacturing market globally. Europe represents the No. 2 market. Japan is forecast to generate double-digit growth for the next few years. Growth markets also include developing regions such as Asia-Pacific.

Asian CMOs are making forays into the discovery and development market by acquiring assets in the United States and Europe. Due to low overhead in staffing and technical capabilities, India is in a strong position to capture a significant portion of the increasing contract manufacturing organization market.

Large pharmaceutical companies and other worldwide entities have been taking advantage of using India's leading cost-competitive and quality manufacturing hubs.

Companies continue to shift manufacturing operations to low-cost countries such as India and China at a high rate. Industry analysts widely believe that this trend is expected to increase for the foreseeable future.

According to Alkermes reps, during the past decade pricing pressures have driven manufacturing contractors to establish operations in emerging markets. "Offshoring has resulted in companies setting up facilities in India, China, Singapore, South Korea and more recently Malaysia," Alkermes officials noted. "Considerable investment has continued to flow into Asia with many western CMOs expanding operations there, particularly in China. As the industry becomes more price-competitive, the option to outsource certain projects to lower-cost Asian regions, in particular for the production of large volume products, will become a valuable alternative. This trend will have a significant impact on the global CMO business.

"However, while there are many companies willing to consider outsourcing in Asia, many remain closer to the more established territories of North America and Europe. Western-based facilities will remain competitive with an edge on quality, reliability, proximity and familiarity with proximal markets."

Even though outsourcing to low-cost countries may offer considerable savings and growth possibilities, companies may not have the technical or regulatory capabilities that some businesses need.

Aseptic/sterile production and injectable manufacturing processes, for example, require a significant investment in terms of expertise, equipment, process, technology and quality control. CMOs can provide innovative, state-of-the-art processes and production technologies to support the rapid technical transfer of products from R&D to commercial manufacturing. Effectively managing a CMO relationship is critical to satisfy regulatory requirements and meet the overall commercial intention of the project.

The categories comprising the worldwide pharma contract manufacturing market include injectables, solid and liquid dosage forms. Solid dosage is the largest market segment in terms of revenue. Injectables as well as solid and liquid dosage forms are segments with strong revenue growth potential.

A new wave of contracts concentrated on biosimilars has impacted the indus-



try. "A number of programs focused on biosimilars have launched in traditional Western markets, as well as in emerging markets," Dr. Klyushnichenko states. "The importance of these projects is dictated by process efficiency and price reduction and by the improvement of immune response in vaccine development."

Contract manufacturing organization structures differ from specialized single-focus providers to outsourcing subsidiaries of major international pharma companies. Companies that focus on creating specific products or processes are better able to navigate the difficult regulatory environment and distribution channels for such product types.

Certain companies prefer to launch a new product in-house to maintain the highest level of control over the process and then select to outsource at a later date once they have become comfortable with managing the product's potential risk.

Pharma customers are attempting to do more volume with fewer vendors to leverage pricing, Mr. Goodman observes. "For CROs and CMOs, that means having greater capabilities to set themselves apart," he says. "Logistics capabilities appear to be an area where they have the greatest need and where VWR International has been able to play a significant role in helping CROs and CMOs rise above the crowd."

Additionally, pharma technologies constantly change and the capital investment required to produce niche products is becoming increasingly cost-prohibitive and risky.

According to Dr. Klyushnichenko, pharmaceutical companies are going through

a difficult time, as dictated by their restructuring and increased activity in searching for new products. This subsequently creates a larger pipeline of both preclinical and clinical candidates, he reports.

The pipeline of new candidates may not be steady and a majority of those candidates will not survive to the point of commercial manufacturing. "Therefore, it is very risky for pharmaceutical companies to invest in extensive clinical manufacturing without a clear expectation of success for those candidates," Dr. Klyushnichenko explains.

Pharmaceutical companies' overhead per employee is much higher, in general, than the CMOs that they are contracting to. "In order to minimize the risk, it makes sense to maintain the current infrastructure and hold off on facility expansion," Dr. Klyushnichenko says. "The most logical step is to outsource the required services to contract manufacturing companies initially and then decide on future investments according to each candidate's potential for success."

"Pharmaceutical and biotech companies still look at CROs and CMOs as a necessity to produce new products in a cost-efficient manner," Mr. Goodman shares. "Growth is expected this year after a lull from the recent economic challenges."

## MARKET MOVES

The marketplace is undergoing significant upheaval in certain areas. One major trend is large drug companies selling their manufacturing plants to remove assets from their balance sheets.

"The drug and medical-device sector has been making the transition from vertically integrated to an ecosystem of interconnected suppliers for the past several decades, and this trend is increasing," says David Chapin, CEO of **Forma Life Science Marketing**. "This puts increasing competitive pressure on suppliers, but efficiency alone will not be enough; the winners will need to be clearly differentiated."

The basic driver for the shift away from a vertically integrated business model to an ecosystem of suppliers is three-fold: efficiency and resource utilization, the resulting cost containment, and risk avoidance/risk sharing, Mr. Chapin observes.

According to Mr. Chapin, this transition occurred in other (non-pharmaceutical) sectors well before the pharmaceutical

sector. One hundred years ago, the auto industry was highly vertically integrated. Now, that sector has an ecosystem of suppliers. The major car companies handle very little of the component manufacturing, focusing only on design, assembly and marketing.

"Current trends in the pharma sector, such as preferred provider relationships and major drug companies selling their manufacturing plants to get those assets off the balance sheets, have been presaged in other industries," Mr. Chapin shares.

To reduce long-term costs, many large pharma companies are consolidating their manufacturing processes and increasing their reliance on contract manufacturing. "The result is a balancing act to preserve profits, retain quality and reduce global supply-chain risk," Mr. Lanza notes.

According to Mr. Lanza, some companies are in the infancy of examining their supply chains, but others such as **Bristol-Myers Squibb Co.** have aggressively moved to streamline and consolidate their manufacturing processes both internally and in the outsourced context.

A few years ago, Bristol-Myers Squibb closed more than half of its manufacturing plants in a broad restructuring aimed at cost savings of \$1.5 billion by 2010.

During 2010 **Bend Research Inc.**, a leading independent technology-based drug-formulation development and manufacturing organization, extended its drug-discovery enablement and development services agreement with Bristol-Myers Squibb.

Under the terms of the three-year deal, Bristol-Myers Squibb is using Bend Research's formulation development and manufacturing services for preclinical and clinical development. Bend Research is manufacturing drug product intermediates and drug products in its cGMP facility for Bristol-Myers Squibb clinical trials.

The market for contract research, development and manufacturing organizations is inevitably growing since the majority of pharmaceutical companies are going through mergers & acquisitions, restructuring, and work-force reduction according to Dr. Klyushnichenko.

Dr. Klyushnichenko says the market leaders in the contract manufacturing industry are frequently large and well-established companies. "They set up the rules, policies and regulations, which drive the

## KEY FINDINGS FROM PATHEON CMO MARKET ASSESSMENT

- The market for commodity CMOs is large, but only modest growth
- Customers seek partners who can manage complexity (small volumes), surge capacity, and deliver low prices and quality
- Pharma companies do not expect to significantly shift production to emerging markets, except to meet local demands
- Pharma companies outsource contract manufacturing to companies that are their Phase III CTM partners if vendor has scale

Source: Patheon

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entire industry," he says. "Also, they may provide a higher success rate at a higher operational cost and, subsequently, a higher price for the client. In the ideal situation, the client should be able to 'drive' the drug development and control the risks and the price of the services."

The basic goal of contract organizations is to be flexible and address industry needs. "The core value of contract organizations is the competence and experience of their staff," Dr. Klyushnichenko says. "As pharmaceutical companies are going through massive layoffs, there is an increased availability of experienced scientists and manufacturing workers in the market."

Many pharmaceutical companies, in an attempt to be viewed as more than drugmakers, are choosing to focus on selling medicines and abandoning the role of production. **Merck & Co.**, **Pfizer Inc.**, and **Roche** are some of the large pharmaceutical companies that have decreased their manufacturing footprints by outsourcing a significant part of their API needs.

On the flip side, other companies have chosen to redirect their energy and expertise by offering contract manufacturing services to outside customers.

Because pharma company contract manufacturing groups are typically internal operations, specific revenue figures are not reported. As a result, industry leaders are not clearly identified. Most industry analysts agree however that **Boehringer Ingelheim GmbH**, which supplies small-molecule APIs and biopharmaceuti-

cals, has one of the largest operations in the world.

With the recent purchase of **Amgen Inc.**'s Fremont, Calif., facility, **Boehringer Ingelheim** has added biologics process development and manufacturing to its contract manufacturing capabilities. Amgen had been the company's customer for more than 10 years.

The **Boehringer Ingelheim** contract manufacturing portfolio includes 16 licensed biopharmaceuticals manufactured in globally licensed multi-product facilities, a growing pipeline of New Biological Entities (NBEs), and a growth strategy in the Contract Manufacturing Business (CMB).

Many contract businesses also produce and sell generic APIs and intermediates. Industry analysts observe that because so many products are going off patent, large pharma companies are in a better position if they stay in the game and draw revenue from producing generics on their own.

**Abbott Laboratories**, for example, is not a pure-play contract manufacturing organization. Since the 1960s, Abbott has expanded its concentration to provide customers with high-quality, innovative, cost-effective Biologics, High Potency and Finished Goods Contract Manufacturing services, and APIs. The company uses the same assets as in the production of its own pipeline products.

Custom and generic APIs – biologics and small molecules – make up about 70% of the group's output. The remaining 30% consists of finished drug products.

On a similar vein, **Sanofi SA** announced plans to change its focus from chemical industrial activities to biotechnology and vaccine production in its French facility by 2014. Beginning in 2008, the company has invested at least \$900 million in the shift.

During the next few years, **Pfizer** has plans for a transformation. The New York-based company has announced its intention to close eight plants and reduce operations at another six plants.

The strategy reportedly will benefit **Pfizer CentreSource (PCS)**, Pfizer's contract manufacturing group. For many years, PCS has supplied steroid APIs and intermediates and offered sterile-dosage-form manufacturing. New access to Pfizer facilities in Illertissen and Freiburg, Germany, enables PCS to produce highly potent oral solids. A plant in Strängnäs, Sweden, adds microbial fermentation.

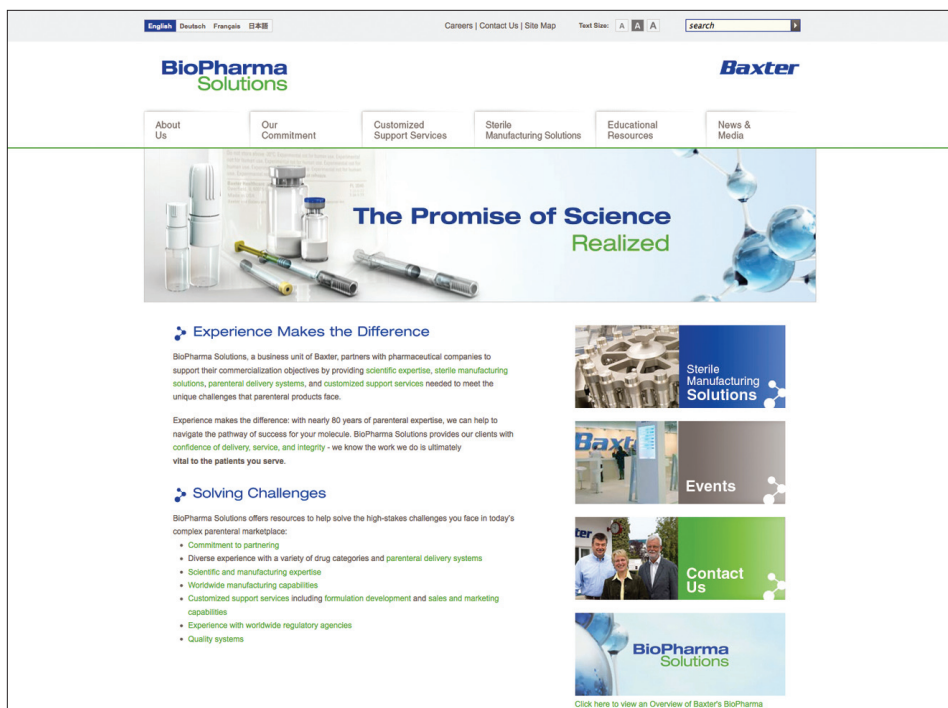
Restructuring efforts at other contract businesses are not as positive. **Genzyme Corp.** announced plans to divest its pharmaceutical intermediates unit in an effort to turn around the company's core therapeutics business. Based in Liestal, Switzerland, the third-party manufacturing business chemically synthesizes pharmaceutical materials including lipids, peptides, amino-acid derivatives and small molecules, and offers drug-delivery technologies.

**Roche** launched an operational excellence program in November 2010 that includes streamlining its manufacturing network. The company plans to sell its site located in Boulder, Colo., which produces peptides for Roche and outside customers.

**GlaxoSmithKline plc** is a relative newcomer to the contract business. When the business was established in 2005, the London-based company concentrated on selling generic penicillin and antibiotics. GlaxoSmithKline has expanded the company's scope to include small-molecule APIs and bulk pharmaceutical proteins.

**Elan Drug Technologies** merged with **Alkermes Inc.** in September 2011 to form **Alkermes plc**. Elan Drug Technologies, a drug formulation and manufacturing business unit, was formerly part of **Elan Corporation plc**.

There are some contract operations that have dedicated facilities. **Merck**, for example, created the **Merck BioManufacturing Network** in 2010 to target the biologics market. The unit combines the **Avecia Biologics Ltd.** business that Mer-



ck purchased in late 2009 and **Diosynth Biotechnology**, which came with Merck's 2009 acquisition of **Schering-Plough** Corp. The network has facilities in Billingham, England, and Research Triangle Park, N.C.

**Baxter International** Inc. purchased a plant in Bloomington, Ind., nearly 10 years ago, with the intention of using the facility for contract work. Baxter's **BioPharma Solutions** division is not an API supplier, but carries out sterile filling and finishing of drugs. BioPharma Solutions works out of Indiana as well as sites in Germany, Illinois, and California.

Although drug-company CMOs may not be the lowest-cost option, they can compete effectively with the independent companies because they offer more scientific expertise and service capabilities. Drug-company CMOs give customers a sense of security that other CMOs cannot because their operations are experienced in scale-up and commercial production.

A drug-company contract business, however, must still work within the parent organization's vision for manufacturing its own products.

## FDA STEPS IN

News came in August 2011 that after more than 70 years in business, **Ben Venue Laboratories** Inc. will exit the CMO business. A spokesman with parent company Boehringer Ingelheim reported that the move

enables BI to repurpose Ben Venue's resources to benefit its **Bedford Laboratories** business.

Industry analysts contend that the end of Ben Venue is Boehringer Ingelheim's way of dealing with the recent drug-shortage issues facing the Bedford Labs business and to focus on the company's compliance-improvement efforts. Drug shortages are prevalent across most of the pharma sector.

Problems at the Ben Venue plant have contributed to a supply shortage of **Doxil**, Johnson & Johnson's treatment for ovarian cancer and multiple myeloma.

Other products and companies affected include Pfizer's **Torisel** kidney-cancer treatment; **Velcade**, a multiple-myeloma treatment jointly marketed by Johnson & Johnson and **Takeda Pharmaceutical** Co.; and Bristol-Myers Squibb's cancer drug **BiCNU**.

The regulation requirements for drug development and manufacturing are strict and well-defined by FDA and other regulatory agencies. "There is no difference whether the drug is manufactured at the original pharmaceutical company or the contract organization," Dr. Klyushnichenko says. "FDA will take a more strict approach to contract companies in order to ensure drug safety. The changes are expected in the area of biosimilars and regenerative medicine as the industry puts more focus on these."

Mr. Lanza believes that FDA will require more regulations and heightened audit

requirements in the wake of recent foul-ups involving some contract manufacturers. In addition, he predicts that large pharma companies will assign internal resources in risk management to avoid similar problems within their own supply chains and to meet the requirements of the regulatory agency.

FDA recognizes the significant public-health consequences that can result from drug shortages and takes tremendous efforts within the regulatory agency's legal authority to address and prevent drug shortages. These shortages take place for many reasons such as manufacturing and quality problems, delays, and discontinuations.

When quality/manufacturing issues are discovered by a company or the public and reported to the Food and Drug Administration or are found by regulators upon inspection, FDA works closely with the company to address risks involved to prevent harm to patients. FDA considers the impact a shortage would have on patient care and access and works with companies to restore supplies while ensuring patient safety.

U.S. regulators work with other companies that manufacture the drug, asking them to ramp up production, if possible, to prevent or mitigate a shortage. FDA works to communicate information about shortages based on info provided by the manufacturers.

There was a record amount of shortages in 2010. There has been a growing number of shortages in 2011, particularly involving older sterile injectable drugs. Reports indicate that there are about 180 drugs on FDA's Drug Shortage List.

The majority of the drugs that fall into this category are generic oncology products, and are centered around a small subset of companies such as **Hospira** Inc., **Teva Pharmaceutical Industries** Ltd. and Bedford Labs, according to industry analysts. Nearly all of the drugs listed are injectable products.

Because Ben Venue manufactures several such products for Bedford Labs, industry analysts believe that Boehringer Ingelheim has made a bold statement by closing the doors to its CMO business.

Executives with Boehringer Ingelheim indicated that the CMO will be phased out over the course of several years and that in the meantime, the company is working with customers to find alternative manufacturing sites for their products.



The compliance problems appear to be with Ben Venue's manufacturing operations, which have been cited in the past by regulators from the European Union and Canada in addition to FDA. In August 2011, Health Canada announced that more than a dozen drugs imported by several different companies may be indefinitely in short supply as a result of deficiencies identified at Ben Venue.

Other industry analysts contend that the rising number of drug shortages in recent months may be linked to the increased concentration of drug manufacturers.

Although the exact circumstances differ, a parallel has been drawn between Ben Venue's struggles and **Albany Molecular Research** Inc.'s purchase of the sterile CMO business of **Hyaluron Inc.** during 2010.

In June 2010, Albany Molecular Research announced the acquisition of Hyaluron, expanding the company's contract manufacturing capabilities to include cGMP manufacturing and ster-

ile filling of parenteral drugs to the biopharmaceutical industry. Albany Molecular Research acquired all facilities and equipment as well as a highly trained and experienced staff of professionals with expertise in sterile GMP manufacturing. The purchase price, including debt, totaled about \$27 million.

Hyaluron has provided high value-added contract manufacturing services in sterile syringe and vial filling using specialized technologies such as lyophilization and **Bubble-Free Filling**, a unique patented technology developed and owned by Hyaluron. Hyaluron has provided these services for small-molecule drug products as well as biologicals, from clinical phase to commercial scale.

By Aug. 23, 2010, Albany Molecular Research had received a warning letter from FDA regarding the company's Massachusetts plant. The warning letter did not restrict the production or shipping of goods from the facility, according to company reps. FDA's warning was related to manufacturing procedures at the plant.

Unlike Ben Venue, Hyaluron was not producing drugs that have a critical impact on patient access.

The sterile drug product manufacturing sector is the most scrutinized pharmaceutical manufacturing operation. The controls, equipment and procedures required to manufacture sterile drug products are many times more costly and time consuming to implement compared with oral solid dose manufacturing.

Ben Venue was subjected to additional scrutiny as many of its products are aseptically lyophilized products, which require even more intense controls.

Industry reports indicate that the U.S. government is seeking ways to form a national stockpile of critical drugs. Reportedly, the aim is to stockpile active ingredients that can be shipped to pharmacies for aseptic compounding as necessary.

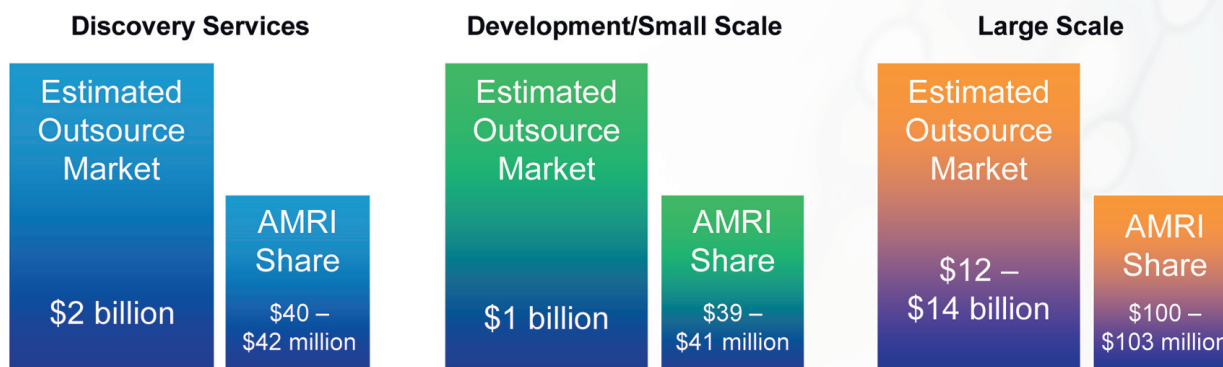
## WORLDWIDE OPPORTUNITY

There are many factors that will contribute to growth in the global contract man-

## Market Opportunity Contract Services



- Predict long-term growth due to increased outsourcing by Big Pharma and entrance of more virtual Biotech, non-profit organizations
- Historically fragmented market subject to significant consolidation



Data Sources: William Blair & Co, Jefferies & Co., Merrill Lynch, Kalorama Research

Source: AMRI

ufacturing market, such as U.S. tax rates, reduction of risk in the supply chain and multiple contract manufacturing partners, which alleviate supply issues. The U.S. tax rate is the second highest in the world. If a company can “offshore” functions, profits can be shifted offshore, resulting in those profits being taxed at a lower effective tax rate.

The contributing growth factors to the global contract manufacturing market can be divided into two major types: those that relate to turmoil and those that relate to opportunity, according to Mr. Chapin.

“The factors related to turmoil include: increased costs for drug development, the fracturing of the blockbuster business model, a sputtering global economy driving outsourcing and off-shoring, a decrease in the efficiency of the drug development process, the uncertainty of the regulatory climate worldwide, and increased global competition,” he says.

Among the factors that relate to opportunity are better and easier communication worldwide (making outsourcing and off-shoring easier), increased worldwide demand for effective drugs, devices and services, the discovery and development of radically new types of therapies such as large molecules, tailored or personalized therapies and drug-device combinations. “All of these will contribute in various ways to the growth in the market for global contract pharmaceutical manufacturing,” Mr. Chapin says.

Mr. Chapin believes that successful suppliers have both a clear focus and unique differentiation. “A clear focus is necessary because one cannot be ‘all things to all people,’” he says. “Unique differentiation is necessary because without uniqueness one’s offering will be perceived as a commodity. Commodity suppliers can never win the struggle to control the buy/sell relationship; there are a host of other acceptable substitutes.”

Mr. Chapin believes that if buyers have a wide variety of choices, they will set prices and dictate terms. Unique differentiation will shift some power in the buy/sell relationship back to the sell side of the equation, allowing suppliers to fend off commoditization.

Dr. Klyushnichenko believes that there are both external and internal factors contributing to the growth of the contract pharmaceutical manufacturing market. “The external factors will be driv-

en by the dramatic changes in the entire global pharmaceutical market, where the competition is dictated by the cost of manufacturing – whether it is conducted in Western countries or in Eastern Europe, Asia, or Southeast Asia,” he says.

With new players coming to the contract manufacturing market, the geographic location and cheaper labor leads to lower prices in some of these markets. The internal factor influencing the growth of contract development and the manufacturing industry is the quality of the services, according to Dr. Klyushnichenko.

All categories of drugs and dosage forms lend themselves to a contract manufacturing strategy. “The outsourcing of older, even off-patent, drugs started this trend decades ago, but the trend is moving upstream to newer, more cutting edge therapies, and even to therapies that are very difficult to produce,” Mr. Chapin states.

Given that a certain level of quality is mandated by regulatory bodies, effective contract manufacturers cannot differentiate themselves on their quality.

The key for manufacturers will be the two-edged sword of cost efficiency and expertise/uniqueness. “These are two opposite forces: cost efficiency assumes a standardized offering, for example, ‘We can make that exact generic cheaper than that other factory,’ while expertise/uniqueness assumes a non-standardized offering, for instance, ‘We are the only company in the world that can make this large protein,’” Mr. Chapin says.

An effective competitive strategy has to offer one or both: cost/efficiency or expertise/uniqueness. “It is possible to offer both, but it is not easy, as the business decisions that flow from the choice to focus on cost/efficiency (such as a factory location where land is cheap) tend to be antithetical to those that flow from the choice to focus on expertise/uniqueness (such as a factory location where highly trained employees are plentiful),” Mr. Chapin notes. “That being said, these two choices are not completely antithetical. With the right set of choices, a contract manufacturer can offer both cost/efficiency as well as uniqueness/expertise.”

The reliance on contract manufacturers allows companies to leverage disciplines that they do not have in-house or would need to seek out and acquire, according to Mr. Lanza. Many middle-market pharma companies are operating un-

der the philosophy of ‘Why build in a slow economy when you can buy for a relatively higher return on investment?’ he observes.

New trends in the pharmaceutical industry need to be monitored and addressed. The industry needs to have an open mind to innovative ideas such as the development of strategic alliances with academic and governmental institutions, Dr. Klyushnichenko observes.

“Strategic decision makers at pharmaceutical and biotechnology companies are actively studying the market due to the steady increases in global pharmaceutical contract manufacturing and research worldwide – including the contract manufacturing of OTC and nutritional products, as well as bulk and dosage form drugs,” Dr. Klyushnichenko shares.

According to Dr. Klyushnichenko, an effective CMO possesses a focus on a particular type of operation, determined by the experience of personnel and the financial stage of the company; flexibility, attention to client needs; clear and timely communication; transparent project management; development of new technologies; addressing the general needs of the pharmaceutical market and the expansion into new areas; and development of strategic alliances with academic and governmental institutions.

## EXPERTISE AND QUALITY

Being able to specialize and customize services are key to CMOs winning and maintaining contracts with pharma companies, according to Alkermes. “With ever-increasingly sophisticated products entering the market, it is important to offer a range of specialized value-added services to clients,” Alkermes reps say. “Having a broad range of specialized skills and expertise is critical in getting product to commercial stage. While it is important to offer a broadened portfolio of services, the range and diversity of skills required to move up the value chain and offer a broader service takes considerable time and effort to develop.”

Contract manufacturers provide pharmaceutical companies with expertise and specialized competencies that they do not have in-house because it is not financially feasible, according to Dr. Klyushnichenko.

Dr. Klyushnichenko observes that many CMOs have highly qualified scientists, en-

gineers and associates with years of experience in project management, quality systems and regulatory compliance. Some, however, do not.

According to Dr. Klyushnichenko, this allegedly has been a problem in the manufacturing of nutritional supplements. Since more than 95% of supplements in the United States are contracted out, the quality of the product is highly dependent on not only the manufacturer's verification that all ingredients are tested for compliance and contain a certificate of analysis, but also on the company's manufacturing procedures. Dr. Klyushnichenko also cautions that companies need to consider whether their associates are biochemists or at least have the scientific knowledge to formulate professional grade nutritional supplements.

"Outsourcing provides options," Mr. Lanza shares. "A company will need to weigh the options of build versus buy and base its decision on which one provides the greatest return on investment. Some options of outsourcing allow pharma companies to develop resources more to the research and development and use the outsourcing function as a low-valued addition to the supply chain."

Contract manufacturers with niche products and services or access to exclusive active pharmaceutical ingredients (raw materials) possess the greatest advantages. "The need for highly skilled teams to create drugs with very complex formulas is driving the creation of more effective contract manufacturers globally," Mr. Lanza explains.

The United States currently possesses the highest skill set, however, the industry is showing an increase in contract manufacturers in India, China, Italy and Korea that possess the highly skilled labor needed to produce these compounds.

## M&A AND PARTNERSHIP STRATEGIES

The contract researching and contract manufacturing industries are highly fragmented and the trend of consolidation is likely to continue, according to Mr. Goodman. The industry, he says, is a highly competitive one with tremendous cost pressures.

Alkermes plc was formed in September 2011 following the merger of Alkermes Inc. with Elan Drug Technologies. EDT was a profitable, world-class drug formulation and manufacturing business

that was formerly a unit of Elan Corporation plc, a neuroscience-based biotech company. The merger was officially announced in May 2011 and was completed four months later.

The transaction was anticipated to be immediately accretive to cash earnings. This strategic move accelerates Alkermes' path to building a sustainably profitable biopharma company with expertise in developing treatments for central nervous system diseases and a broad, diversified portfolio of products and pipeline based on proprietary science and technologies.

As a result, Alkermes plc has diverse revenue streams from 25 commercialized products, with future near-term growth expected to be driven by five major products: **RISPERDAL CONSTA, INVEGA SUSTENNA, AMPYRA, VIVITROL and BYDUREON**. The combined company is projected to have growing product, royalty and manufacturing revenues exceeding \$450 million annually and resources to prudently invest in an innovative pipeline of proprietary drugs.

"We are very excited about the creation of Alkermes plc – a unique, global, diversified company and a leader in CNS

medications," commented Richard Pops, CEO of Alkermes. "Through this transaction, we have strategically combined two highly innovative companies with proprietary technologies and important commercial products, creating a strong platform for accelerating future growth and increasing shareholder value."

According to Shane Cooke, executive VP and head of EDT, "The combination of Alkermes and EDT is a strong strategic fit at the right time when both businesses are strong and positioned for growth. With EDT's two recently approved drugs, INVEGA SUSTENNA and AMPYRA, driving revenue growth, the EDT business is an ideal complement to Alkermes' portfolio of approved and development-stage drugs. This combination creates opportunities for our employees and provides a platform for future growth."

Elan received \$500 million in cash and 31.9 million ordinary shares of Alkermes plc, representing one-quarter of the new entity. Based on the closing share price of Alkermes Inc. on Sept. 15, 2011, of \$16.52, the entire transaction value amounted to \$1 billion.

Within a few days after the merger was completed, Alkermes announced the es-

## STRATEGIC AND FINANCIAL BENEFITS OF THE ALKERMES AND ELAN DRUG TECHNOLOGIES MERGER

Upon merging with Elan Drug Technologies effective September 2011, Alkermes plc now has the following strengths:

- Immediate profitability on a cash earnings basis and diversified, growing revenues from 25 commercial products
- Robust revenue growth with expected Adjusted EBITDA margin expansion
- Five high-growth commercial products (RISPERDAL CONSTA, INVEGA SUSTENNA, AMPYRA, VIVITROL and BYDUREON), all with long patent lives and significant growth potential in large therapeutic areas. In particular, two of these products, RISPERDAL CONSTA and INVEGA SUSTENNA, are commercialized by Johnson & Johnson and represent very important long-acting injectable atypical antipsychotic medications for schizophrenia and bipolar I disorder
- A strong, CNS-focused pipeline of proprietary and partnered product candidates in clinical development, including several late-stage proprietary product candidates
- Complementary new drug development capabilities that leverage proprietary science and innovative medicinal chemistry capabilities. Proprietary technologies include EDT's NanoCrystal technology for poorly water soluble drug compounds; EDT's proprietary technologies for oral controlled release drugs; and Alkermes' long-acting injectable drug technologies
- GMP manufacturing facilities in Wilmington, Ohio, Gainesville, Ga., and Athlone, Ireland, with world-class capabilities for producing complex drug products.

Source: Alkermes



tablishment of corporate operations in Ireland and new headquarters located in Dublin. The company, including Alkermes' headquarters and operations in Athlone, County Westmeath, has more than 450 employees based in Ireland and 1,200-plus employees worldwide.

Marking its first day of operations in Ireland, Alkermes announced a multiyear, multimillion dollar manufacturing deal with one of the world's top 10 pharma companies. Alkermes will manufacture the company's finished pharmaceutical product, which will be produced at Alkermes' Athlone facility. Alkermes expects this agreement to generate \$15 million to \$20 million in annual manufacturing revenue by 2016. The Athlone facility is one of three major manufacturing plants owned by Alkermes plc at which the company produces proprietary, partnered and contract-manufactured drug products.

"We are a strong, global company with a diversified product portfolio, and we look forward to accelerating our growth to create value in our business and for the patients we serve," Mr. Pops says. "Alkermes is excited to have our operations based in Ireland, which we view as a gateway to the European Union and global pharmaceutical market."

Alkermes plc is a fully integrated, global biopharmaceutical company that applies its scientific expertise and proprietary technologies to develop innovative medicines that improve patient outcomes. The company has a diversified portfolio of more than 20 commercial drug products and a substantial clinical pipeline of product candidates that address central nervous system (CNS) disorders such as addiction, schizophrenia and depression. Alkermes has an R&D center in Waltham, Mass., and manufacturing facilities in Athlone; Gainesville, Georgia; and Wilmington, Ohio.

According to Alkermes officials, as manufacturing processes become more complex and regulatory requirements become more onerous, pharmaceutical companies are developing longer-term, more beneficial strategic arrangements.

"This often results in pharma companies engaging with fewer partners, but these providers need to be able to deliver a full service offering to compete for business," company reps noted. "For a pharma company to strategically outsource, it must reinvent this relationship through persistent discussions with its pre-

ferred partners on planning, common objectives and the responsibility of operating more effectively against key metrics.

"These companies, are looking first and foremost for quality and on-time delivery of product from their outsourcing partners. Once a pharmaceutical company can view its manufacturing partner as an extension of its own organization, it can include them in strategic decision making processes and facilitate data transparency as partners."

**Akorn Inc.**, a niche generic pharmaceutical company, entered into an agreement during October 2011 to acquire certain assets of **Kilitch Drugs (India) Ltd.**, a leading contract manufacturer of sterile injectables in India. Akorn also agreed to acquire certain assets of **NBZ Pharma Ltd.** The transaction amounts to nearly \$52 million in cash and future contingent payments totalling up to about \$6 million based on the achievement of certain milestones and financial targets.

The target assets consist of Kilitch Drugs' (KDIL) plant in Paonta Sahib in Himachal Pradesh, India, along with the associated contract manufacturing and international business, and certain product transfers from KDIL's Navi Mumbai plant and NBZ Pharma. The acquisition was expected to close after receiving local regulatory approvals as well as meeting certain customary conditions and consents within about 90 days of the acquisition announcement.

"We are excited about this acquisition as it expands both our capacities and capabilities for sterile injectables," says Raj Rai, CEO of Akorn. "With this platform we plan to offer a speed to market, high quality, comprehensive and cost effective solution to our domestic customers specifically for critical care products in categories such as anti-infectives and cancer that are consistently in short supply.

"Strategically, we will also establish a global footprint giving us access to the fast growing emerging markets. Finally, this acquisition provides us with a road map to become a leader in the generic injectable market."

Akorn is a niche pharmaceutical company engaged in the development, manufacture and marketing of multisource and branded pharmaceuticals. The company has manufacturing facilities located in Decatur, Ill., and Somerset, N.J., where the company manufactures ophthalmic and injectable pharmaceuticals.

Kilitch Drugs is an Indian pharmaceutical company engaged in the manufacture and marketing of generic pharmaceutical formulations in several dosage forms such as injectables (liquid and dry), solids, and liquids. Kilitch has two formulation manufacturing facilities, in Navi Mumbai and Paonta Sahib. The company has forayed into marketing and distribution of ophthalmology products in India and certain overseas markets.

## CRO ACTIVITY

In addition to contract manufacturing organizations, the pharmaceutical market uses outsourcing services from providers in the form of contract research organizations. CROs are emerging as prominent players in the pharma industry and are no longer viewed as less innovative competitors to pharma R&D. CROs are evolving as significant industry change makers.

Big pharma embraces the global CRO industry for clinical development, but more recently has begun to incorporate the use of CROs into corporate strategy plans.

In March 2011, for example, Bristol-Myers Squibb and **WuXi PharmaTech Inc.** entered into a strategic partnership to perform stability studies of small-molecule new chemical entities to support global marketing applications.

WuXi will build, equip and operate a dedicated, fully cGMP-compliant 25,000-square-foot analytical testing facility in Shanghai to store and test stability samples and to conduct other services for Bristol-Myers Squibb. WuXi will employ a dedicated staff for stability testing, sample management, analytical testing, pharmaceutical science, quality assurance, metrology, and other services including stability data reporting in support of all worldwide dossier filings by Bristol-Myers Squibb.

"This new agreement expands our already productive relationship with Bristol-Myers Squibb, a valued customer for many years," says Ge Li, Ph.D., chairman and CEO of WuXi PharmaTech. "We will continue to help them to improve their R&D productivity with our innovation-driven, cost-effective and fully integrated R&D service platform."

According to Mark Powell, Ph.D., senior VP of non-clinical development for Bristol-Myers Squibb, "WuXi PharmaTech is an important partner for Bristol-Myers Squibb's

research and development organization. This agreement will expand the scope of our relationship with WuXi and enhance the presence of Bristol-Myers Squibb in China. It is also an example of our R&D organization executing our company's BioPharma model by using selective integration to leverage the strengths and talents of both Bristol-Myers Squibb and a valued partner."

**Takeda Pharmaceuticals International Inc.**, a wholly owned subsidiary of Takeda Pharmaceutical Co., announced on Feb. 15, 2011, that its Pharmaceutical Development Division has entered into strategic partnerships with **Covance** and **Quintiles**, two of the world's largest full-service contract research organizations.

Under terms of the transactions, Covance and Quintiles are working in close partnership with Takeda to plan and execute global development programs to support new compounds in all therapeutic areas, except oncology. Takeda has access to the clinical development capabilities and central laboratory services of Covance and Quintiles. Each partner company provides dedicated resources to support Takeda's development pipeline. Takeda intends to use a worldwide program-level sourcing strategy to increase operational efficiency.

Through these relationships, Takeda is moving toward a fully virtual outsourcing model combining its expertise and capabilities with those of Covance and Quintiles. This process is anticipated to improve productivity and facilitate Takeda's global growth.

"Takeda is focused on growing its global drug development footprint, especially in Asia, while at the same time ensuring quality and increasing efficiency of our operations," says Robert Ahlbrandt, Ph.D., senior VP of global development operations for Takeda's Pharmaceutical Development Division. "Our new strategic partnerships with Covance and Quintiles will improve the agility and productivity of our drug development activities, helping us to deliver innovative new medicines to patients globally."

On Oct. 14, 2011, WuXi PharmaTech announced the acquisition of **Abgent Inc.**, a provider of biological research reagent products and services based in Suzhou, China, and San Diego. Financial terms of the acquisition were not disclosed.

In September 2010, Covance entered a partnership with Sanofi that could be

valued at as much as \$2.2 billion for 10 years. Covance is providing drug-development services to the Paris-based company, and will receive an estimated \$1.2 billion to \$2.2 billion in payments. As part of the deal, Covance purchased Sanofi's facilities in Porcheville, France, and Alnwick, United Kingdom, for about \$25 million. Covance is operating those facilities for at least five years.

Sanofi is using Covance services for drug-discovery support, toxicology, chemistry, clinical testing, central laboratory, and market-access services. The deal for the two facilities gives Covance the ability to offer chemistry, manufacturing, and controls services, which can include drug formulation and ingredient manufacturing.

Similarly, Pfizer has outsourced some of its R&D to the company's contract research organizations such as Covance, **Charles Rivers Laboratories** and **Parexel International Corp.**

On April 26, 2011, **Omnicare Clinical Research (CR)** was acquired by **Nautic Partners LLC**, a private-equity firm based in Providence, R.I. The signing of the deal marks the separation of Omnicare CR from former parent company **Omnicare Inc.** official and achieves the company's most visible step in a comprehensive two-year plan to accelerate Omnicare CR into the future.

With 25-plus years of quality service, Omnicare CR has established its own strategic business-unit model to best serve the most complex trials. During the last five years, Omnicare CR has successfully completed more than 1,500 studies globally with more than 337,000 participating patients. As the CRO takes this next step forward, added support from Nautic will enable Omnicare CR to meet customer needs even more quickly.

"Our new affiliation with Nautic is very exciting for all of us at Omnicare CR," stated Dr. James M. Pusey, president and CEO of Omnicare CR. "This marks a new era for our business that will provide us the ability to more efficiently make vital, strategic decisions, placing us in control of our own destiny. The group in the best position to benefit from this reorganization is our current and future customer base. With our renewed strength, Omnicare CR will be able to deliver an even higher level of customer service while maintaining the teams currently in place who support our customers on a day-to-day basis."

According to Dr. Pusey, the affiliation with Nautic was the best possible partnership for the company. "The interest in Omnicare CR has been intense and our new partnership with Nautic gives us the opportunity to further specialize our business model, invest in the company's future and grow our high-quality organization," Dr. Pusey commented.

Since the company's founding during 1986, Nautic has completed 110-plus investments. The Omnicare CR accord continues the firm's successful history of investing in the healthcare services arena.

"Nautic will fully support Omnicare CR on a strategic level and with additional capital for growth," says Chris Crosby, managing director of Nautic. "We have complete confidence that with our added support, company leadership will maximize efforts around the great work that has already been done, adding to Omnicare CR's profitability."

Omnicare CR's senior leadership anticipates added growth among its specialized business units. These include early phase, Phase II/III, late phase, medical device, technical services and pharmaceuticals.

"We're looking forward to a bright future with support from Nautic. As Omnicare CR continues to grow, exciting times lie ahead for our employees and our customers across the globe," Dr. Pusey noted.

Omnicare CR was founded in 1985 as **Biopharm**, then merged with a public company, changing its name to **IBAH**. That business was acquired by Covington, Ky.-based Omnicare in the late 1990s. Omnicare CR was integrated with **Clinimetrics Research Associates**, another CRO owned by Omnicare Inc., to create one entity.

During June 2011, Omnicare CR announced its rebranding as **Theorem Clinical Research**. Theorem continues to provide full-service clinical trial management with a continued concentration on its core CRO operations – early Phase, Phase II/III, late Phase – and its specialized business units: Pharmaceuticals, Medical Device, and Technical Services (Biometrics & Clinical Data Management).

Other mid-tier CROs acquired in recent years include the August 2010 purchase of **United BioSource Corp.** by **Medco Health Solutions**; **Avista Capital's** acquisition of **INC Research** that same month; **inVentiv's** acquisition of **i3**, announced

during January 2011; and the **Warburg Pincus** purchase of **RPS**, announced in December 2010.

**Aptiv Solutions**, a leader in designing and executing adaptive clinical trials and medical device studies, in October 2011 acquired **SRA Global Clinical Development**. SRA GCD is the CRO division of **SRA International** Inc. based in Durham, N.C., with offices in Paris, France and Milton Park, England.

With 15 years of service to the pharma and biotechnology industry, SRA GCD and its predecessor companies have formed a substantial business by delivering high-quality clinical trial and regulatory services worldwide. SRA GCD's regulatory consulting team located near London adds significantly to Aptiv Solutions' well-established and highly regarded regulatory services group. The additional talent from SRA GCD accelerates Aptiv Solutions' worldwide leadership in regulatory services.

"We believe the GCD business, as a part of Aptiv Solutions, has greater opportunity to pursue a wider range of initiatives that align with its mission," says Bill Ballhaus, president and CEO of SRA International.

"We are delighted to welcome the roughly 100 SRA GCD experienced professionals to the Aptiv Solutions team," stated Pat Donnelly, chairman and CEO of Aptiv Solutions. "Assimilation of staff into Aptiv Solutions is already under way, and our primary focus will be to continue to provide best-in-class service to the current SRA GCD clients. With this acquisition we continue to broaden our client base and add significant expertise and scale to Aptiv Solutions."

On Aug. 22, 2011, Aptiv Solutions announced the acquisition of **Medical Device Consultants** Inc. MDCI is a provider of expert medical device consulting as well as clinical trial management and execution. Aptiv Solutions is a leading provider of clinical trial management services to the medical device arena. This transaction adds new complementary regulatory and quality assurance capabilities to the company's portfolio of offerings and bolsters its existing clinical trial management services.

Founded during 1980, MDCI has offered regulatory, quality assurance, compliance, and clinical trial management services to the medical device and diagnostic industries. The company is a recog-

nized leader in addressing regulatory and clinical trial requirements for emerging growth firms and well-established medical device and diagnostic innovators. MDCI has developed, prepared and filed 600-plus successful 510(k)s, participated in the development of more than 20 successful PMAs, and managed hundreds of clinical trials to support medical device approvals and clearance in the United States, Europe, worldwide.

## PRODUCTION CHALLENGES

When manufacturing operations are outsourced, the responsibility for the product remains with the New Drug Application (NDA) or Biologic License Application (BLA) holder. The contract manufacturer must remain in compliance with cGMP regulations to ensure quality and also adhere to commitments made in the NDA/BLA.

Developing and implementing a cohesive strategy with the contract manufacturer is of utmost significance to prevent the manufacture of products that do not meet cGMP standards. If not manufactured properly, products may negatively affect the NDA/BLA holders' reputation, increase liability and/or cause product recalls. These issues could spiral out of control and eventually result in increased burdens to the NDA/BLA holder, such as product stock-out, increased resource use, and heightened cost to the company.

The quality systems for FDA-regulated products are known as current good manufacturing practices (cGMPs). To help ensure that their products consistently meet applicable requirements and specifications, manufacturers must establish and follow quality systems.

The worldwide trends predicted in the next decade will have major implications for FDA, according to industry analysts. As a result of changes worldwide, the manufacturers and products regulated by FDA will face intense pressure to lower costs and increase worker productivity. In response, FDA is forming relationships with worldwide and domestic partners, pushing for strong global safety standards.

With the production of more FDA-regulated products abroad, companies and products are subject to complex paths via multi-step supply chains to reach America.

These changes are predicted to in-

crease the already high volume of FDA-regulated products that are imported into the United States. Products from new markets are expected to enter America only after going through a long and complicated process to convert globally sourced materials into finished goods. Industry analysts predict a spike in cases of fraud and other issues unless FDA makes dramatic revisions to its worldwide product safety and quality approach.

Industry experts have noted a steady and important increase in spending on pharmaceutical R&D, even as the amount of NME approvals has decreased in the past 10 years. The industry must concentrate on ways to drive down production costs particularly as consumers and payors will continue to insist on access to lower-cost medical products and services.

Companies are increasingly moving their manufacturing activities to new and different locations, looking to global supply chains to reduce production costs. Industry analysts believe that more than 40% of the final assembly in the pharma industry is performed outside of the producer's home country, in an effort to the lower production costs.

The cost of formulation of an API reportedly costs 15% to 40% less to produce in India than in the United States.

U.S. imports of pharma products have grown about 13% annually during the past seven years and accounted for 350,000-plus import lines in 2009. The increase in imports has contributed to a rising trade deficit in pharma products.

During 2000, the United States imported \$1.7 billion more in pharma products than the country exported. By 2008, that discrepancy had grown ten-fold to \$18 billion. About 80% of active ingredients found in pharma products sold in the United States originated overseas.

The United States is expected to continue increasing the volume of FDA-regulated products imported. Industry analysts believe that growth in imported products will outpace the growth of domestic products, resulting in an even higher proportion of medical products coming from overseas.

Aseptic fill/finish manufacturers are held to the highest quality standards and regulation. There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization.

Terminal sterilization typically involves



filling and sealing product containers under high-quality environmental conditions. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container and closure have low bioburden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

In an aseptic process, the drug product, container and closure are first subjected to sterilization methods separately as appropriate, and then combined. Because there is no process to sterilize the product in its final container, containers need to be filled and sealed in an extremely high-quality environment. Aseptic processing involves more variables than terminal sterilization.

Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration.

Each of these manufacturing processes necessitates validation and control. Each process could introduce an error that ultimately could result in the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers or closures before or during aseptic assembly poses the risk of contamination and thus requires careful control. Whereas a terminally sterilized drug product undergoes final sterilization in a sealed container, thereby limiting the possibility of error.

According to FDA guidance, sterile drug manufacturers should have a keen awareness of the public-health implications of distributing a nonsterile product. Poor CGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to patients.

Some aseptic fill/finish providers have not been in line with best aseptic fill/finish practices. During August 2010, for example, Bristol-Myers Squibb received a warning letter from FDA stating, "During our March 17-31, 2010 inspection of your manufacturing facility, **Bristol-Myers Squibb Holding Pharma Ltd.**, located in Manati, Puerto Rico, investigators from the Food and Drug Administration (FDA) iden-

tified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (C.F.R.), Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 351(a)(2)(B)) in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP."

**Gilead Sciences** Inc. received a similar letter during September 2010, referencing a Jan. 25, 2010, to Feb. 12, 2010, inspection of the company's pharmaceutical manufacturing facility located at 650 Cliffside Drive in San Dimas, Calif.

Many of these violations fall under the category of environmental excursions that were not properly addressed, facility maintenance that can affect aseptic manufacture and a litany of other microbiological issues, according to industry experts.

## FDA ISSUES GRANT

**The National Institute for Pharmaceutical Technology and Education** (NIPE) was awarded a grant from FDA valued up to \$35 million for five years to improve drug manufacturing standards. The regulatory agency hopes the grant, as reported in October 2011, will help to reduce health-care costs, create jobs, and improve drug safety.

The estimated cost of bringing a drug to the U.S. market exceeds \$1 billion, and an increasing number of drugs and drug ingredients are being imported from abroad. By investing funds in drug development and manufacturing research, manufacturing competitiveness may improve in the United States. In addition to creating high-paying jobs on home soil, this approach may help to decrease manufacturing costs as well as improve the quality and safety of medicines in America.

"Over the last several years, NIPE has contributed a great deal of research toward our understanding of quality pharmaceutical manufacturing," shares Helen N. Winkle, director of FDA's **Office of Pharmaceutical Sciences**. "Progress in this area will mean safer, more efficient, and less costly drug production here in

the United States, and we are looking forward to NIPE's findings."

NIPE Inc. is an academic not-for-profit organization committed to fundamental research and education in pharmaceutical product development and manufacturing. The organization intends to increase science and engineering-based understanding of this area so that novel state-of-the-art technologies can be developed and science-based regulations can be implemented. These technologies will allow for new drug discoveries to be brought to market faster with less variability, higher predictability of performance and at a significantly lower cost.

"Outsourcing of drugs and drug intermediates are increasing at an alarming rate, potentially threatening overall quality of our drugs accompanied by huge job losses in this country," explains Prabir Basu, executive director of NIPE. "Development and manufacturing costs can be reduced, quality of our drugs can be improved, and outsourcing trends can be reversed by developing science-based standards for drug development and manufacturing."

FDA grant will support programs to rectify these drug development and manufacturing problems. This will be done by creating ways to reduce time to market, enabling new performance attributes, improving small-batch production, promoting continuous manufacturing, saving money or energy, or reducing environmental impact from the manufacture of products.

"We are thrilled to see the FDA's commitment to invest in the science of pharmaceutical manufacturing," Mr. Basu says. "I sincerely hope that other federal funding agencies will take the lead from the FDA and will take similar steps to fund this critical area of translational and manufacturing research to improve health care in the United States."

NIPE partners with 10 universities located in the United States that are leaders in pharma science and engineering. The member universities are **Duquesne University, Illinois Institute of Technology, Purdue University, Rutgers University, the University of Puerto Rico, the University of Connecticut, the University of Iowa, the University of Kentucky, the University of Maryland, Baltimore (UBM), and the University of Minnesota**. This university partnership is considered one of a kind.

# GLOBAL CONTRACT MANUFACTURING COMPANIES REVIEW

THIS SECTION OF THE REPORT PROFILES SOME OF THE WORLD'S LEADING COMPANIES AS WELL AS UP-AND-COMERS IN THE AREA OF CONTRACT MANUFACTURING; SOME COMPANIES WERE ALREADY DETAILED ON THE PRECEDING PAGES OF THIS REPORT.

## AAIPHARMA SERVICES CORP.

AAIPharma Services is a top provider of pharma product development and manufacturing services. The company has cGMP manufacturing facilities based in Charleston, S.C., for parenteral products and in Wilmington, N.C., for solid oral dosage forms.

With 30-plus years of experience, AAIPharma specializes in analytical chemistry, formulation development, clinical packaging, oral drug delivery and contract manufacturing. The Wilmington, N.C.-based company serves 300-plus large pharma and biotech companies.

AAIPharma provides flexible capabilities for processing a diverse array of pharma drug products such as controlled substances as well as toxic or potent compounds. AAIPharma's facilities are FDA and EMA approved, and produce products for clinical and commercial supplies in U.S. and European markets.

The company has manufacturing expertise in clinical manufacturing activity ranging Phase I to Phase III studies, with scale-up and validation support to address commercial launch and supply DEA-compliant Schedule I to Schedule V controlled substances; level 3 and 4 toxic/potent compounds; difficult-to-make

products; commercial niche products including orphan and veterinary drugs; and sterile products for small molecules and biologics such as proteins, peptides, monoclonal antibodies and other large molecules.

AAIPharma passed inspection of the company's Durham, N.C., analytical lab by FDA during June 2011 with no inspectional observations. The May 2011 audit was the fourth since 2003 during which these lab operations were not issued an FDA-483 citing any inspection concerns. FDA performed its audit during 2011 in the Durham lab's new location, which AAIPharma moved into in 2010.

"Once again passing the FDA inspection without issue reflects the strong focus on compliance and accurate documentation that is the legacy of AAIPharma Services," stated Christopher Smith, VP of corporate quality assurance and regulatory affairs for the company. "Having this laboratory testing facility thoroughly audited is a reassurance to our global clients that their pharmaceutical products developed and tested here for clinical and commercial uses will be of the highest quality and meet regulatory standards."

Mr. Smith notes that the successful FDA audit in Durham occurred after two Good Manufacturing Practices (GMP) certificates were issued by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) to AAIPharma. The EU GMP Certificates followed audits of AAIPharma's Charleston manufacturing and laboratory operations for parenteral products and its Wilmington inspection, labelling, packaging, shipping and lab operations supporting Charleston.

"Earning these EU GMP Certificates lets our global clients know they will have no issues shipping pharmaceuticals from these facilities into Europe, or into countries such as Canada and Australia that have mutual recognition agreements (MRAs) with the European Union," noted Pat Walsh, CEO of AAIPharma. "It gives our clients confidence in AAIPharma Services as their preferred provider of drug development and manufacturing, from compound to clinic around the world."

AAIPharma and **CritiTech Inc.**, a nan-

otechnology company that improves the delivery of therapeutic molecules, announced a strategic alliance on July 8, 2010. The deal expanded the reach of CritiTech's technology.

This alliance enables pharma and biotechnology companies to select a novel drug-delivery option in early animal toxicology and clinical studies where there is a drug-delivery challenge that cannot be solved via conventional approaches. Drug-product development and manufacturing are performed by AAIPharma. Drug-product intermediate manufacturing is conducted by CritiTech. Both companies are connected via AAIPharma's best-in-class project-management expertise.

The company offers its own proprietary drug-delivery technologies and other technologies through AAIPharma's alliance partners, including **Emisphere Inc.** The alliance has provided another drug-delivery option for parenteral administration to complement AAIPharma, which already had an established oral drug-delivery franchise.

CritiTech's technology is intended to improve the delivery of therapeutic molecules with low aqueous solubility or poor bioavailability. The key benefit of the technology is the body's improved ability to absorb these difficult-to-formulate drugs. The CritiTech technology enables parenteral administration of drugs that previously could not be administered through this route.

"The Alliance with AAIPharma services allows us to share the established CritiTech technology, used in our **Nanotax** product currently in development, with a broad range of potential customers," says David Johnston, CEO of CritiTech. "The collaboration with AAIPharma services and their outstanding product development and manufacturing capability allows us to provide additional drug delivery options throughout the drug product development cycle and to more fully exploit CritiTech technology."

According to L. Lee Karras, CEO of AAIPharma Services, "The alliance with CritiTech allows us to add a breakthrough drug delivery option for our pharmaceutical and biotech customers, whether

### AAIPHARMA SERVICES HAS MANUFACTURING EXPERTISE IN:

- Clinical manufacturing activity that ranges from Phase I-III trials, with scale-up and validation support to address commercial launch and supply
- DEA-compliant Schedule I-V controlled substances
- Level 3 and 4 toxic/potent compounds
- Difficult-to-make products
- Commercial niche products such as orphan and veterinary drugs
- Sterile products for small molecules and biologics, including proteins, peptides, monoclonal antibodies and other large molecules

Source: AAIPharma Services

they are developing a new product or improving an existing product already on the market. The combination of the CritiTech technology and AAI Pharma Service's best-in-class drug product development and contract manufacturing services will be of tremendous value to customers. This new offering is in line with our strategy to become the leading provider of complex drug development services to the pharmaceutical and biotechnology industries."

CritiTech is a technology company concentrated on a unique and improved delivery of therapeutic molecules and compounds through its patented nanotechnology. The technology is licensed from the Department of Chemical Engineering at the **University of Kansas** and the **Higuchi Biosciences Center**. The technology can be applied to the oral route of administration and additional delivery pathways including buccal, rectal, inhalation, vaginal or transdermal. CritiTech lab operations are based in Lawrence, Kan.

**Water Street Healthcare Partners LLC** acquired AAI Pharma Services Corp. from **AAI Pharma Inc.** during 2009 and established the entity as a stand-alone company. Water Street is leveraging its team's industry expertise and years of experience operating worldwide pharma businesses to expand the company's core services. Water Street's goal is to form AAI Pharma Services into the leading provider of pharma drug-development services via a combination of organic growth and strategic acquisitions.

Water Street dedicated up to \$75 million in equity financing to expand the business capabilities with the goal of building it into a top provider of pharma development services. The new company was named AAI Pharma Services Corp.

In addition to providing significant capital resources, Water Street offers extensive pharma expertise that benefit the company, employees and customers on its new strategic direction.

During 2008, pharma and biotech companies invested \$115-plus billion in drug R&D worldwide. Up to one-quarter of that expense is estimated to have been outsourced. As requirements and standards for drug approvals continue to intensify and development costs increase, companies are expected to continue outsourcing more drug development. Analysts predicted the market for outsourced

drug development services will grow at a compound annual rate exceeding 10% through 2015.

"The rising complexity of drug development and the costs related to maintaining those capabilities in-house are leading global pharmaceutical and biotech companies to increasingly turn to outside resources for assistance," noted Al Heller, an operating partner at Water Street with 30-plus years of pharma experience including leading operations for **G.D. Searle**. "AAI Pharma Services goes beyond traditional levels of support to provide customers with unique expertise and capabilities that creatively address challenges that arise during drug development and manufacturing. The company is highly regarded for collaborating with customers to ensure they consistently achieve high-quality results. This is the unique value proposition that we intend to build on."

AAI Pharma Services was Water Street's second platform investment during 2009 and first investment in the life-sciences sector.

"We are pleased that Water Street continues to complete investments in sectors of health care that we have identified as attractive for growth," commented Tim Dugan, managing partner of Water Street. "Over the past 30 years, the AAI Pharmaceutical Development business has consistently grown to achieve strong results. As a stand-alone entity, AAI Pharma Services is much better positioned to focus on and expand its core business. We will leverage our team's deep expertise and relationships in the pharmaceutical industry to build on its strong foundation through a combination of organic growth and strategic acquisitions. Ultimately, our goal is to create greater long-term value for customers and the company by establishing AAI Pharma Services as the leading provider of drug development services."

Chicago-based Water Street is a top private equity company concentrated exclusively on health care. With \$1-plus billion of capital under management, Water Street is one of the most active investors in the health-care arena. Water Street has a strong record of building market-leading companies across key health-care growth sectors. The company has partnered with some of the world's largest health-care companies on its investments including Johnson & Johnson, **Medtronic** and **Smith & Nephew**. Water Street's

team consists of industry execs and private-equity professionals with decades of experience investing in and operating worldwide health-care businesses.

## ABBOTT LABORATORIES

Abbott is a broad-based, worldwide health-care company dedicated to the discovery, development, manufacture and marketing of products spanning the continuum of care. These products range from nutritionals and lab diagnostics through medical devices and pharma therapies.

Abbott Contract Manufacturing services include a full line of high-potency manufacturing capabilities for API and Finished Goods production across a diverse range of scale such as formulation in tablets and capsules.

State-of-the-art manufacturing facilities along with the company's depth of expertise help Abbott to develop and deliver products and processes from small-scale clinical-trial supply to larger commercial manufacturing. Abbott's Quality control laboratories are equipped with the latest design technology for chemical and microbiological analytical testing to meet customer needs.

The company offers potent manufacturing services on two continents, with facilities based in Sligo, Ireland and Wyandotte, Michigan. Each location has unique features that can support the development and manufacturing of Abbott's customer's product.

The company's high-potent manufacturing site in Sligo started operations during 2003 and meets FDA, ICH and EU requirements. The 110,000 square-foot facility has the capability to manufacture an extensive array of potent pharmaceuticals from APIs to Finished Goods. The plant uses new design concepts for handling potent compounds to containment levels up to OEB 5 (<1mcg/m<sup>3</sup>).

The Wyandotte, Michigan facility has produced high-potency intermediates and APIs since 1999. The 80,000 square-foot site offers turn-key solutions for high-potency chemical production for controlled drugs and delivers containment levels up to OEB 3(>10 mcg/m<sup>3</sup>). The location additionally offers an advanced process development laboratory and analytical testing.

Abbott Contract Manufacturing services consist of a full line of finished goods





# Contract Manufacturing and Active Pharmaceutical Ingredients

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## Depth of Expertise

Abbott has more than 120 years of product development, manufacturing, quality and regulatory experience to apply to your needs.

 smart
 secure
 strong

### Cost Effective Potent Manufacturing



**Abbott Ireland Potent API and Drug Product Manufacturing**  
ISO Class 8 + PharmedA + Containment Levels up to BBS (x1 magnify)

#### DEVELOPMENT

**API Production Capacity**

- Hydrogenation capability (4000 L)
- Production suites (8) ranges 5-250 kg
- Contained production and transfers
- Kilo lab scaling to Kg inspected

#### COMMERCIALIZATION

**Drug Product – Solid Oral Dosage**

- Single pot High Shear granulators
- In-Bin (IBC) blending 50-240 L
- 150,000 capsules/hr.
- 300,000 tablets/hr. and coating
- Licensed for clinical trial supply

### Fulfilling Capacity – Contract Manufacturing – C&EN News Link

### News and Events

Interphex 2011 Presentations

- Process Qualification – Linking C&Q to Process Validation
- Operational Strategies for Lean Sigma Manufacturing
- Selection, Design and Risk Based Qualification of a Tablet Coater for the Development and Launch of Highly Potent Compounds

The Power of a Promise

### Come see us at

**CONTRACT PHARMA**  
Contract Pharma  
September 22-23  
Hyatt Regency  
New Brunswick,  
New Jersey

**CPhI worldwide**  
CPhI  
October 25-27  
Booth 42H39  
Messe Frankfurt  
Frankfurt, Germany

**BioProcess**  
CONFERENCE & EXHIBITION  
IBC  
Oct. 31 - Nov. 4  
Booth 223  
Long Beach  
Convention Center  
Long Beach,  
California

manufacturing capabilities to address clients' needs from start to finish. Services support material procurement, process optimization, formulation, testing and stability.

Abbott has 120-plus years of experience in manufacturing and packaging finished pharmaceuticals globally.

**Abbott Bioresearch Center Inc.** in Worcester, Mass., is a multi-use cGMP biological API manufacturing site. The facility has successfully completed 20-plus development programs for Abbott and third-party products. The Bioresearch Center has been part of successful collaborative development and manufacturing partnerships in biologics since 1995.

In addition to the bioresearch center, Abbott provides a secondary large-scale commercial biologics production facility situated in Barceloneta, Puerto Rico. **Abbott Biotechnology Ltd.** is equipped with state-of-the-art manufacturing for drug substance and fill finishing of drug product to meet customer needs.

## THE AENOVA GROUP

Aenova, with headquarters in Pöhl, Germany, offers customers a complete portfolio of services spanning development,

procurement of raw materials, production and analysis through to packaging and logistics. The core competence of Aenova is the development and manufacture of solid oral dosage forms. Aenova's product portfolio spans the entire spectrum of solid dosage forms including soft capsules, tablets, effervescent tablets, sugar-coated tablets and hard capsules.

According to the company, with vast expertise of the market and many years of experience Aenova develops the ideal product to suit every requirement, target group and sales channel. The company's success stems from its specific, forward-

looking know-how, which is Aenova's benchmark for measuring progress.

Many examples of innovation have developed out of the company's development lab including gelatine-free soft capsules, which Aenova introduced as **VegaGels** in 2000. The use of the company's development expertise for the continued development of indications for solid oral dosage forms keeps Aenova at the forefront of the marketplace.

As one of the top international manufacturers of solid dosage forms, the Aenova Group opened a new integrated production site during September 2011 that clearly distinguishes it from competitors. This bolsters Aenova's reputation as a provider of guaranteed quality and a top innovator in the area of contract manufacturing. This also allows Aenova to increase its production efficiency significantly, as a result of improved processes.

The new tablet production line, which is the first of its kind in Europe, was projected to debut at the end of September 2011. According to the company, the production line's high levels of productivity will clearly differentiate it from the competition. By improving the efficiency of the production processes, the company can reduce processing times and increase production volumes.

As a result, Aenova's yearly production capacity has increased by 2 billion tablets. Until September 2011, all Aenova plants combined to produce 10 billion tablets a year. The ideal batch size for pharma products in the new facility is about 3,000 kg. The plant can be used to manufacture large volumes of dietary supplements.

The Tittmoning, Germany site is the company's competence center for powder technology. There, Aenova produces



# Aenova – Your Global Partner for Solid Dosage Forms

Aenova is a leading international manufacturer of solid oral dosage forms such as soft capsules, tablets, effervescent tablets, sugar-coated tablets and hard capsules. A globally operating group with a wealth of knowledge and expertise, we are making excellent progress in the healthcare sector. For customers in the pharmaceutical and healthcare industries, we offer a comprehensive portfolio of products and services that is unique in terms of coverage across both these sectors.

We help you to successfully launch your products and extend your healthcare portfolio. Whether your company offers branded or private label products, Aenova is an ideal partner. Our expertise in the galenic development of new active ingredients, combined with high-performance, state-of-the-art production facilities, makes us the provider of choice for the pharmaceutical and healthcare industries.

With ground-breaking innovation and customised solutions, we are making a significant contribution to the success of our clients, and an important contribution to human health.

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granules, tablets, film-coated tablets and dragées and provides its customers with individual packaging solutions. The investment in the Tittmoning facility will elevate its significance in the long term. As part of the expansion process, 40 new jobs were created for skilled workers. The Aenova Group had already hired about 65 new employees during the previous 12 months, which puts it in a good position for further growth, according to the company.

With the company's new production facility, Aenova has become a pioneer in contract manufacturing in terms of technology and process management. Aenova managers say the company is in an ideal position to withstand worldwide competition, to expand its existing business and to acquire new customers.

Aenova Holding was established during 2008 following the merger between two prominent medium-sized companies: **Dragenopharm Apotheker Püschel GmbH** and **SWISS CAPS AG**. This transaction has helped the Aenova Group become one of the leading manufacturers and suppliers of medicines and dietary supplements in oral dosage forms for the pharma and healthcare arena.

The group generated about EUR 250 million in revenue in 2010 and employs 1,500 people at facilities in Germany (Tittmoning, Berlin, Bad Aibling and Warstein), Switzerland (Kirchberg and Bioggio), France (Lyons), Romania (Cornu) and America (Miami).

## AESICA PHARMACEUTICALS LTD.

Founded during 2004, Aesica is a top full-service provider of contract research, development and manufacturing services for Formulated Products and APIs. Aesica develops long-term strategic partnerships with clients, responds quickly and effectively to market demand, and develops tailored solutions for specific needs.

Aesica's vision is to become the No. 1 supplier of API and formulated products to the pharma industry.

On Sept. 29, 2011, Aesica announced plans for additional growth and expansion after significant investment from **Silverfleet Capital**. The European private-equity firm agreed to a majority investment with Aesica. Executive members of the company have reinvested for a large minority stake in Aesica.

The investment allows the company to continue its rapid expansion into new

markets and achieve management's vision of becoming the leading supplier of APIs and formulated products to the worldwide pharma industry. With six manufacturing facilities across Europe and sales reps across the United States, Europe and Asia, Aesica intends to build on the success of 2011. For 2011, the com-

pany expected turnover of 180 million euros and to extend its current capabilities and worldwide manufacturing sites.

Silverfleet replaced LDC as Aesica's long-term partner. Since the initial 2004 investment LDC has provided management with financial and strategic support to implement a rapid and impres-

## AESICA'S API SERVICES:

### Development Lab

- Process development
- Route optimization
- Mettler RC1 calorimeter
- Short path distillation services
- Parallel reaction capability

### Kilo Lab

- Multi-stage complex processes
- Reactions up to 50L scale
- Operates to cGMP standards
- Distillation, drying facilities & hydrogenation
- 5L Hastelloy filter drier
- Operates to cGMP standards
- GMP storage facility

### Pilot Plant

- Walk-in drum booth with extraction
- Hastelloy filter drier with glovebox isolation technology
- Glass-lined reaction vessels up to 250 liter volume
- Ideal for 10kg to 100kg manufacture
- -20°C to 150°C reaction temperature capability
- Operates to cGMP standards
- Complemented by kilo laboratory operating at 50 liter scale

### Analytical Development

- Automated HPLC & GC
- IR & UV; LC - MS
- GC headspace analysis
- Particle size by laser diffraction
- GCMS
- Preparative HPLC
- Photostability cabinet for stress stability studies
- ICH compliant in-house stability sample storage & analysis
- ICH compliant analytical validation & technical transfers completed according to defined protocols
- Reference materials supplied with CoA
- All equipment qualified & certified

### Commercial Scale Plants

- 2 computer controlled multi-purpose plants working to cGMP standards
- 6 manufacturing units able

- to produce APIs and GMP intermediates working to cGMP standards
- Manufacturing in campaigns from 3kg to 800mt
- Home Office licence for controlled drug production
- Reactors from 1m<sup>3</sup> to 10 m<sup>3</sup>
- Reaction temperature ranges from -15°C to 150°C
- Filter dryers from 0.35m<sup>2</sup> to 6m<sup>2</sup>
- Bespoke software solutions for complex inter-reaction chemistry
- Sophisticated isolation facilities for solids & liquids
- Clean room facilities for finished product handling
- Solvent recovery unit integrated within the manufacturing plant
- High vacuum (< 3 mbar) distillation & drying equipment
- Screw feeders for controlled solids charging to reactors
- Plant scale hydrogenation, hydrochloric acid gas & bromine technology
- Approvals to supply into U.S. and other major markets
- MHRA certification & FDA approval
- ISO 14001 & ISO 9001 accreditation

### Potent Drug Capability

- Handle high potent drug classes, up to SafeBridge Category 3
- Operates at scales of 1kg to 20kg
- 450L glass lined reaction vessels
- Preparative HPLC system for isomeric separation
- 270L Multi Purpose Processor (MPP)
- 50L Hastelloy filter dryers
- Manufacturing areas under negative pressure
- Inter-locked doors for personal and material entry/exit
- Product packaging in a HEPA filtered glovebox
- Raw material charges and product discharge utilizing split butterfly valves and Contained Transfer Couplings (CTCs)

Source: Aesica Pharmaceuticals

sive expansion plan. The expansion plan has concentrated on enhancing Aesica's manufacturing capabilities, developing new service lines, adding new products to its portfolio and increasing the company's presence in major international growth markets.

"We have known the team at Silverfleet Capital for a number of years and chose them as our financial partner because of their deep knowledge of our market and their experience and successful track record of building global businesses of scale through buy and build strategies," stated Dr. Robert Hardy, CEO of Aesica.

Aesica has more than 30 years of pharma manufacturing expertise. Three acquisitions of manufacturing facilities in Germany and Italy show Aesica's dedication to enhancing the company's service offering to the worldwide pharma and biotech industries.

Company managers say Aesica's long-term strategic plan was to establish a manufacturing presence in the United States and Asia during 2012. With the support from Silverfleet Capital, Aesica can continue expansion into new markets and the company can evolve and grow more quickly.

Healthcare is one of Silverfleet Capital's core segments. Silverfleet Capital previously has invested in Sterigenics and EDP. Key to the success of Sterigenics and EDP was the delivery of strong earnings growth via the successful execution of buy-and-build and roll-out strategies. These moves extended their international footprint.

"Global outsourcing of pharmaceutical manufacturing was worth \$44 billion in 2010 and is forecasted to grow at about 7% per annum for the foreseeable future," noted Adrian Yurkwich, partner at Silverfleet Capital with responsibility for healthcare who led the deal and joined the board as a non-executive director. "Aesica is in a strong position to benefit from that growth through further expanding its international footprint in Europe, the United States and Asia and by increasing the number of strategic partners it works with. Aesica has an excellent management team who has achieved very impressive growth and we look forward to working in partnership with them."

In response to market demand for a more efficient and rapid scale-up of the non-GMP to GMP phases of a product's CMC development, Aesica has encouraged clients to

use the company's integrated API and Formulation Development Service.

Aesica is widely regarded for the company's expertise in transitioning lead candidate API from medicinal chemistry into GMP development. The parallel approach between Aesica's API Development and Formulation Development teams ensures clients will be taken into preclinical and clinical development more efficiently and effectively. This process will save time, reduce cost and simplify outsourcing demands.

Using one supplier for a product's CMC development allows single transfer costs, familiarity of the API and enables knowledge to be shared between the team throughout each stage of the process. During the optimization process, Aesica provides non-GMP grade material to its Formulation Development scientists to allow for early Preformulation evaluation to take place simultaneously. Once the GMP material has been synthesized, Aesica's Formulation team manufactures the clinical trial supply materials. Stability testing for Drug Substance and Drug Product is performed at Aesica.

"Clients are assigned a dedicated scientific project manager and the team works together as one to design and conduct an efficient CMC development path for our clients' lead candidate," Dr. Hardy says. "By unifying our expertise and capability, clients can be assured that their needs are being managed by a single outsourcing partner and in addition to a more rapid scale-up process there are also significant cost saving benefits.

"Here at Aesica, we are committed to providing our clients with a quality and responsive service and by integrating our API and Formulation Development expertise we ensure seamless communications and effective delivery to take clients into Preclinical and Clinical development. Working with our experts, clients can simplify their outsourcing demands and benefit from a single analytical technical transfer, speeding up whole development process significantly. Our experienced team is able to provide support for API to SafeBridge Category III, controlled drugs and the formulation of all dosage forms."

#### **ALKERMES PLC**

Alkermes is a fully integrated, worldwide biopharmaceutical company that ap-

plies scientific expertise and proprietary technologies to develop innovative medicines for improving patient outcomes. Alkermes has a diversified portfolio of 20-plus commercial drug products and a substantial clinical pipeline of product candidates that address CNS disorders including addiction, schizophrenia and depression. With headquarters in Dublin, Ireland, Alkermes has an R&D center in Waltham, Mass., and manufacturing facilities located in Athlone, Ireland; Gainesville, Georgia; and Wilmington, Ohio.

During September 2011, Alkermes announced the establishment of the company's corporate operations in Ireland and new headquarters based in Dublin. Alkermes, including the headquarters and operations in Athlone, County Westmeath, has 450-plus employees based in Ireland and more than 1,200 employees globally.

Alkermes plc was created following the merger of Alkermes Inc. with Elan Drug Technologies. EDT was a profitable, world-class drug formulation and manufacturing business formerly part of Elan Corp.

On the company's first day of operations in Ireland, Alkermes announced a multiyear, multimillion dollar manufacturing deal with one of the world's leading pharma players. Under the terms of the pact, Alkermes will manufacture the company's finished pharmaceutical product, which will be produced at Alkermes' Athlone site. Alkermes expects this deal will generate \$15 million to \$20 million in annual manufacturing revenues by 2016. The Athlone facility is one of three major manufacturing plants owned by Alkermes at which the company produces proprietary, partnered and contract-manufactured drug products.

"Alkermes plc's decision to establish its headquarters in Ireland is further demonstration of this country's continued ability to attract companies, like Alkermes, in growth industries, to set up operations here," says John Perry, TD, Minister of State for Small Business. "Today's announcement showcases that Ireland is very much open for business and is an excellent location to host operations of multinational companies. The additional announcement of a new contract for the Athlone facility is an indication of its track record for successful innovation and high-quality manufacturing."

"We are a strong, global company with a diversified product portfolio, and we



look forward to accelerating our growth to create value in our business and for the patients we serve," stated Alkermes' CEO. "Alkermes is excited to have our operations based in Ireland, which we view as a gateway to the European Union and global pharmaceutical market."

In early November 2011, Alkermes plc announced its first quarterly financial results since the merger between Alkermes Inc. and EDT. For the company's second quarter of fiscal 2012, which ended on Sept. 30, 2011, Alkermes plc reported revenues totaling \$72.0 million. For the same period in fiscal 2011, Alkermes Inc. reported revenue of \$49.2 million. For the three-month period ended Sept. 30, 2011, the company reported a net loss of \$22.3 million, or a basic and diluted loss per share of 22 cents, based on U.S. Generally Accepted Accounting Principles (GAAP).

The financial performance reflects a full quarter of operations of Alkermes Inc. and 14 days of operations of the former EDT business, along with Alkermes plc's consolidated balance sheet as of Sept. 30, 2011.

For second-quarter fiscal 2012, Alkermes plc reported Adjusted EBITDA of

\$13.3 million, or a basic and diluted Adjusted EBITDA per share of \$0.13 and \$0.12, respectively. This performance includes \$3.4 million of Adjusted EBITDA from EDT for the 14-day period following the close of the merger.

"This quarter marks the beginning of a new phase of growth for Alkermes, as we begin to realize the financially transformative effects of the EDT transaction," Mr. Pops noted. "We are now fully executing on our strategy to build Alkermes for growth in both the near- and long-term. In the near-term, we will see the growth in revenues from the expansion of our portfolio of commercial products. Over the long-term, we will realize the value of our advancing pipeline of new drug candidates. We are committed to our vision of building Alkermes plc as a global leader in the development of innovative products for a broad range of CNS diseases for the benefit of patients and healthcare systems around the world."

Alkermes plc generates revenues from a broad portfolio of products, including five key growth brands: RISPERDAL CONSTA, INVEGA SUSTENNA, AMPYRA, VIVITROL and BYDUREON.

Manufacturing and royalty revenues from RISPERDAL CONSTA totaled \$44.3 million July-September 2011 versus \$42 million for second-period fiscal 2011.

Net sales for VIVITROL amounted to \$9.9 million for second-quarter fiscal 2012, compared to \$6.5 million for the corresponding time frame during fiscal 2011, a 52.8% year-over-year increase. First-quarter fiscal 2012 revenue totaled \$9.7 million. Second-period fiscal 2012 marked the ninth consecutive quarter of growth for VIVITROL.

R&D revenues for July-September 2011 included a \$7 million milestone payment in connection with the EU market introduction of BYDUREON.

The EDT portfolio contributed \$9.1 million to second-period fiscal 2012 revenues during the 14-day period after the close of the merger.

"Our second quarter results were driven by the strong performance of our long-acting atypical antipsychotic franchise, as well as growing sales of VIVITROL and milestone revenue triggered by the EU launch of BYDUREON," noted James Frates, Chief Financial Officer of Alkermes. "Next quarter, we will report the first complete quarter of financial results of our combined organization, which will more fully reflect our diverse product portfolio. Moving forward, we will continue to focus on growing revenues and delivering on our Adjusted EBITDA goals."

As of early November 2011, for full-year fiscal 2012 Alkermes expected total revenues to range from \$350 million to \$380 million, up from a previous range of \$205 million to \$229 million. These revenue expectations include no changes from the Alkermes Inc. guidance provided on May 18, 2011, and reflect additional revenues from the EDT portfolio.

## ALKERMES CAPABILITIES OVERVIEW

Since 2001, Alkermes has helped develop 12 products that have been launched in the U.S. and international markets. The company has more than 500 people devoted to development, scale-up and manufacturing activities with the majority of Alkermes' staff having 10-plus years of pharma experience.

### Modern Solid Oral Dose Facilities to Fit Partners' Precise Product Requirements

Alkermes Contract Pharma Services offers a significant advantage in outsourcing – an extensive range of services and expertise integrated into one company – based in the United States and Europe. This approach reduces the necessity for technical transfers from product development and clinical trial suppliers to commercial manufacturing sites, allowing for efficient scale-up from formulation to commercial production. By providing the whole process in this integrated manner, Alkermes has been able to recommend ways to improve

production methods – reducing client risk and also improving efficiencies.

### Capabilities and Facilities

- Dedicated formulation, development, scale-up and commercial manufacturing
- Modern facilities in Europe and the United States
- Tech transfer
- 2.5 billion units annually in solid oral dosage form manufacturing capacity
- 270,000 square feet of cGMP manufacturing facilities
- Excellent compliance record
- Packaging facilities in the United States and Ireland
- Mature infrastructure
- DEA-approved controlled substance manufacturing plant in the United States
- Manufactures product for U.S., European, and Japanese markets as well as the emerging markets of India, China and Brazil

Source: Alkermes

## ALTHEA TECHNOLOGIES INC.

San Diego-based Althea is a contract development and manufacturing organization that specializes in cGMP manufacturing, analytical development, formulation development, aseptic filling into vials and syringes, and protein delivery technology for recombinant protein and parenteral products. In one location, Althea has the capacity to meet early-stage and commercial requirements.

In conjunction with these manufacturing operations, the company offers comprehensive development services such as

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**ALTHEA**

Biologics Manufacturing Protein Analytics Stability Testing Aseptic Fill & Finish



**OVERVIEW**

PROCESS DEVELOPMENT  
cGMP MANUFACTURING  
FORMULATION

### Biologics Manufacturing Overview

Our Biologics Manufacturing Group (BMG) supports clients with cell banking, process development, cGMP manufacturing, and formulation of the API. With our experience and expertise demonstrated by our track record of >150 cGMP lots of drug substance, we know that the successful production of cGMP product depends upon the fluid integration of process and analytical development, cGMP manufacturing, QC analytics, and product formulation. At Althea, you have all of these groups working hand-in-hand, for you and your product. Throughout process development and cGMP manufacturing, BMG works closely with our protein analytics group to ensure product integrity every step of the way.

In addition to the efficient production of your bulk drug substance, our complementary final drug manufacturing capabilities allow you to leverage the full value and efficiency of Althea's fully integrated manufacturing program in providing you with finished product in vials or syringes. As your program advances in the clinic, you'll have the assurance of knowing that Althea has the capacity to scale your process to larger product volume requirements without changing facilities. Leveraging this capacity eliminates the need for redundant technology transfer and qualification of additional service providers. With this fully integrated development and manufacturing plan, we can truly take your program from concept to vial.

**PROJECT MANAGEMENT & BUSINESS PROCESS**  
Working with you from start to finish.

**QUALITY & REGULATORY**  
Taking pride in our history of quality.

**Core Services**

Process Development

- Fermentation
- Product Recovery
- Purification

Microbial and Yeast Expression Systems

Product Expertise

- Recombinant Protein
- Plasmid DNA
- Vaccines

Fermenter Capacity

- Up to 1,000 liters

Complex Formulations

- Vaccines

upstream and downstream process development, analytical development, lyophilization cycle and formulation development, product release and ICH-compliant stability testing. Althea's formulation technology platform includes **Crystalomics**. This technology that offers a formulation solution for large-molecule products that must be delivered at high concentrations or as sustained-release forms.

Since being founded during 1998, Althea has been inspected by FDA at least twice (2005 and 2008) without any 483s issued, and by at least 12 different QPs. The company's cGMP facilities have produced 250-plus cell banks, more than 150 cGMP protein and plasmid DNA lots, and over 900 cGMP fill and finish lots. The company has the experience, expertise, capacity, and flexibility to serve as a strategic partner for drug development and manufacturing requirements.

Althea announced during June 2011 that following a comprehensive FDA Pre-Approval Inspection in April 2011, the company received a license to manufacture and package a commercial parenteral product for the U.S. marketplace. The product will be filled and packaged at Althea's new, state-of-the-art commercial manufacturing site in San Diego.

This site, the third on the company's campus, was built to accommodate the growing demand Althea has experienced in its drug product and biologics manufacturing business units. To support this growth, Althea has expanded its analytical development, stability testing and

formulation development capabilities for larger clinical and commercial projects.

"We are very pleased with the successful outcome of our initial PAI and anticipate working with our clients to bring several other products to commercialization over the coming months," said Rick Hancock, president of Althea Technologies. "Our entire team feels very gratified to have achieved this major milestone. This accomplishment is the result of thoughtful and diligent investment in expanding our quality systems, facilities and operational capabilities in a climate that has been challenging for many companies in our industry."

As of June 2011, in the previous 12 months Althea installed and validated a fully automated, **INOVA H3-5** syringe filling line that can accommodate high viscosity and shear-sensitive products. This line can accommodate different glass or plastic syringes and cartridges in batch sizes exceeding 100,000 units. This is a critical component of Althea's commercial manufacturing expansion.

## AMATSI

Formerly known as **CRID Pharma**, Amatsi is a pharma contract development and manufacturing organization. Amatsi offers a large suite of services such as galenic development, analytical development, quality controls (GLP/GMP), clinical supplies manufacturing (sterile/non sterile), packaging, distribution, ICH stability studies, and regulatory support.

On Feb. 28, 2011, Amatsi and **Avogadro** announced plans to unite as the French leader in this sector. This move was supported by **Acto Capital**, a direct investment company of **Groupama Private Equity**, now the main shareholder of the Amatsi group that has been formed. The directors of Amatsi-Avogadro remain shareholders as well.

With 2011 revenue of 20 million euros 175-plus employees located in France and the United States, Amatsi and Avogadro offer their clients – mainly pharma groups and biotechnology companies – a diverse array of drug-development services. By combining expertise and know-how, the group is in position to provide customers with an expansive variety of services.

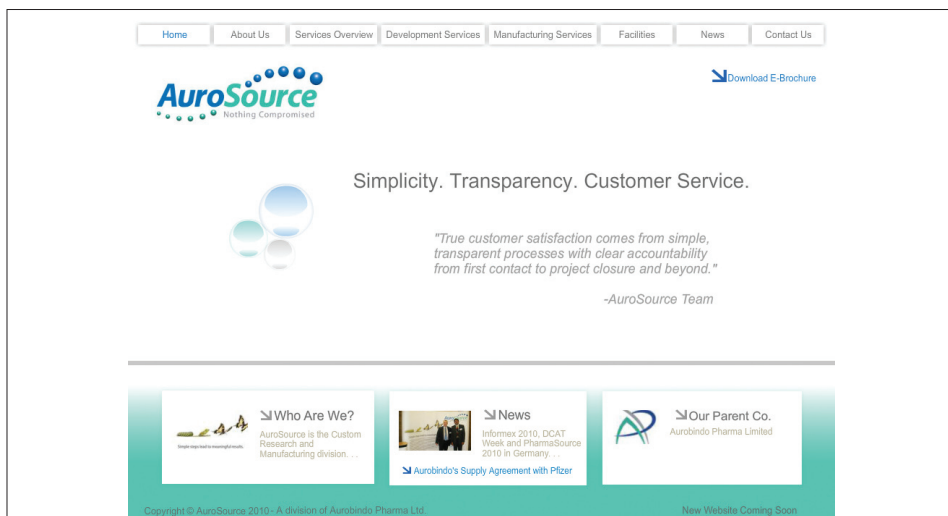
"With the support of Avogadro's team, we can offer a larger range of facilities to our clients, increased development capabilities as well as a stronger quality assurance framework," noted Jean-Pascal Conduzorgues, president of Amatsi. "Together with André Weil, president of Avogadro and Jean-Pierre Arnaud, CEO, I am very pleased to see our companies bringing together their strengths whilst still maintaining our common values of responsiveness, flexibility and customer service."

## AUROBINDO PHARMA LTD.

Hyderabad, India-based Aurobindo manufactures generic pharmaceuticals and APIs. The company's manufacturing facilities are approved leading regulatory agencies such as FDA, MHRA, WHO, Health Canada, MCC South Africa, AN-VISA Brazil. Aurobindo's robust product portfolio is spread across six major therapeutic/product fields – antibiotics, anti-retrovirals, CVS, CNS, gastroenterologicals and anti-allergics – supported by a strong R&D program. The company is marketing these products 125-plus countries.

During March 2010, Aurobindo Pharma introduced **AuroSource**, a service-oriented and customer-centric division within the company that provides custom R&D and manufacturing (CRAMS) services for large, mid-sized and emerging biotechnology and pharma companies worldwide.

AuroSource partners with these companies and cultivates opportunities to research, manufacture and develop compounds spanning the entire drug life cycle. AuroSource is uniquely poised to deliver



fully consolidated or customized manufacturing solutions for APIs, intermediates, pre-formulations and formulations across every stage of the pharma life cycle; regulatory, R&D expertise from the preclinical stage through the post patent expiration phase in drug development; and premium solutions for product life-cycle management such as life-cycle extensions and line extensions.

Aurobindo is one of India's largest pharma companies with \$800-plus million in yearly sales. Aurobindo was founded during 1989 and has 15 manufacturing facilities for both API and finished dosage, including 10 that are FDA-approved. The company has significant R&D capabilities that include 750 talented scientists spread across five facilities specializing in process chemistry development, dosage-form development and pre-formulations.

AuroSource is setting up a modern R&D facility at Pashamylaram, India, to house an additional 140-150 scientists. Expansion plans were drafted to also begin offering services in areas such as medicinal chemistry and other discovery services.

"AuroSource is uniquely positioned to smoothly transition our competence in drug development to customers within this market segment," says Ramprasad Reddy, chairman of Aurobindo Pharma. "We stand to become an invaluable partner in enabling them to streamline and simplify their development and manufacturing processes so they can focus primarily on creating life-saving, low-cost products and contribute to making global healthcare more affordable."

Dr. M. Sivakumaran, director on the board of Aurobindo Pharma, stated, "By combining our research and development expertise with significant capability

and facilities, our customers can securely outsource drug development projects while significantly reducing their need to absorb fixed costs around capital investments. AuroSource not only possesses the tools, expertise, assets and financial backing to support outsourcing efforts, but we also have a renewed commitment to optimize the internal selling processes in a seamless manner for our customers which include virtual and small biotech companies, mid-sized partially integrated companies and large vertically integrated companies."

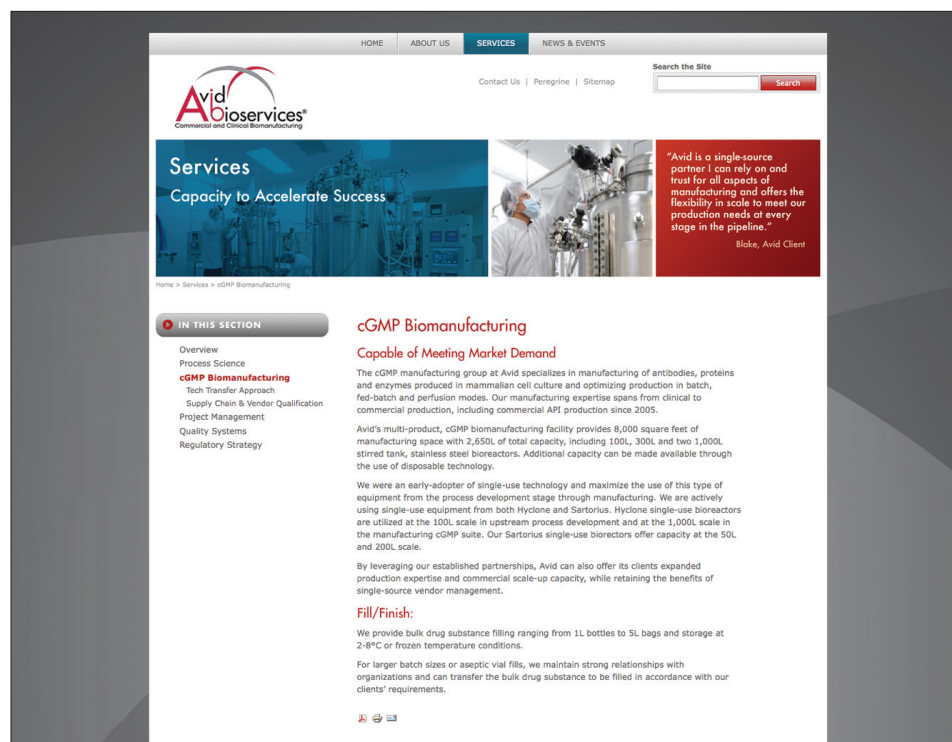
Dr. R. Ananth, president of AuroSource, commented, "We offer unmatched manufacturing competence and superior research capabilities, while keeping the whole outsourcing experience in the

hands of our customers and enhancing the transparency of the whole process. We are committed to giving each of our customers an unparalleled experience by keeping the process simple for them."

## AVID BIOSERVICES INC.

During 2002 Avid was established as the manufacturing arm for its parent company **Peregrine Pharmaceuticals Inc.** to serve clients in the biotech and pharma industries. Avid's role as in-house manufacturing support for a clinical-stage biopharma company gives the company a unique perspective on what is necessary to develop, advance and commercialize a biologic. Company managers understand the full investment required for development, the significance of product quality to facilitating accurate, efficient progression via the development cycle, and the potential benefits to patients from new therapeutic options.

Peregrine is a biopharma company with a portfolio of innovative monoclonal antibodies in clinical trials for treating cancer and serious viral infections. Peregrine is pursuing three separate clinical programs in cancer and hepatitis C virus infection with the company's lead product candidates **bavixumab** and **Cotara**. The company has in-house cGMP manufacturing capabilities through its wholly owned subsidiary Avid, which provides development and biomanufacturing





ing services for Peregrine and outside customers.

Based in Orange County, Calif., Avid's Tustin facility is committed to mammalian cell culture. The site supports pre-clinical through commercial production of monoclonal antibodies, recombinant proteins and enzymes.

Avid Bioservices provides a comprehensive array of high-quality cGMP manufacturing services for the biotech and biopharma industries to support manufacturing of cGMP commercial and clinical products. With 10-plus years of experience producing monoclonal antibodies and recombinant proteins in batch, fed-batch and perfusion modes, Avid's services consist of cell banking, stability testing, clinical and commercial product manufacturing and purification, bulk packaging, final product filling and regulatory strategy, submission and support. Avid additionally provides different process-development activities such as cell-line optimization, analytical methods development and product characterization.

On Sept. 30, 2010, Avid secured a biomanufacturing contract to supply clinical material to **Affitech A/S**, the antibody medicines company. The initial contract for dedicated services provides for several large-scale cGMP manufacturing runs along with other cGMP-related services.

"Given our long-term relationship, Avid is an ideal partner for providing biomanufacturing services for our fully human antibody AT001/r84, as they have direct experience with Peregrine's anti-VEGF technology platform as well as this novel antibody we discovered from this technology," stated Martin Welschof, managing director of Affitech. "Over the coming year, we look forward to having Avid's support as we expedite our clinical development plans for AT001/r84 for select growing pharmaceutical markets."

AT001/r84 is a fully human, selective therapeutic antibody to vascular endothelial growth factor (VEGF) that has shown encouraging effects on immune cells in preclinical models. Using Peregrine's anti-VEGF antibody technology platform, Affitech discovered AT001/r84.

On April 5, 2010, Avid expanded its commercial supply relationship with **Halozyyme Therapeutics Inc.** with new manufacturing deals. The companies entered into a long-term strategic relationship with Halozyyme designating Avid a preferred supplier for future products requiring Av-

id's process development and biomanufacturing capabilities and expertise. Avid has manufactured commercial product for Halozyyme since 2005 in its cGMP facility.

As part of the new pacts, the companies amended and extended their existing commercial supply deal for recombinant human hyaluronidase, **rHuPH20**, used in two of Halozyyme's marketed products. The companies inked a new commercial supply pact for other rHuPH20 products.

"We are pleased to strengthen our already robust supply chain for rHuPH20 with these new agreements with Avid, supporting our existing products as well as partnered product candidates," stated Jonathan E. Lim, M.D., president and CEO of Halozyyme. "Expanding our commercial supply relationship with Avid is a testament to the strong relationship we have developed over the past five years."

Christopher E. Eso, VP of business operations for Avid, noted, "We are delighted to extend the **Hylenex** and **Cumula** supply agreement, and expand our long-term relationship with Halozyyme as we partner with them to support their current and future commercial and clinical process development and biomanufacturing needs. Our solid client relationships and dedicated team at Avid have been critical to ensuring our clients' success."

## BAYER AG

Bayer Pharmaceutical Manufacturing Services is dedicated to providing its contract manufacturing partners with the unsurpassed quality and compliance associated with Bayer during the past century. The company is driven to achieve its partners' pharma manufacturing goals by offering a diverse, flexible operation guided by industry knowledgeable project managers and pharmaceutical manufacturing professionals.

Bayer's goal is to understand the needs of its customers, and by using the company's proven track record for the manufacture of quality pharma products, exceed customer expectations. With the flexibility and innovation of its precision manufacturing expertise, Bayer Pharmaceutical Manufacturing Services provides partners with a comprehensive array of solutions to ensure quality, reduce costs, provide reliability of supply, and better align manufacturing strategies. Strategically lo-

cated in Shawnee, Kan., the 52-acre facility serves as a central production and distribution hub for all of its clients in North America and globally.

The facility includes two main production facilities. Shawnee I consists of lab services, packaging, and administration capabilities. FDA and European Union-approved Shawnee II is a dedicated pharma manufacturing site equipped with state-of-the-industry utilities systems such as WFI water system, zoned HVAC, HEPA filtration, dedicated steam supply, and class A-F manufacturing environments.

Additionally available at the Kansas pharma manufacturing location is a world-class, fully climate controlled warehousing and distribution center. Commissioned during November 2004, this site has point-of-use distribution capabilities.

Bayer Pharmaceutical Manufacturing Services is considered a trusted partner for reliable pharma contract manufacturing. For 100-plus years, Bayer has maintained a worldwide reputation for unsurpassed quality and dedication to its partners and customers. With EU-approved and FDA-approved industry facilities featuring different technical capabilities, Bayer Pharmaceutical Manufacturing Services is designed to deliver precision manufacturing for a wide range of pharma equipments.

Bayer's end-to-end solutions consist of product transfer, manufacturing and packaging, as well as warehousing and distribution services for sterile injectables, solid doses, non-sterile liquids, and creams and pastes. Complementing the company's manufacturing capabilities is a full-service lab facility showcasing chemical, microbiological and stability program management services.

## BIOMAY AG

This Vienna-based company develops vaccines for the specific immunotherapy and prevention of allergic diseases. Founded during 1984, Biomay has pioneered the recombinant allergen field in cooperation with its strong academic network. The company's product candidates are based on recombinant allergen derivatives (hypoallergens) and nucleic acids. With an excellent safety profile, the products have the potential for prophylactic use.

Biomay is also a contract manufacturer for clinical-grade recombinant proteins,




ABOUT BIOMAY

SCIENCE & TECHNOLOGY

GMP CONTRACT SERVICES

RECOMBINANT ALLERGENS

CONTACT

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SCOPE OF SERVICES

FACILITIES & CAPACITIES

PLASMID PRODUCTION

### cGMP Contract Manufacturing Services

Biomay offers cGMP contract manufacturing services for the production of recombinant biologicals as active pharmaceutical ingredients (APIs). Biomay's multi-product GMP facility allows the manufacturing of microbial-based biopharmaceuticals like recombinant proteins, allergens, antibody fragments and plasmid DNA (DNA vaccines). Production of recombinant proteins with *Escherichia coli* as expression host has ever been Biomay's core focus and key expertise. In addition, the capacities and know-how for processing of other bacterial hosts or yeasts like *Pichia pastoris* are available.

As a Contract Manufacturing Organization (CMO), Biomay's goal is to offer a highly attractive price-performance ratio for its clients. Biomay's ideal production scale is in the magnitude of multiple grams of clinical-grade recombinant protein or plasmid DNA.

Biomay's quality management system conforms with the international GMP regulations. Biomay has been certified by the Austrian authorities (AGES) according to the EU directives (2001/83/EC, 2001/20/EC) and the Austrian medicinal product act (§ 63 AMG).



Qualified processing equipment

SEARCH

NEWS

**Biomay Initiates Development of its Novel Ragweed and Japanese Cedar Allergy Vaccines – Project Granted and Awarded by ZIT (Nov. 3, 2011)**

Biomay announces today that the company received 500.000 Euro funding supporting the development [Read more >>](#)

**Biomay announces Initiation of First Phase II Trial with its Grass Pollen Allergy Vaccine BM32 (Oct. 25, 2011)**

Biomay announces today that the company has initiated a first-in-patient phase II trial with its BM32 [Read more >>](#)

**Biomay Appoints Clinical Advisory Board (Oct. 1, 2011)**

Biomay announces the appointment of world leading allergy specialists to its Clinical Advisory Board [Read more >>](#)

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plasmid-DNA and minicircles, produced with microbial systems. The company's CMO services include cell banking, process and assay development, GMP manufacturing, quality control, stability testing and regulatory support.

**Boehringer Ingelheim RCV GmbH & Co. KG**, one of the worldwide leaders in the production of biopharmaceuticals, and Biomay announced on Feb. 1, 2010, a collaboration in providing contract manufacturing services for GMP-grade plasmid DNA. The alliance includes a transfer of **Boehringer Ingelheim's** plasmid DNA manufacturing technology to Biomay sites. Each company will coordinate the marketing activities of its complementary plasmid DNA services.

The collaboration provides a comprehensive solution for GMP-grade plasmid DNA from milligram to gram quantities offered by Biomay, and from gram to kilogram quantities provided by **Boehringer Ingelheim RCV**. This concept will ensure use of competitive plasmid DNA technology and uninterrupted supply of product from early clinical development to commercial, which will significantly reduce time-to-market.

"This collaboration with **Boehringer Ingelheim RCV** as one of the leading plasmid DNA manufacturers will position Biomay as a small but important international player in the business of GMP-grade plasmid DNA contract manufacturing,"

says Max Bayer, CEO of Biomay. "We are now ideally prepared for GMP production of plasmids for third party clients as well as for our own allergy DNA vaccine program. With the technology provided by **Boehringer Ingelheim RCV**, Biomay can now offer their premier services at an attractive price-performance ratio."

According to Dr. Monika Henninger-Erber, VP of industrial customer business and product supply at **Boehringer Ingelheim RCV**, "We are very pleased that our cutting edge plasmid DNA technology is now also accessible for early-stage clients who require smaller amounts of GMP-grade plasmid DNA as offered by Biomay. Our applied technology will secure scalability, product comparability, high yields and attractive pricing throughout the development chain. Besides, our clients will find the high quality services they are used to expect from **Boehringer Ingelheim**. The local vicinity of both Vienna based companies and their good business relationship is another key benefit for our customers."

**Boehringer Ingelheim** is one of the top 20 pharma companies globally. With headquarters in Ingelheim, Germany, BI operates through 145 affiliates worldwide with 42,000-plus employees. Founded during 1885, the independent, family-owned company is dedicated to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

**Boehringer Ingelheim RCV** is a 100% affiliate of **Boehringer Ingelheim Corp.**, the largest privately owned pharma company. During the early 1980s, the Austrian affiliate pioneered the microbial production of proteins and has continued to develop its expertise since then. **Boehringer Ingelheim** is recognized as one of the world's premier Contract Manufacturing Organizations offering as a "one-stop-shop" a comprehensive line of services from cell banking to large-scale GMP manufacture of drug substance and drug product.

The Vienna location is specialized in the development and manufacture of biopharmaceuticals derived from microbial fermentation technology. Dedicated to technology leadership, the site is applying high-yield expression systems (bacteria and yeast), media design, matrix assisted refolding, crystallization and efficient downstream processing for the production of plasmid DNA products, proteins, antibody fragments and protein scaffolds. The business operates three GMP plants with a capacity of up to 12,000 L. The plants are approved "multi-product" facilities for the manufacture of products registered with EMEA and FDA.

## BOEHRINGER INGELHEIM GMBH

As a leading company for the contract manufacturing of biopharmaceuticals, **Boehringer Ingelheim** offers the entire production technology chain in development and production at its facilities in Biberach, Germany; Vienna, Austria; and Fremont, Calif. The large-scale manufacturing sites deliver biopharmaceutical products such as therapeutic proteins, fusion proteins, protein scaffolds, monoclonal antibodies, antibody mimetics and plasmid DNA.

The locations in the United States and Germany are specialized in highly efficient mammalian cell culture systems with yields well above industry standard. The Austria site offers high-expression in bacteria and yeast with exceptionally high productivities through proprietary systems. In the plasmid DNA manufacturing segment, **Boehringer Ingelheim** in Austria has set the standard. The company supplies early to late-stage clinical trials with gene-therapeutics and DNA vaccines for its international clients.

**Boehringer Ingelheim's** customers benefit from a track record of 19 launched

biopharmaceutical products that have been developed and produced in the company's state-of-the-art facilities following its one-stop-shop concept. Collaborating with Boehringer Ingelheim is an attractive strategic option for global partners who want to speed up product development while minimizing investment risk, according to company executives. The company's contract development and manufacturing strategy consists of flexible modules covering the entire process chain from cell line development to fill and finish.

Boehringer Ingelheim is one of the world's top 20 pharma companies. With headquarters in Ingelheim, Germany, the company operates through 145 affiliates in 50 countries and 42,000-plus employees. Founded during 1885, the family-owned company is focused on researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

Boehringer Ingelheim is a pioneer in industrial biotechnology. With a workforce of 2,300-plus employees at its locations in Austria, Germany and the United States, the company has world-leading facilities committed to the development and production of biopharmaceuticals using mammalian cells, microorganisms and yeast as host organisms.

In microbial fermentation, the company uses the most modern technologies for production, coupled with state-of-the-art

extraction and purification procedures in fermentation scales up to 6,000 liters and with a total capacity of about 12,000 liters. Besides interferons, various proteins, scaffolds and antibody fragments, the company also manufactures plasmid DNA for gene therapy on a commercial scale.

In mammalian cell culture, Boehringer Ingelheim is Europe's top manufacturer for therapeutic proteins and monoclonal antibodies with a total capacity of 200,000 liters. The company has state-of-the-art development facilities including a 2,000 liters pilot plant for production of clinical-trial material. BI offers the entire process chain from genetic engineering to the therapeutic drug product including fill and finish and global registration.

All of BI's development and manufacturing processes are carried out according to GMP standards. Boehringer Ingelheim has registered biopharmaceuticals with the European, Canadian, Japanese and U.S. regulatory authorities. The company has generated many successful long-term partnerships in biopharma production with the world's top pharma and biopharmaceutical players.

On March 24, 2011, Boehringer Ingelheim formally acquired Amgen's biopharma development and manufacturing site in Fremont, Calif. This acquisition involves leasing buildings, acquiring physical equipment and assuming manufacturing processes conducted at the Fremont site. The state-of-the-art facility employs

300-plus employees and consists of more than 200,000 square feet for labs, manufacturing and process development suitable for clinical and market supplies. The purchase deal was inked during January 2011. The companies agreed not to disclose details of the acquisition price.

"Presence in Fremont, Calif., aligns with our growth strategy in several ways," says Simon Sturge, corporate senior VP of Biopharmaceuticals for Boehringer Ingelheim. "The strategic decision to have a state-of-the-art contract manufacturing facility in the U.S. Bay Area biotechnology cluster will give Boehringer Ingelheim a greater opportunity to serve current and future customers. In addition the technological expertise present at Fremont will complement our goal to further increase Boehringer Ingelheim's world leading position in the process development and manufacture of Biopharmaceuticals."

As a fully integrated manufacturing site, the Fremont site complements the existing capabilities and technology found across the existing Boehringer Ingelheim biopharma network situated in Biberach/Germany and Vienna/Austria.

Boehringer Ingelheim has been a contract manufacturer for Amgen for 10 years and will continue to support the biotech firm's delivery of safe and effective medicines to patients globally. "We look forward to our continued contract manufacturing partnership with Amgen," Mr. Sturge reports.

The Boehringer Ingelheim contract manufacturing portfolio includes 16 licensed biopharmaceuticals manufactured in globally licensed multi-product facilities, a growing pipeline of NBEs, and a growth strategy in CMB. The company's objective is to remain a leader in contract manufacturing as an industry benchmark for operational excellence including technical expertise and state-of-the-art technology.

BI is one of the world's leading companies for contract development and manufacturing of biopharmaceuticals. All types of services from mammalian cell line or microbial strain development to final drug production and global market supply can be delivered within a one-stop-shop concept. The company has brought 18 molecules to market and has many years of experience in multiple molecule classes including monoclonal antibodies, recombinant proteins, interferons, enzymes, fusion molecules, novel scaffold proteins and plasmid DNA.

The screenshot displays the Boehringer Ingelheim website's 'Contract Manufacturing' page. The header includes the company logo, navigation links (Home, Contact, Site Map), a search bar, and the date '10 November 2011'. A left sidebar contains a menu with links to News Centre, Corporate Profile, Corporate Responsibility, Global Activities, Research & Development, Clinical Trials, Products, Contract Manufacturing (highlighted), Biopharmaceuticals, Small Molecules: APIs and Formulations, and Careers. The main content area features a large image of a person in a lab coat and safety glasses, with the title 'Contract Manufacturing' overlaid. Below this, a section titled 'Contract Manufacturing' describes the company's role as a contract manufacturer for pharmaceutical corporations. Further down, 'Our contract manufacturing businesses' are listed, including 'Biopharmaceuticals' and 'Small Molecules: APIs and Formulations', each with a brief description and a 'read more' link. A 'Contact us' sidebar on the right provides the company's address, phone, fax, and email. The footer contains copyright information, a 'back to top' link, and various utility links like Print Page, Recommend, Accessibility Statement, Terms of use, Imprint, and RSS Feed.



## BEN VENUE LABORATORIES INC.

Founded during 1938, Ben Venue is a leading contract manufacturer of highly complex, sterile injectable drug products for the worldwide pharma industry. Ben Venue has been under contract with the **National Cancer Institute** since 1967 to develop parenteral dosage forms for many anticancer agents. The company has manufactured various AIDS-specific medicines in conjunction with the NCI. Ben Venue employs 1,300-plus people.

A division of Ben Venue, Bedford Laboratories supplies the United States and international markets with multisource and specialty injectable products. Bedford Laboratories has headquarters in Bedford, Ohio, and is a subsidiary of **Boehringer Ingelheim Corp.** located in Ridgefield, Conn.

Announced during August 2011, Ben Venue intends to exit the pharmaceutical contract-manufacturing business during the next several years due to a Canadian ban on the importation of some of the company's drugs.

Ben Venue manufactures injectable and inhaled drugs for major companies such as Pfizer and Johnson & Johnson. Ben Venue is planning to concentrate on Bedford Laboratories' generic drug business.

## CAMBRIDGE MAJOR LABORATORIES INC.

Cambridge Major Laboratories (CML) is a top global chemistry outsourcing partner to the pharma and biotech industries. CML produces pharma intermediates and APIs, ranging from early preclinical development to commercial manufacture.

As a leader in advanced chemistry services, the company has a reputation for delivering some of the most challenging projects while meeting strict time lines. CML's reach is worldwide. Operating three facilities in the United States and Europe, the business entity is organized by five key integrated centers of excellence: process chemistry, API manufacturing, analytical services, solid state chemistry and quality assurance

During April 2010, CML, **Avantium Pharma**, **Xcelience LLC**, and **Beckloff Associates** formed a consortium of expert client-concentrated companies to launch **Chemistry Playbook**. This is a series of proven, modular, expedited CMC

solutions designed to accelerate drug development from carbon to commercialization. Chemistry Playbook was formed to provide customers with end-to-end solutions and create efficiencies within one supplier network.

Quality can vary across functional business units within larger service providers, but Chemistry Playbook's consortium model guarantees functional expertise and accountability at all stages. Features and services include Gantt charts and handoffs for individuals or the entire team, as well as integrated commercial and billing processes to provide natural pull and ease of conducting business.

Beckloff Associates offers regulatory oversight; CML provides API services; Avantium Pharma offers solid state characterization; and Xcelience offers formulation development expertise.

On Sept. 19, 2011, **Cambridge Major Laboratories Europe** successfully completed the company's first regulatory pre-approval inspection (PAI) for a commercial API. The audit of the Weert facilities was performed during a two-day period starting Aug. 31, 2011. At the same time, the general certificate to manufacture drug substance intended for clinical trial application was renewed for an additional three years.

"This is a major step forward for CML Europe," noted Peter van Tilburg, general director. "We have consistently invest-

ed in staff, procedures and facilities over the last ten years, and this approval demonstrates our commitment to the highest quality standards. It is a result of all the hard work undertaken by every single team member, and our common vision for the future of CML: we will continue to invest in our systems and staff: we want to be the best at what we do."

According to Roger McDonald, European business development director for CMLE, "We are already recognized as a development powerhouse. This approval demonstrates our ability to provide top-quality services to clients at all development phases – from candidate nomination right through to commercial launch. Considering the recent announcement of successful FDA inspection at our new Grant Drive facility in the US, we feel this is a great testament to the quality CML Corporate is committed to meet. We want to be the long-term partner of choice for clients."

On May 12, 2011, CML announced the first FDA inspection and commercial introduction of an API for the company's newest facility in Germantown, Wisc. CML's two manufacturing sites were the subject of an FDA inspection, which included a pre-approval inspection and a general quality systems inspection of each location.

The regulatory agency's inspection represents the first for CML's newest, large-

### CML AND "5 CENTERS OF EXCELLENCE"

Cambridge Major Laboratories (CML) is a leading worldwide chemistry outsourcing partner to the pharma and biotech industries. The company produces pharma intermediates and Active Pharmaceutical Ingredients (API), from early preclinical development to commercial manufacture. Operating from FDA-inspected facilities in the United States and Europe, the entity is organized along five key integrated Centers of Excellence:

- \* Process Chemistry
- \* API Manufacturing
- \* Solid State Chemistry
- \* Analytical Services
- \* Quality Assurance

According to the company, CML's philosophy revolves around R&D and a deep passion for chemistry. Almost half of all CML scientists have a Ph.D. as CML is well-positioned to deliver on the most challenging and complex chemistry projects. CML's strong R&D to support early scale up during preclinical development ensures that molecules will transition into first-in-human studies as smoothly as possible. The company has the resources to meet the entire clinical and commercial API needs of customers. CML has developed and scaled-up hundreds of projects successfully.

*Source: Cambridge Major Laboratories*

scale API manufacturing facility and the seventh inspection during the past nine years. As the company continues to commercialize APIs, the amount of pre-approval inspections has consistently grown. The company manufactures more than one dozen commercial products such as innovative new drugs, generic substances, and medical imaging agents.

"The inspection and subsequent commercial launch is a major milestone for CML which is the first for our new, state of the art large scale API facility," stated Brian Scanlan, president and CEO of Cambridge Major. "Our objective, as always, is to ensure that our systems are in compliance with FDA requirements. I am very pleased with the outcome of the inspection which demonstrates the full devotion of the management and employees."

Within two months of the successful FDA pre-approval inspection, U.S. regulators announced approval of the product. This represents the first commercial product produced in CML's new large-scale facility. The regulatory approval adds to the company's momentum as CML continues to add employees and services to support its continued growth.

"The NDA approval is a significant milestone for our newest facility and a clear sign that we are open for business at the facility," Mr. Scanlan commented. "This particular CML facility is truly state-of-the-art and affords CML the capacity for growth and to continue serving customers with the highest level of service."

#### CATALENT PHARMA SOLUTIONS INC.

From development services to advanced delivery technologies to supply solutions for drugs and biologics, Catalent Pharma Solutions offers strong expertise, broad offerings and unique technologies. With 75-plus years of experience, Catalent aids customers to get more molecules to market faster, enhance product performance, and ensure reliable product supply. With headquarters in Somerset, N.J., Catalent has 8,000-plus employees at 24 facilities globally and fiscal-year 2010 revenue exceeding \$1.7 billion.

On Aug. 22, 2011, Catalent agreed to acquire the Clinical Trial Supplies business of **Aptuit** LLC for a cash consideration of \$410 million on a cash and debt-free basis. The deal substantially expands Catalent's Development & Clinical Services business, transforming it into the No. 2 pro-

vider worldwide in clinical supply solutions. The transaction adds significant development and clinical manufacturing expertise and capacity. Following closing of the accord, Aptuit will concentrate on its market-leading integrated discovery to mid-phase development business.

"This transaction builds important expertise, scale and capability for our Development & Clinical Services business to better meet our customers' needs globally," commented John Chiminski, president and CEO of Catalent. "This transaction also strengthens Catalent's global leadership in development solutions and advanced delivery technologies for drugs and biologics."

The company's Development & Clinical Services business offers clinical supply services, analytical chemistry, respiratory product development, regulatory consulting, and biologics cell line development. Catalent has made substantial recent investments to extend the capabilities and capacity of the development and clinical services business. Catalent provides the widest range of expert development services, which can drive more efficient development time lines, and help customers bring more compounds and better products to market quicker.

Aptuit's remaining business maintains state-of-the-art discovery, development and manufacturing facilities located in the United States, Europe and Asia. The company offers the most complete set of integrated early development capabilities in the industry such as discovery, early development, solid state chemistry, sterile

fill parenterals, high potency APIs through Class V and formulation development. Aptuit is committed to supporting the worldwide biotechnology and pharma industry by accelerating time lines, maintaining quality, and reducing the cost of bringing drugs to the marketplace.

"This agreement puts Aptuit in a better position to focus on the scientific excellence that our customers want," according to Timothy C. Tyson, chairman and CEO of Aptuit. "Focusing on our expertise in discovery and development services leverages our leadership position, and allows us to concentrate on delivering high-growth, high-value scientific services from discovery to mid-phase development."

Aptuit is a worldwide pharma services company concentrated on delivering contract development and manufacturing services and streamlining the drug development process for biotech and pharma innovators. The company's employees deliver an integrated suite of product development services to 800-plus companies globally, driven by a deep dedication to client service, quality, and an unrivaled track record of scientific excellence.

During October 2011, Catalent announced the expanded geographic reach of the company's Analytical Development Services business with the opening of a European Development and Clinical Services Laboratory in Swindon, U.K. This expansion occurs soon after the expanded clinical supply service capabilities in Schorndorf, Germany.

## CATALENT PHARMA SOLUTIONS

### Substantial Competitive Advantages

#### Unique position in the market

- Market leader in nearly every offering
- Expertise at improving drug performance
- Technologies drive long-term relationships
- Global leader in delivery of drugs and biologics

#### Embedded and vital to the industry

- We produce 30 doses every second
- From orphan drugs to blockbusters, we're scalable and agile to meet demand
- Involved with nearly half of new US NCE drug approvals over last five years
- 1 in 10 oral innovator drugs in development globally are in a Catalent dose form

Source: Catalent Pharma Solutions



"This is part of Catalent's continuous investment to strengthen our position as the number one global partner for drug development and formulation services," noted Scott Houlton, president of Catalent's Development & Clinical Services business. "Our customers have asked for expanded testing services in Europe, and value the expertise and security that come from working with a company with the depth and breadth of Catalent. This expansion will enable us to better meet customer needs in Europe for analytical testing, including clinical and commercial release testing of their products."

Catalent has 20-plus years of proven industry experience providing Analytical Development Services in the United States from Research Triangle Park, N.C. This new lab is situated within Catalent's Swindon campus, joining the development and commercial supply operations for Catalent's market-leading oral fast dissolve Zydis technology.

The lab systems being implemented are designed to meet regulatory requirements in the European Union, America and other major markets. The laboratory services initially offered include: raw material and finished product release testing, qualified Person release, method development and validation, compendial testing, microbiology, and stability testing and storage.

During September 2011, **Toyobo Biologics Inc.** (TBI) entered into a partnership deal to jointly promote Catalent's proprietary **GPEX** technology in the Japanese market. Toyobo Biologics is a major biologics supplier and contract provider of large-scale clinical and commercial bioreactors in Japan.

Used for mammalian cell line development, GPEX technology creates stable, high-expression cell lines. These cell lines will speed biologics drug development to clinic in one-third the time of traditional approaches.

"Toyobo's established business reputation in the Japanese market and its biomanufacturing capability makes the partnership a natural synergy to co-promote Catalent's GPEX technology," noted Kent Payne, VP and general manager of Catalent's Development Services business. "Together, Catalent and Toyobo can now offer an advanced cell line development solution for customers in the Japanese market, from gene expression through commercialization of product."

TBI owns and operates a state-of-the-art GMP manufacturing plant in Shiga, Japan, with bioreactors varying from 100L up to 4,000L. "We are confident TBI's strong position in the Japanese market, combined with access to Catalent's proprietary GPEX technology, will create new opportunities to enhance our ability to serve our customers in the region," commented Yukihiro Sogabe, president of TBI. "We look forward to capitalizing on these opportunities and leveraging future successes together."

Through a retrovector technology, GPEX ensures the stable transduction of targeted cells, approaching 100% efficiency. This efficiency level eliminates the requirement for selectable markers, enabling stable clonal cell lines to be produced in under than five months. GPEX technology has a proven track record of success with an extensive degree of mammalian cell types and proteins, having produced more than 200 different antibodies worldwide and 60-plus recombinant proteins.

TBI was established as a stand-alone business during November 2001 as a spin-off from the pharma division of **Toyobo Co. Ltd.**, which has been involved in the development of biopharmaceuticals using mammalian cell culture technology. According to TBI, the company has become a leading business in Japan that can be entrusted for the manufacturing of biopharmaceuticals under GMP conditions. TBI has extensive experience with a wide array of cell types and protein drug candidates including antibodies and biosimilars.

Catalent Pharma Solutions' Consumer Health business completed the first phase of a multi-million dollar expansion of its facility in Aprilia, Italy, during September 2011.

Catalent is a specialist in overcoming solubility, stability and bioavailability issues for a diverse range of liquid and semi-solid formulations. Innovative products manufactured at the Aprilia site include **Vegicaps** capsules. These easy-to-swallow plant-derived capsules are free from animal derivatives and gluten.

"We needed to expand capacity for both traditional gelatin and Vegicaps capsules to ensure reliable supply of strong customer demand," stated Gerry Purnell, European Commercial Director for Catalent's Consumer Health business. "Customers are increasingly considering

Vegicaps capsules because the technology accommodates a wide range of formulations and provides access to markets that require products free from animal derived gelatin."

Catalent's Aprilia facility was expanded to include a new dedicated gelatine production area. New encapsulation machinery was added for the production of traditional gelatin and Vegicaps capsules, raising output by almost 33%. Catalent added key processing equipment, including a new turbo emulsifier to replace open roll-milling equipment. Capacity within inspection and drying areas was increased, and workflows and environments were reviewed and enhanced to maintain high standards of safety and current.

According to the company, the Aprilia expansion offers customers a complete turnkey service from product conceptualization to formulation, development, production and packaging. Catalent provides comprehensive quality and analytical support throughout Europe. The facility's capabilities include a comprehensive range of services such as market registration, analytical testing and market release by Qualified Persons.

"The improvements have been approved by the appropriate regulatory authorities, and we will continue to expand our facility in Aprilia throughout 2011 to bring more products, such as chewable capsules, to market," noted Stefano Arena, general manager of Catalent's Aprilia site. "The ongoing expansion will not only benefit our customers in the consumer health market, but will also allow us to offer more services to the pharmaceutical and cosmetics sectors too."

Catalent Pharma Solutions entered into a license deal with **Pantec AG** during February 2011. Pantec is a privately held development company located in Switzerland. The pact covers the exclusive global development rights to the **Lyopan** fast-dissolve technology for healthcare products.

"We are pleased to add the Lyopan technology to Catalent's oral dose technology offering, which will enable us to provide our pharmaceutical partners with an enhanced choice of drug delivery technologies to improve the performance of their treatments," commented **Ian Muir**, Ph.D., president of Modified Release Technologies for Catalent. "The Lyopan technology is ideally suited to



deliver a wide dose range of active pharmaceutical ingredients in a fast-dissolve tablet. These are key considerations for situations where patient adherence, ease of swallowing and lack of access to water are important issues to address."

Lyopan is a proprietary technology for development and manufacture of fast-dissolve lyophilized tablets. These include OTC products such as allergy treatments or travel medications. The technology requires significantly less water than existing technology. This advantage helps reduce energy consumption, sublimation and drying time. Due to these advanced characteristics, the technology offers the potential for improved taste-masking capabilities and may increase the range of drugs and consumer products that can be used in a fast-dissolve dosage formulation.

The acquisition of Lyopan technology is another example of Catalent's continuing investment in advanced oral dose solutions and novel technologies. The technology advances Catalent's oral-dose capabilities, potentially allowing for the delivery of improved, compliance-enhancing treatments across an extensive array of applications such as CNS drugs, allergy medications, and dosage forms for pediatric and geriatric populations. According to Catalent, Lyopan technology lends itself easily to the development of prescription and OTC products.

"With its long history of developing lyophilized fast-dissolve products, Catalent is the ideal partner to launch our innovative Lyopan technology," stated Hans Peter Rohrer, chairman of Pantec.

The acquisition of Lyopan additionally has clear synergies with several of Catalent's existing technologies including **Zydis** fast dissolve. This unique, freeze-dried oral solid dosage form disperses instantly in the mouth without water.

Catalent's Modified Release Technologies business provides the most oral dosage-form solutions with innovative, advanced formulation and process technologies. These include tablets, capsules and other forms for sustained or modified release. The company has a proven record of introducing advanced orally disintegrating tablet (ODT) technologies to the market, such as Zydis fast dissolve.

On Aug. 3, 2011, Catalent's Clinical Supply Services business expanded its worldwide cold-chain supply capabilities in the United States, United Kingdom,

and Germany pursuant to a commitment to help clients get more products to market quicker.

Catalent's expansive cold-chain supply and distribution capabilities enable customers to use the company's innovative packaging methods and logistical planning to protect physical properties of biological products during transport and storage. The expansions are to be implemented in every major area of Catalent's cold-chain storage and distribution, including 2 to 8 degree Celsius and -80 degree Celsius capabilities, in some instances more than tripling existing capacity for storage and distribution.

"Cold-chain storage and distribution capabilities are in increasing demand throughout the industry and our customers are looking to Catalent to provide these services as a trusted partner who can ensure the integrity of their end to end cold-chain needs," stated Frank Lis, VP and general manager of Clinical Supply Services. "The steadily increasing number of biological products in development, particularly in prefilled syringes, is fueling the need for refrigerated storage and distribution."

The enhanced worldwide cold-chain expansion, along with Catalent's offerings in comparator sourcing, clinical packaging and labeling, manufacturing and blinding, distribution and warehousing allows Catalent to better meet the requirements of virtually any size clinical trial with any drug worldwide.

"Due to the rapid increase in demand from our customers, these expansions were undertaken with future growth and development needs in mind," noted Dan Gourley, director of Global Logistics at Catalent's Philadelphia location. "Today's investment will allow us to quickly scale-up and meet customer demands should future market growth dictate the need."

Catalent expected the cold-chain expansion at Catalent's European facilities in Bolton, United Kingdom, and Schorn-dorf, Germany to be completed by year-end 2011.

#### **CEDARBURG HAUSER PHARMACEUTICALS**

Cedarburg is an experienced, contract development and manufacturing company for API and pharma intermediates that combines the benefits of working

with a CRO and a contract manufacturing organization. This pharma contract research organization can help with early-stage preclinical active pharma ingredient or pharmaceutical intermediate development.

Cedarburg is additionally a global leader in natural product extraction, isolation and purification as well as the synthetic modification of natural products from plant, marine and microbial sources. Cedarburg produces API and pharma intermediates from natural products along with ingredients for personal-care products and dietary supplements.

Cedarburg's process development chemists allow customer APIs to be successfully scaled up to the quantities necessary for toxicity trials, clinical trials and commercialization. The company has the knowledge and experience to efficiently guide customers via the complexities of the submission process by preparing and submitting CMC filings or FDA filings for APIs.

On March 17, 2009, **Cedarburg Pharmaceutical Inc.** acquired **InB: Hauser Pharmaceutical Services**. The acquisition bolstered Cedarburg's position as a leader in the rapidly growing CDMO market. The deal additionally leveraged the trusted reputation and synergistic capabilities of each company to offer clients a more fully integrated manufacturing platform strategically concentrated on helping clients move new chemical entities to the marketplace.

Hauser's experience in natural products, isolation/ purification and cGMP manufacturing augmented Cedarburg's synthetic chemistry and cGMP manufacturing expertise and effectively expanded the overall service capabilities offered to clients. The acquisition increased Cedarburg's extensive inventory of unit operations and comprehensive analytical instrumentation to include NMR and MALS and additionally amplified Cedarburg's toll manufacturing capabilities for the production of APIs and key intermediates.

Cedarburg Hauser Pharmaceuticals was created to offer customers a wide array of best-in-class pharma services to meet clients' development and production needs. The combined company offers proven turn-key cGMP compliance systems and seasoned professionals specialized in providing highly customized process and analytical chemistry from the bench through commercial production.

With 70,000-plus square feet of multi-purpose U.S.-based FDA-registered facilities (process development labs, kilo and commercial-scale manufacturing suites, analytical and microbiology labs, stability and material sample storage), the combined operations concentrate on these specialty categories: highly customized NCEs requiring complex chemistry, cytotoxic and potent APIs, naturally derived and semi-synthetic APIs, controlled substances, commercial cGMP API manufacturing, and high-value dietary supplements and cosmetics.

"The acquisition allows us to maximize the true potential of both organizations as one fully integrated contract development and manufacturing organization building value for our shareholders, employees, and customers," stated said R. Anthony (Tony) Laughrey, president and CEO of Cedarburg, in March 2009. "The merger will also speed up the development and manufacturing of products currently in our product pipeline. The new Cedarburg Hauser is well positioned to provide increased efficiency for our clients as they move their critical process development and manufacturing projects through clinical development and ultimately into the commercial arena."

#### **CHARLES RIVER LABORATORIES INTERNATIONAL INC.**

Charles River Laboratories provides essential products and services to help pharma and biotech companies, government agencies and leading academic institutions worldwide accelerate their research and drug development initiatives. Charles River has about 8,000 employees around the globe concentrated on providing clients with exactly what they need to improve and expedite the discovery, development through first-in-human evaluation, and safe manufacture of new therapies for the patients who need them.

Charles River announced on July 29, 2010, the company's mutual agreement to terminate its previously announced acquisition deal with WuXi PharmaTech. Charles River additionally announced that its board of directors authorized a new \$500 million stock repurchase program.

The termination pact provides for Charles River to pay WuXi a \$30 million breakup fee for full satisfaction of the parties' obligations under the acquisition

agreement and includes mutual releases of any claims and liabilities arising out of or relating to the transaction.

"We believed that this transaction, which would have created the premier early-stage contract research organization, would have resulted in long-term strategic benefits for our business and our shareholders," says James C. Foster, chairman, president and CEO of Charles River. "We also value our stockholders' views and given their concerns about the proposed transaction, and our commitment not to proceed without their support, we have decided that terminating the transaction is the appropriate action to take."

"Although we are disappointed in the outcome of the proposed transaction, our overall strategy remains unchanged. We intend to be the premier early-stage CRO and will continue to build our early development capabilities – specifically our discovery services – in order to support our clients' efforts across a broader portion of the drug development pipeline. We will enhance our portfolio of essential products and services, deepen our scientific expertise and maintain our standards of exceptional client service, all of which distinguish Charles River as an industry leader and make us the strategic partner of choice in early-stage drug development."

Charles River's board of directors has authorized the repurchase of up to \$500 million of the company's common stock. Charles River is exploring alternatives for timely execution. The stock purchases may be made from time to time via different methods, including open-market repurchases such as block trades, 10b5-1 plans or otherwise in compliance with Rule 10b-18 of the federal securities laws and/or privately negotiated transactions. Funds for the repurchases are expected to come from cash on hand, cash generated by operations, the company's existing credit facilities or other financing.

Charles River previously bought about 11 million shares under its previous \$600 million stock repurchase authorization, and as of July 15, 2010, had about 66.3 million shares of common stock outstanding. That authorization, under which there was a remaining balance of \$145 million, was canceled.

Repurchases may be commenced or suspended at any time or periodically without previous notice, depending on Charles River's view of market conditions

and other factors. There were no specific plans for the shares that may be purchased under the program.

On Oct. 13, 2010, Charles River announced an exclusive, long-term marketing and distribution transaction with **Transposagen Biopharmaceuticals Inc.** Lexington, Kentucky-based Transposagen is a provider of unique genetically modified rat models.

Through this deal, Charles River has become the exclusive, worldwide provider for **Transposagen's p53** and **Bcrp TGEM Knockout Rat Models** and associated downstream services using these models. The companies agreed to a research and development collaboration, whereas scientific management from each entity will hold technical discussions and cooperatively work towards the creation of select, new genetically modified rat models.

The exclusive license for these two research model lines has expanded Charles River's industry-leading portfolio of research models and services to offer novel knockout rat models – an emerging tool in drug discovery and development research – to its pharma, biotech, academic and government clients. Transposagen's showcase TGEM model, the p53 TGEM Knockout Rat Model, is expected to be a valuable tool in oncology research. The Tp53 gene (tumor protein 53) is believed to be the most commonly mutated gene in human cancers. The p53 TGEM Knockout Rat Model is the only fully phenotyped p53 knockout rat model on the market.

The Bcrp TGEM Knockout Rat Model lacks the expression of the drug transporter Bcrp gene (breast cancer resistance protein 1, or Abcg2), which has a role in multi-drug resistance in cancer therapy and the uptake of drugs in cells, as well as fetal protection during pregnancy. These novel rat models, created using Transposagen's innovative TGEM technology, are expected to play a critical role in unwinding the complex function of both Tp53 and Bcrp genes in disease progression and treatment, as well as provide new opportunities to examine the pharmacokinetics, pharmacodynamics, efficacy, and carcinogenicity and other potential toxicities of novel therapeutic compounds.

"Charles River is extremely pleased to offer knockout rat models to our clients for the first time by partnering with Transposagen Biopharmaceuticals, a leader

in the creation of genetically modified rat models," says Dr. Iva Morse, corporate VP, global research model services, at Charles River. "Knockout rat models are a new and emerging tool in drug discovery and development, and Transposagen's p53 and Bcrp TGEN Knockout Rat Models are expected to become widely accepted for research in oncology and other therapeutic areas."

#### **DIVIS LABORATORIES LTD.**

Established during 1990 with R&D as the company's major function, Divis concentrated on developing new processes for the production of APIs and Intermediates. In just a short time, Divis expanded its breadth of operations to provide complete turnkey solutions to the domestic Indian pharma industry.

With five years of experience, expertise and a proven track record of helping many companies with their turnkey and consulting needs, Divis established its first manufacturing facility during 1995.

Built on a 500-acre site at Hyderabad (Unit-I), the plant consists of 13 multipurpose production blocks and has space for additional growth and expansion.

Divis set up the company's second manufacturing facility at Visakhapatnam (Unit-II) during 2002 on a 350-acre site. The facility has 14 multipurpose production blocks.

Each site is primarily engaged in the manufacture of: APIs and Intermediates for Generics; Custom Synthesis of API's and Advanced intermediates for discovery compounds for pharma giants; Building blocks for Peptides; Building blocks for Nucleotides; Carotenoids; and Chiral ligands.

Complete cGMP guidelines are met in each facility. The company's Unit-1 at Hyderabad was successfully inspected by U.S. regulators during September 2000, April 2004 and February 2008. The company's Unit-2 at Visakhapatnam was successfully inspected by FDA in November 2006 as well as April 2009.

Divis undertakes FTE/Contract Research on process development for discovering new compounds for top MNCs globally and partners with them for the supply of APIs. Divis has a worldwide outlook and benchmarks its quality standards to the best in the world, according to the company.

With four R&D centers, two pilot plants,

two large-scale manufacturing units including a cGMP/ISO/FDA accredited facility, Divis claims to be an ideal partner for custom synthesis, process development and mass manufacturing of customer's own discovery product.

#### **DR. REDDY'S LABORATORIES LTD.**

Dr. Reddy's Laboratories, established during 1984 in Hyderabad, India, is an integrated worldwide pharma company. Dr. Reddy's is dedicated to providing affordable and innovative medicines for healthier lives. Through the company's three businesses – Pharmaceutical Services and Active Ingredients, Global Generics and Proprietary Products – Dr. Reddy's offers a portfolio of products and services such as APIs, custom pharmaceutical services, generics, biosimilars, differentiated formulations and NCEs. Therapeutic concentration is on gastrointestinal, cardiovascular, diabetes, oncology, pain management, anti-infective and pediatrics. Major markets consist of India, United States, Russia and CIS, Germany, United Kingdom, Venezuela, South Africa and Romania.

Dr. Reddy's inked a definitive deal during May 2008 to acquire **BASF's** pharma contract manufacturing business and related facility in Shreveport, La. This accord was funded using Dr. Reddy's internal cash reserves or other committed credit facilities. This business involves the contract manufacturing of generic prescription and OTC products for branded and generic companies in America.

The acquisition included the relevant business, customer contracts, related ANDAs and NDAs, trademarks, as well as the manufacturing facility and assets at the Shreveport facility. The facility is designed to manufacture solid, semi-solid and liquid dosage forms. Employing about 150 people at the time of the acquisition announcement, the site has a proven track record of compliance with regulatory authorities including FDA.

"Dr. Reddy's is committed to building a leading global generics business over the next few years," reported Satish Reddy, managing director and COO of Dr. Reddy's Laboratories. "And as we drive significant growth in our key markets, we will continue to expand our supply chain network into these markets to enable us to respond to local market needs as well as provide competitive solutions to our customers globally. The acquisition

of BASF's finished dosage manufacturing facility in the United States will enable us to strengthen our supply chain for North America and provide a strong platform for pursuing additional growth opportunities."

"We are excited about this acquisition as this facility provides us with a profitable revenue base built on strong customer relationships with branded and generic companies," stated Mark Hartman, president, North America Generics, Dr. Reddy's Laboratories. "It also provides us with an additional platform to further expand our portfolio of prescription generics, OTC capabilities and product portfolio and the ability to supply generic products to US government agencies."

"We are pleased with Dr. Reddy's decision to acquire BASF's contract manufacturing business and facility at Shreveport, Louisiana and are encouraged by Dr. Reddy's growth-oriented view of the business," said Martin Widmann at that time, Head of BASF's Pharma Ingredients and Services global business unit.

BASF is a leading global chemical company. BASF has about 110,000 employees, six Verbund sites and nearly 385 production sites in most countries. In addition to chemicals, the company's business segments include plastics, performance products, functional solutions, agricultural solutions, and oil & gas.

On July 28, 2011, **Fujifilm Corp.** President and CEO Shigetaka Komori and Dr. Reddy's Laboratories' Vice-Chairman and CEO G V Prasad signed a Memorandum of Understanding. The companies entered into an exclusive partnership in the generic drugs business for the Japanese market and agreed to establish a joint venture in Japan. The new joint venture will have 51% stake owned by Fujifilm and 49% stake owned by Dr. Reddy's.

The new company will develop, manufacture and promote competitive and high-quality generic drugs using Fujifilm's advanced quality control technologies the company has built up through its photo film business and Dr. Reddy's expertise in cost competitive production technologies for active pharmaceutical ingredients and formulations accumulated throughout the years by supplying to markets worldwide. The joint venture is expected to launch its first products in Japan in the next three to four years. The joint venture will design products that fit the specific requirements of the Japanese market, aim-



## Infrastructure

**Investing for future : 18 bn finished dosage units in FY11 expanding to 25+ bn units**

### Current Infrastructure

- ❑ **API Manufacturing** : India – 6, UK – 1, [All USFDA approved], Mexico – 1
- ❑ **Finished Dosages Manufacturing** : India – 6 [2 USFDA approved]  
US – 2 [USFDA approved]
- ❑ **Biologics Facility** : India – 1 [audited by multiple regulatory agencies]
- ❑ **Custom Pharma Services** : 3 Technology Development Centers – [2 in India & 1 in Cambridge, UK]
- ❑ **R&D Centers** : Integrated Product Development Organisation [IPDO] in Hyderabad, India  
NCE R&D center in Hyderabad, India  
Aurigene R&D center in Bangalore, India

Source: Dr. Reddy's Laboratories

ing to deliver reliable, high-quality generic drugs that will contribute to the growth of the generic drug market.

"Fujifilm continues to build upon its ongoing commitment to delivering pharmaceutical business," Mr. Komori stated. "With the execution of the Memorandum of Understanding with Dr. Reddy's Laboratories Ltd., Fujifilm will have excellent capability in developing and manufacturing across active pharmaceutical ingredients (API) and formulations of generic drugs. Through Fujifilm's superior material process technology and quality control system, we aim to contribute to the adoption of high quality and affordable generic drugs in Japanese market. Fujifilm will advance its effort in the pharmaceutical business using its leading-edge, proprietary technologies to help enhance the quality of life of people worldwide."

Mr. Prasad stated, "We are very excited to partner with Fujifilm Corporation, a highly reputed Japanese company and a leading global brand, to bring world-class, high quality generic drugs to the people of Japan. We are confident that Fujifilm's advanced R&D capabilities, quality systems and market know-how backed by Dr. Reddy's cost competitive, high-quality generic drug development & manufacturing and experience as a major global generics player will help the joint venture establish a strong presence in the Japanese pharmaceutical market. Our planned entry into Japan underscores our

commitment to bring affordable and innovative drugs to more patients worldwide."

Fujifilm Corp. is one of the major operating companies of **Fujifilm Holdings**. Since being founded during 1934, the company has built up a wealth of advanced technologies in the area of photo imaging. In line with efforts to become a comprehensive healthcare company, Fujifilm is applying these technologies to the prevention, diagnosis and treatment of diseases in the Medical and Life Science fields. The company is additionally expanding growth in the highly functional materials business, including flat-panel display materials, and in the graphic systems and optical devices businesses.

## FAMAR HEALTH CARE SERVICES

Famar is recognized as a leading manufacturer and service provider to the Health and Personal Care arenas. Famar's organization of excellence delivers a competitive advantage to the company's customers. Famar has established a network of 11 pharma production sites, three development centers, one health and beauty R&D unit and three distribution centers in France, Greece, Italy and the Netherlands. This network provides a wide array of development, manufacturing, packaging and logistics services for every dosage form.

Famar's success as a top service pro-

vider derives from the significance the company attaches to meeting and exceeding customers' expectations while delivering quality products, on time, at a competitive cost. Famar's commercial manufacturing solutions consist of production of prescription, OTC, food supplements, generics, and health and beauty products in the following forms: solid, semi-solid and liquids, sterile and freeze-dried, and specialized manufacturing of Beta lactam.

The integration of the Sanofi manufacturing facility in Madrid within the Famar network is official. As of July 1, 2011, the two parties came to a written deal finalizing the framework and the principles of the collaboration. The facility, which produces solid and sterile forms and supplies 50-plus markets, will serve as another platform for developing Famar's service offering. The company will continue to supply Sanofi with certain products from the plant on the basis of a strong and sustainable supply pact. Also, as part of this project, Famar has introduced a significant investment plan to expand the facility's sterile capacities and offering.

The plan involves the formation of a new 1000m2 sterile core with two compounding rooms, linked to three filling and packaging lines. The new area will be concentrated on sterile ophthalmic and nasal spray products with a yearly capacity ranging between 30 and 35 mio consumer units. The area was to be operational by year-end 2011.

During January 2009, Famar concluded the acquisition of the **McNeil** manufacturing site of Orléans la Source by Famar, as announced in 2008. For Famar, with an existing site in Orléans, the McNeil manufacturing facility of Orléans la Source presents many advantages. For example, this facility enables Famar to develop a new, modern and very efficient platform in France, intended primarily for OTC and prescription products.

This acquisition also results in an organization well suited to face the requirements of a very competitive market. This project allows Famar to bolster the competitiveness of its service offering to the pharma industry, based on a more polyvalent and efficient site, with capacities that enable strong development going forward.

The acquisition was based on these elements: a long-term manufacturing deal for certain Johnson & Johnson products; the implementation of a productivity im-

provement plan at the McNeil manufacturing site; the implementation of a new organization regrouping the two locations; and ultimately, the consolidation of the Famar Orléans production site and the McNeil manufacturing site.

Because of this transaction, Famar has developed one of the largest and most modern sites in Europe in the area of OTC and prescription products. The facility covers effervescent, powders, liquids and semi-solids forms and offering a large capacity, in line with the quality and cost requirements of the company's customers.

Since the Saint Rémy facility acquisition from Abbott during 2007, Famar has developed this site as its sterile and lyophilization center of excellence. Famar has implemented a major capacity expansion with the construction of a second sterile area SVP2, operational since August 2008, for aseptic filling and freeze drying services (2ml to 100ml vials). This area operates with two lyophilizers of 37sqm each, and is designed to potentially accommodate a third lyophilizer of similar capacity.

These new CIP/SIP double door freeze-dryers are steam sterilized, equipped with liquid nitrogen, and loading and unloading steps are conducted in class A. Famar has a total freeze drying capacity of more than 166sqm with five industrial lyophilizers, and one pilot unit for products transfer and lyophilization cycle time optimization.

## FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LTD.

Fujifilm Diosynth Biotechnologies is one of the leading GMP contract manufacturing organizations worldwide for the biopharma arena. The business comprises the former Diosynth Biotechnology based in Research Triangle Park, N.C., and **MSD Biologics** UK Ltd. (previously Avecia Biologics) located in Billingham, United Kingdom. Fujifilm Diosynth offers an extensive breadth of process development and cGMP drug manufacturing experience to meet the company's client needs at every phase of product lifecycle, from efficient protein expression, process design and GMP manufacture through to process validation and commercial production.

On June 20, 2011, Fujifilm Corp. and **Mitsubishi** Corp. agreed to a contract manufacturing partnership for biophar-

maceuticals. The companies agreed to transfer the ownership of 20% equity interests in Fujifilm's wholly owned biopharma contract manufacturing subsidiaries, **Fujifilm Diosynth Biotechnologies U.S.A.** Inc. and Fujifilm Diosynth Biotechnologies UK Ltd., to Mitsubishi. Mitsubishi is set to become involved in the business management of each location alongside Fujifilm in a joint effort to strongly promote the expansion of the biopharma contract manufacturing business.

Fujifilm Diosynth Biotechnologies U.S.A. and Fujifilm Diosynth Biotechnologies are leading contract manufacturers of biopharmaceuticals that Fujifilm established on April 1, 2011, following the acquisition from Merck. The companies have advanced biotechnology that uses microbial and mammalian cell culture to efficiently produce proteins for use in biopharmaceuticals. They are equipped with extraction and purification process development capabilities, analytical capabilities, experienced human resources and manufacturing facilities that enable them to deliver a high-yield down-stream process. Fujifilm oversees these companies' business operations with its expertise in production and quality management, developed throughout many years through the company's photographic film business, as well as its knowledge in high-molecular materials including collagen.

Fujifilm Diosynth Biotechnologies announced plans during June 2011 to expand the company's existing contract manufacturing capabilities with the addition of a 1,000L **Xcellerex** Single-Use Bioreactor to its RTP, N.C. plant. This expansion reinforces the dedication to lead the

worldwide Biologics CMO industry through continuous innovation and implementation of new technologies, service delivery and quality, as announced by Japan-based parent company Fujifilm Corp.

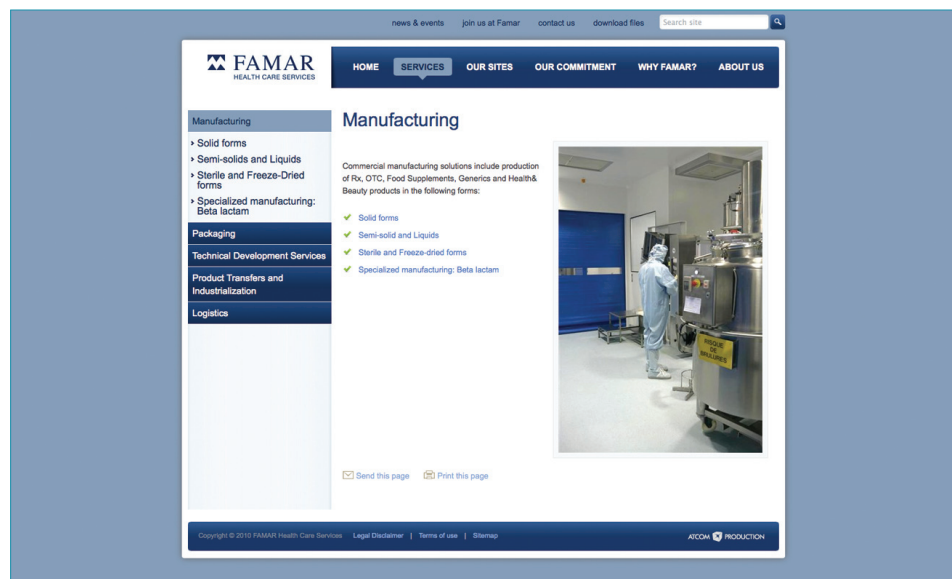
The addition of the 1,000L single-use bioreactor, single-use mixers, and single-use harvest filtration will supplement existing seed train and purification equipment as part of a hybrid implementation method. This project is the continuation of a continuing cell-culture capacity expansion by Fujifilm Diosynth Biotechnologies. This addition complements the 200L Xcellerex single-use bioreactor that already was in operation at the company's Process Development Laboratories in Cary, N.C., and the existing 2,000L stainless steel train situated in the RTP, NC cGMP manufacturing site.

"Single use technologies are uniquely suited for multi-product contract manufacturing with the added advantage that the operations are easily transferable between sites and are easily expandable for increased supply needs," commented Stephen Spearman, president of Fujifilm Diosynth Biotechnologies USA. "The **XDR-1000** can be operated at working volumes ranging from 200- 1,000L."

John Foy, senior director of business development and logistics at Fujifilm Diosynth RTP, noted, "The flexibility of scale will allow us to better serve the demands of companies requiring material for pre-clinical studies, early to mid-phase clinical production and beyond."

The expansion is expected to be validated and fully operational by first-quarter 2012.

On Feb. 28, 2011, Fujifilm Corp. and



Merck entered into a definitive deal. Fujifilm acquired the Merck BioManufacturing Network, a leading provider of contract manufacturing and development services for the biopharma industry and wholly owned by Merck.

"Fujifilm continues to build upon its ongoing commitment to delivering pharmaceutical business," Mr. Komori stated. "This acquisition provides an important addition to our pharmaceutical business with diverse capabilities and technical expertise in production of protein therapeutics."

Fujifilm purchased all of the equity interests in two Merck subsidiaries – **Diosynth RTP LLC** and **MSD Biologics** – which combined owned all assets of the Merck BioManufacturing Network and its facilities in Research Triangle Park, N.C., and Billingham, United Kingdom; and including manufacturing contracts; business support operations and a highly skilled workforce. As part of the deal with Fujifilm, Merck committed to certain continued development and manufacturing activities with these two companies. Financial details of the accord were not disclosed.

"When Merck/MSD combined its biopharmaceutical manufacturing services businesses in the United States and U.K. into the Merck BioManufacturing Network, we established one of the world's leading biopharmaceutical contract manufacturing organizations," commented Willie A. Deese, executive VP and president of Merck Manufacturing Division. "With

this transaction, Merck/MSD becomes a key customer that will continue to benefit from the expertise and experience of the combined businesses in biologics development and manufacturing."

## GALLUS BIOPHARMACEUTICALS LLC

Gallus is a premier biologics contract manufacturing organization located in St. Louis. Gallus operates an FDA-approved, commercially certified facility formerly owned by J&J's **Centocor** division. The Gallus facility has capabilities for mammalian cell culture and protein purification in perfusion and fed batch mode, and is being expanded to offer additional development and clinical services capabilities. The facility produces two leading commercial biologics products that are distributed worldwide.

On May 24, 2011, Xcellerex Inc. and Gallus entered into a collaboration. The alliance quickly provides Gallus with expanded cGMP biomanufacturing capacity by leveraging the key advantages of the turnkey Xcellerex FlexFactory GMP manufacturing platform suite. The strategic collaboration provides Gallus with world-class, scalable, flexible and cost-efficient manufacturing and lab technology to expand its contract manufacturing business. This partnership will provide Xcellerex's customers unprecedented access to a commercial, FDA-approved, biomanufacturing facility.

Through this deal, Gallus is acquiring

several Xcellerex bioproduction systems for new suites and labs at the company's existing manufacturing facility. Along with single-use XDR bioreactors to quickly expand capabilities in an existing commercial manufacturing suite, Gallus acquired small-scale 10L bioreactors for its expanded development lab and a turnkey FlexFactory cGMP manufacturing line with XDR single-use bioreactors up to 2,000 liter scale for clinical supply.




Such rapid capacity expansion with single-use technology not only allows Gallus to offer more services and options to its customers, but also augments the company's existing, multi-suite commercial capacity with novel, proven single-use Xcellerex bioreactors. Through the collaboration, Xcellerex and Gallus will provide customers with access to Gallus' established biomanufacturing expertise in a world-class facility that has been inspected and approved by every major regulatory authority.

"Gallus has a unique contract manufacturing business model that enables us to respond to clients' changing capacity needs quickly, and achieve rapid, high quality production at a competitive price," stated Mark Bamforth, president and CEO of Gallus. "The partnership with Xcellerex allows us to leverage their single-use biomanufacturing platform. This is a strategic investment that rapidly provides us with additional manufacturing capacity and scale-up capabilities to deliver development, clinical and commercial products and services. The first manufacturing suite will be in place by the end of 2011. Additional suites can be added to meet specific customer needs, within the existing facility at our site in St. Louis."

Established during 2010, Gallus' St. Louis facility is producing two commercial products that are approved worldwide. The Gallus business model includes a "condominium" concept that enables a client to "virtually-own" a manufacturing suite for its process development and production needs. This novel approach provides clients with complete flexibility in accessing capacity as necessary.


"Gallus is capitalizing on the extraordinary flexibility afforded by the **FlexFactory**, along with the extensive manufacturing experience of its team, to provide innovative solutions for established as well as development-stage biopharmaceutical companies," says Guy Broadbent, CEO of Xcellerex. "The agreement pro-




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## cGMP MANUFACTURING SERVICES



We can support our clients through the drug development journey from early phase process development to commercial manufacturing.

### cGMP Manufacturing Services



The Gallus cGMP manufacturing facility is conveniently located near the airport in St. Louis, MO, and has been manufacturing commercial products for 25 years. The facility is currently licensed in over 50 countries and has been inspected and approved by every major regulatory body including the Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMA), Brazilian National Health Vigilance Agency (ANVISA), Health Canada and Medicines and Healthcare Products Regulatory Agency (MHRA) for commercial supply of two products. Gallus also offers cGMP mammalian cell bank manufacture as part of a comprehensive process development and manufacturing project.

#### Services

- cGMP clinical supply (Phase I-III) Drug Substance manufacturing (Clinical Services Suite)
- cGMP late phase and commercial supply Drug Substance manufacturing (four suites)
- Master Cell Bank and Working Cell Bank cGMP manufacture
- cGMP Cell Bank Storage
- cGMP Fill / Finish

#### Facilities

- Clinical Services Suite (CSS)
- Commercial Suites
- Dedicated "Condo" Model Capacity

vides us with an important path for us to offer full-scale commercial manufacturing to our customers."

Separately, the companies announced that Mr. Broadbent joined the Gallus board of directors.

## GLAXOSMITHKLINE PLC

GlaxoSmithKline is engaged in the creation, discovery, development, manufacture, and marketing of pharma and consumer healthcare products. Working across an international network of manufacturing locations, GlaxoSmithKline supplies product to patients and customers in 150-plus countries.

GlaxoSmithKline Contract Manufacturing offers a fully integrated supply-chain solution to support projects at every level: from early-stage research and development, to clinical supply, to launch and growth of small, medium, and large-volume products. GlaxoSmithKline has state-of-the-art facilities for the manufacture of: biopharmaceuticals, API, steriles, solid dose, cephalosporins and penicillins and respiratory dose forms.

The company has dedicated state-of-the-art facilities for the manufacture of products from actives through bulk and finished product supply. GlaxoSmithKline has comprehensive lab facilities to support quality, product development, engineering, and physical properties analysis with state-of-the-art instrumentation. The company can offer co-located R&D API Pilot Plants, where the company pro-

vides early-phase clinical requirements as well as commercial scale-up.

GlaxoSmithKline offers full-service high-containment capabilities for potent and cytotoxic compounds from API manufacturing through to finished product in sterile vials, capsules, or tablets.

GlaxoSmithKline formed a long-term strategic deal with **McLaren Group** during September 2011. The partnership, which will run initially until 2016, combines two United Kingdom companies concentrated on innovation and high-tech research.

McLaren Group will share its widely acknowledged leading capabilities in engineering, technology, analytics, and strategy modeling – which the company has developed over many years in its core business of Formula 1 motor sport – to help deliver world-class performance across GSK's worldwide businesses. The partnership will initially concentrate on GlaxoSmithKline Manufacturing, Research and Development and Consumer Healthcare.

A new state-of-the-art learning facility will be constructed as part of the transaction, concentrated on developing United Kingdom engineering skills and processes. The McLaren GSK Centre for Applied Performance will be situated at McLaren's headquarters in Woking, United Kingdom, and will debut during 2013. Employees from each organization and business partners will be able to use the facility to share ideas and collaborate on joint working projects.

"I am delighted to announce this partnership with McLaren which brings together two British companies whose continued success hinges on the ability to innovate and rapidly respond to change and competitor activity," stated Andrew Witty, CEO of GlaxoSmithKline. "McLaren has an unparalleled reputation for innovation built on rigorous analytics and fast decision making. This partnership is another example of GlaxoSmithKline looking outside its sector for inspiration and fresh perspectives on how we can achieve our strategic goals in an ever more challenging and fast changing business environment."

Ron Dennis, executive chairman of McLaren Group and McLaren Automotive, added, "This all-new collaboration between McLaren Group and GlaxoSmithKline – McLaren's first ever such association with a major pharmaceutical corporation – represents a strategic partnership that engages two great British companies at a variety of levels across a number of disciplines in a multi-faceted and ground-breaking way. Specifically, our intention is that GlaxoSmithKline will harness McLaren's world-beating Formula 1-bred technology, processes and operational dynamism, in order to enhance its performance across a wide variety of its divisions in a way that none of its competitors can match. In today's challenging economic conditions, we firmly believe that innovative associations such as ours will play an increasingly significant role in ensuring that the United Kingdom remains globally competitive in the field of scientific innovation."

GlaxoSmithKline Manufacturing supplies medicines and products to patients and customers globally from 2,000-plus production lines in 80 factories. A strategic program is being evaluated to apply McLaren's engineering and technical expertise to GlaxoSmithKline's manufacturing processes. For instance, during a racing season, each Formula 1 team can only use a maximum of eight engines for 20 races. McLaren has therefore developed a unique system of modeling every working component within the car to provide intelligence that can predict potential fatigue and failure. The companies believe that the application of McLaren's approach, technology and processes could lead to improvements in GSK's production line performance, reducing the number of breakdowns and improving cost and customer service.

GlaxoSmithKline's R&D organization is assessing whether the application of McLaren's expertise and technology could help drive improvements in clinical research processes by speeding up trial design and enabling real-time patient monitoring and treatment adjustment. McLaren has developed a system that allows team members to remotely monitor each aspect of the car's performance during a race via wireless technology. This allows the team to make regular minor adjustments every few minutes to avoid having to make significant time-consuming interventions. Working with McLaren, GlaxoSmithKline is exploring the possibility of reapplying this expertise to human studies.

GlaxoSmithKline's Consumer Healthcare business, which markets brands such as **Lucozade**, **Panadol** and **Sensodyne**, will work with McLaren's successful Formula 1 "Mission Control" – the unit that analyses the team's performance and directs decision making to drivers during a Grand Prix – to construct a similar facility at the company's London headquarters. This will allow for quicker responses to competitor activity and customer needs and inform decision making around inventory management, pricing, and retailer stocking. Analytical and performance management tools developed by McLaren will be used to improve GlaxoSmithKline's ability to make quicker decisions around longer-term investment allocations for new consumer product development and innovations.

On June 23, 2011, GlaxoSmithKline agreed to pay \$40.75 million, which will be divided among 37 states and the District of Columbia, as part of a deal reached related to events during the early 2000s at its former manufacturing facility in Cidra, Puerto Rico.

The company decided to settle the matter, which the company initially disclosed in its fourth-quarter 2010 financial results and 2010 annual report, to avoid the expense and uncertainty of protracted litigation and trial. GSK did not admit to any wrongdoing or liability of any type under these states' consumer protection laws in this settlement.

During 2009, GlaxoSmithKline closed the plant because of decreasing demand for the medicines made there. GSK sold the facility in 2010. Before selling the facility, the company brought the building into compliance and to a high level

of performance that satisfied both GSK and FDA.

The company's manufacturing division has a strong track record of quality and compliance with current Good Manufacturing Practice (cGMP) requirements. Different regulatory agencies – including FDA – perform an average of 100-plus inspections annually at 80-plus GlaxoSmithKline manufacturing sites in more than 30 countries. FDA has raised no material issues as a result of the company's very thorough inspections.

GlaxoSmithKline Biopharmaceuticals is a strategic unit within the company's Global Manufacturing & Supply network. With bulk manufacturing sites (United States and the United Kingdom), secondary filling (United Kingdom and Italy) and a central testing laboratory (United Kingdom), GlaxoSmithKline has the experience, knowledge, resources and corporate backing to satisfy every requirement for reliable, cost-effective, and high-quality biopharma contract manufacturing services.

GlaxoSmithKline Biopharmaceuticals is a full-service contract manufacturing partner in the development and manufacture of cGMP biopharm proteins for clinical trials and commercial use. The business' featured services include the low-cost, rapid scale-up and manufacture of mammalian cell-derived proteins at up to 5,000 liter scale and the preparation of formulated bulk products.

## HOSPIRA INC./ONE 2 ONE

Hospira supplies products to markets around the globe. As a world leader in specialty generic injectable pharmaceuticals, the company offers one of the most extensive portfolios of generic acute-care and oncology injectables, as well as integrated infusion therapy and medication management solutions. Hospira is a top provider of contract manufacturing services to proprietary pharmaceutical and biotech companies for formulation development, filling and finishing of injectable pharmaceuticals. Hospira's broad product portfolio is used by hospitals and alternate-site provider including clinics, home healthcare providers and long-term care facilities.

By using the company's expertise and broad capabilities, Hospira's One 2 One business unit is a global leader in the contract manufacturing of parenteral prod-

ucts. The company's expertise stems from the successful manufacture of parenterals for almost 70 years in a variety of delivery systems, vials, flexible containers, cartridges and pre-filled syringes. This experience and concentration on injectable drug product is made available to large and small bio/

## GSK CONTRACT MANUFACTURING BIOPHARMACEUTICALS

### Manufacturing Capabilities

#### Large Molecule/Biopharm

- Large company strength and small company flexibility
- Cost-effective operational scale
  - 75L to 5000L bioreactors in three manufacturing suites
  - 6 production trains with three purification suites
- Over 10 years with a successful track record in transferring and manufacturing multiple products
- Ability to work with a broad range of clients including major pharmaceutical companies
- Highly developed and proven methods for technology transfer
- Fully trained staff experienced in cGMP manufacturing, testing, and release
- Complete supply solution (bulk drug substance manufacture, fill/finish, European release)
- Proven executional excellence: on-time, on-spec performance
- Protection of proprietary technology
- Exemplary and sustained safety record

### Processes and Equipment

- Independent Cell Culture Suites – producing product up to 5,000L scale, with multiple 5,000L scale bioreactors
- Independent Product Purification Suites – providing complete segregation of a client's product
- State-of-the-Art Testing Laboratories – with a full array of testing capabilities
- Advanced computer tracking and control
- cGMP Compliant Warehousing – for raw materials and formulated bulk product

Source: GlaxoSmithKline

One 2 One has a wealth of history and experience in worldwide parenteral commercialization. As a service of Hospira, One 2 One was created from the worldwide hospital products business of Abbott Laboratories and has successfully produced and launched hundreds of sterile injectables.

One 2 One has the manufacturing scale and capacity to accommodate broad-scale, customized commercialization of a wide array of injectable products.

According to the company, One 2 One takes pride in maintaining high qual-

Successful commercialization begins from two to four years before a product's launch, right after proof-of-concept and as the compound moves through Phase II studies. One 2 One continually partners to guide the product from site selection and technology transfer to cold-chain management and distribution.

Lonza is one of the top suppliers to the pharma, healthcare and life-science industries on a global scale. Products and services range from Lonza's customer needs from research to final product manufacture. The company is a world-wide leader in the production and support of APIs both chemically and biotechnologically.

Biopharmaceuticals are a key growth driver of the pharma and biotech industries. Lonza has strong capabilities in large and small molecules, peptides, amino acids and niche bioproducts that play a significant role in the development of novel medicines and healthcare products.

Lonza is additionally a leader in cell-

The company offers the life-science industry world-class contract manufacturing and a complete array of development of services for fine chemicals, advanced intermediates, APIs, biologics, and functional ingredients.

The **GS Gene Expression System**, owned and licensed by the company, is used for the production of therapeutic recombinant proteins and monoclonal antibodies. Almost 100 biotech and pharma companies as well as 75-plus academic labs globally are successfully using the GS Gene Expression System. This system has been established as the industry standard. The GS Gene Expression System is characterized by its speed and ease of use. The higher-yielding cell lines provide cost-efficient production of therapeutic proteins.

Lonza's powerful proprietary GS System uses a robust viral promoter and selection through glutamine metabolism to provide rapid development of high-yielding and stable mammalian cell lines. At least five products have been approved that use the GS System, including **Zenapax** (Roche) and **Synagis** (MedImmune).

The international use of the GS System by commercial organizations and academic institutions has resulted in a large body of published info. New users can draw upon this material to expand their knowledge and skill base as well as improve their use of the system.

Lonza has created hundreds of cell lines with the system. Many have been grown at large-scale and produced product for use in clinical trials and in-market supply. Other GSSystem users have accumulated experience with a diverse array of products where high yields have been attained. Many investigators use the system to develop a manufacturing process and as a tool to create recombinant proteins for biological studies. The reliability of the system as a consistent means of rapidly generating high-producing cell lines quickens time to market.

On Sept. 2, 2011, **Oxford BioTherapeutics** Ltd. (OBT) and Lonza announced a non-exclusive license deal. The pact provides OBT with access to the GS Gene Ex-

Development Services	Drug Delivery Options	Fill-Finish Expertise
<ul style="list-style-type: none"> <li>• Formulation &amp; Process Development</li> <li>• Lyophilization Cycle Development</li> <li>• Pilot Plant Services</li> <li>• Method Development and Validation</li> <li>• Impurity Identification</li> <li>• Technical Transfer</li> <li>• Process Validation</li> <li>• Stability Services</li> <li>• Global Regulatory Support</li> <li>• Packaging Development</li> </ul>	<ul style="list-style-type: none"> <li>• ADD-Vantage® Vials</li> <li>• Ampoules, Bottles, Vials</li> <li>• Cartridges for Pen Devices</li> <li>• Flexible Containers</li> <li>• Reusable™ Syringe</li> <li>• Onco-Tain™ Vial Protection and Containment</li> <li>• Prefilled Syringes with UltraSafe® Needle Guards*</li> </ul>	<ul style="list-style-type: none"> <li>• Biologics</li> <li>• Small Molecules</li> <li>• High potency substances</li> <li>• BetaLactams</li> <li>• Controlled Substances</li> <li>• Lyophilization</li> <li>• Terminal Sterilization</li> <li>• Aseptic Filling</li> <li>• Powder Filling</li> <li>• Sterile Compounding</li> <li>• Disposable Equipment</li> <li>• Gamma Irradiation</li> <li>• Multilingual Labeling and Packaging</li> <li>• QIP Release</li> </ul>



pression System. The deal covers the R&D and commercial use of the system by OBT and contains standard payments as well as license fees that were not initially disclosed.

Licensing of the system expands OBT's access to world-class technologies for the company's maturing pipeline of therapeutic antibodies in oncology. This deal also shows OBT's dedication to strengthening antibody production and preclinical capabilities.

"We are delighted to have access to Lonza's GS Gene Expression System as an addition to our technology portfolio," noted Tom Boone, senior VP of Protein Sciences for Oxford BioTherapeutics. "The speed and ease of use of the GS System will aid the rapid selection of high-producing cell lines and accelerate the production and development of our most promising anticancer agents."

OBT is a top international biotech player concentrated on the development and commercialization of innovative antibody-based cancer medicines, with integrated diagnostics, against novel targets that the company has discovered in its unique Oxford Genome Anatomy Project (OGAP) proteomic database. OBT accesses top antibody technologies and expertise via its partnerships with many global leaders in antibody development such as the **BMS (Medarex) HuMAb** platform, the Amgen (**Abgenix**) **Xenomouse** platform, the transgenic phage technology of **Alere** (formerly **Biosite**) and the **POTELLIGENT** Technology of **BioWa**, and through its development alliances with GlaxoSmithKline and Sanofi.

The diagnostic collaboration with Alere provides the opportunity to develop tailored diagnostics for OBT's therapeutic products. These partnerships have allowed OBT to use the company's unique position to convert its novel oncology targets into a highly attractive pipeline of therapeutic antibodies. OBT's pipeline is expected to deliver innovative and cost-effective first-in-class medicines to fulfill major unmet patient needs in the area of cancer.

The OGAP database marks the world's largest proprietary collection of disease-associated proteins. OGAP oncology consists of proteomic data on 5,000 cancer membrane proteins along with their genomic and clinical info derived from human blood and cancer tissue studies. OGAP contains proprietary target data

on three-fourths of the entire human proteome. More than 1 million human protein fragments have been sequenced in OGAP in 50 different human tissues representing 60 diseases. This includes 25 types of cancer covering 17,000 different genes and more than three quarters of all human proteins and genetic variants in eight-plus million SNPs and haplotypes.

Lonza announced on Sept. 15, 2011, a new manufacturing agreement with **Pasteuria Bioscience**. This deal secures a process transfer and manufacturing plan to produce Pasteuria spores in Lonza's biochemical plant in Kourim, Czech Republic.

Lonza is initiating manufacture of Pasteuria spores, a biological nematicide, in its Kourim facility starting in late 2011. The biological nematicide developed by Pasteuria Bioscience is based on the natural microbe Pasteuria spp., which is found in soil and known to infect and kill harmful nematodes.

"Lonza is excited to use their fermentation expertise in biochemical production to provide innovative, environmentally safe, and cost-effective alternatives to the agri-business and regulated specialty ingredients markets," noted John McGrath, head of Lonza Biological Manufacturing. "The collaboration fits well with Lonza's existing technology and manufacturing expertise and is fully aligned with its biochemical's strategy."

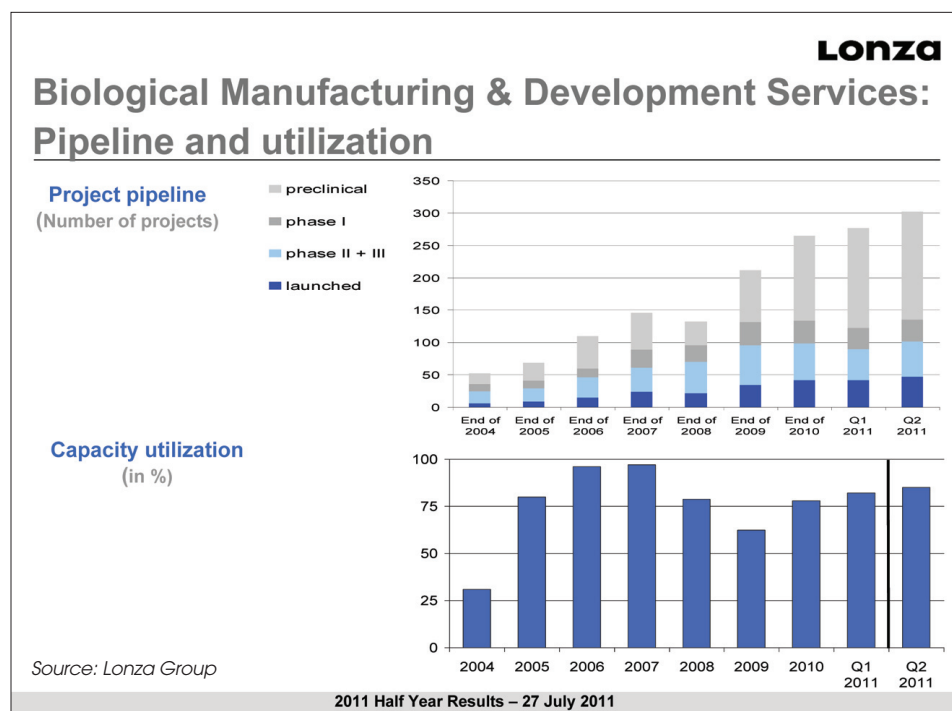
Kelly Smith, Ph.D., chief technical officer for Pasteuria Bioscience, said "Pas-

teuria Bioscience is pleased to partner with Lonza as a manufacturer of Pasteuria products. Lonza offers significant fermentation expertise as well as the ability to scale-up manufacturing in order to meet the global need for Pasteuria spp. bio-nematicides."

Pasteuria Bioscience was founded during 2003 in the **University of Florida's** Sid Martin Biotechnology Incubator where the company headquarters remains. The company was developed to commercialize its revolutionary technology for production of biological nematode control products that are based on the Pasteuria platform. The first Pasteuria-based product **Econem** was commercialized during 2010 for sting nematode control in the golf and sports turf markets. Pasteuria Bioscience is developing products to treat major nematode pests in most agricultural crops including soybean, sugar beet and cotton as well as in specialty crops such as fruits and vegetables.

Lonza announced an exclusive contract during March 2011 for the commercial production of Enobia's bone-targeted enzyme replacement therapy **ENB-0040** (asfotase alfa). The drug is under investigation for treating hypophosphatasia (HPP). Lonza will provide process validation and commercial manufacturing at its large-scale biologics site in Portsmouth, N.H., with an option to extend production to another Lonza site.

"We are pleased that Enobia places confidence in Lonza's manufacturing



capabilities and has entrusted us to support the launch and commercial supply of their lead drug candidate," stated Dr. Stephan Kutzer, COO of **Lonza Custom Manufacturing**. "We very much look forward to a long and successful collaboration."

Enobia announced that the company's successfully completed Phase II juvenile study met its primary endpoint, showing a statistically significant improvement in rickets when compared with historical matched cohort controls ( $p=0.002$ ). Rickets, a softening and weakening of the bones, is often found in children with HPP and can result in fractures, pain and deformity. The positive data follow the successful completion of an earlier study in infants, in which participants continue to show functional and respiratory improvements in longer-term follow-up. A Phase II study in adolescents and adults with HPP is under way.

Enobia is a private Montreal-based company concentrated on the development of therapeutics to treat serious bone disorders for which there are no drug therapies on the market. ENB-0040 is the company's lead program.

Lonza delivered a robust business performance during 2010, with sales rising 3.3% compared with 2009. The company continued to benefit from pharma and biotech companies outsourcing more of their manufacturing and development activities. During 2010, Lonza achieved significant important successes.

Lonza improved capacity utilization, particularly in Biological Manufacturing during second half of 2010. The Microbial Control business produced strong growth. Lonza's project pipeline was significantly increased via the signing of new contracts and multi-product pacts, particularly in Chemical and Biological Manufacturing and Cell Therapy. However, these operating positives were offset by slower pharma product approvals due to a more stringent regulatory environment, as well as increasing raw material costs that impacted the profitability of Lonza's non-pharma businesses, according to company reports.

## PARAGON BIOSERVICES INC.

Paragon Bioservices provides a diverse variety of research and manufacturing services. The company offers contract research, process development and GMP

manufacturing with a concentration on biopharmaceuticals. These services are for companies and government agencies involved in the development of either therapeutic proteins, monoclonal antibodies, vaccines/VLPs and stem cells.

Some complementary services that Paragon offers are molecular biology, antibody and immunology services, cell line development and cell banking, electron microscopy (to support research protocols encompassing the areas of virology, cell biology, vaccines and gene therapy) and bacteriophage production and purification (manufactured in a segregated facility) to provide solutions for biodefense, food safety, animal health and vet applications, human therapeutics and industrial applications.

Paragon's manufacturing operations follow every current GMP guideline. The Baltimore company has been in business since 1990 and has a successful track record of delivering research-grade proteins, process development services, GMP manufacturing (microbial and mammalian platforms) and cell therapies for Phase I and Phase II studies.

"Our focus on biologics and our efficient integration of single-use technologies allows us to keep our overhead low, in comparison to other CMOs, who also provide Phase III and commercial manufacturing," Dr. Klyushnichenko says.

This concentration on traditional recombinant proteins, specialized monoclonal antibodies, virus-like particles and vaccines, stem cells and other products for regenerative medicine necessitates a major investment in modern analytical equipment including electron microscopy and analytical ultracentrifugation. "In order to supplement that, our customers benefit from our strategic alliance with the University of Maryland – where our scientists have access to their state-of-the-art Mass Spectrometry facility, nano-technologies and enormous academic intellectual resources," Dr. Klyushnichenko noted.

With that advantage, Paragon can ensure that all measurements performed by the company's scientists result in comprehensive reports and files with raw data – which are provided for the client to keep the integrity of their intellectual property. If the client requires more intensive studies, Paragon provides effective interface with the university and its vast resources.

Paragon celebrated the company's 20th anniversary during November 2010 by undergoing a second expansion of facilities at the University of Maryland BioPark in Baltimore. The expansion doubles existing GMP manufacturing capacity, includes more research and process development labs, and adds fill and finish capabilities. Completion of the expansion

was expected during the second quarter of 2011.

When completed, the 45,000-square-foot new facility will be the first multiple project GMP contract manufacturing organization in the Baltimore-Metropolitan area and one of only a handful in the Mid-Atlantic region.

"As the demand for the development of biopharmaceuticals continues to increase, Paragon is meeting our customer demands with expansions to our facilities, staff and equipment," commented Marco Chacón, Ph.D., CEO of Paragon Bioservices. "This enhances our ability to produce recombinant proteins, both for research purposes and for Phase I and II clinical trials."

On Oct. 21, 2010, Paragon was awarded a \$4.99 million contract to assist the **U.S. Army Medical Research Institute for Infectious Diseases** (USAMRIID) in its vaccine development efforts. The USAMRIID project involves process development and scale-up production of VLP-type vaccines against Ebola Zaire, Ebola Sudan, and Marburg viruses to support continuing preclinical evaluation of efficacy, potency, and safety of these Filovirus vaccine candidates. Using their extensive VLP production and purification expertise, Paragon will develop a large-scale mammalian process for future GMP manufacturing.

Ebola and Marburg viruses are a serious worldwide health threat. The viruses result in hemorrhagic fever and have up to a 90% fatality rate in humans. There are no vaccines or therapies available for them. These viruses are commonly spread through blood and bodily fluids of infected patients who frequently succumb to hypovolemic shock. Each virus is a potential agent of biological warfare or terrorism as they are additional infectious by aerosol.

"As a scientist and a business man, it is extremely rewarding to be part of an effort that may improve public health, as well as enhance national preparedness," Dr. Chacón stated. "Preventing the spread of Ebola and Marburg viruses is crucial to containing outbreaks and saving lives."

As a division of the **U.S. Army Medical Research and Materiel Command**, USAMRIID plays a key role in national defense and infectious disease research. They are the top medical research lab for the **Department of Defense** and the

### **Biological Defense Research Program.**

Their mission is essentially to carry out basic research on biological threats and to develop appropriate medical solutions, including vaccines, drugs and diagnostics.

### **PATHEON INC.**

Patheon is a top worldwide provider of contract dosage form development and manufacturing services to the pharma and biotechnology industries. Employing more than 4,000 highly-skilled staff, the company's network of modern manufacturing facilities located in North America and Europe provide more than 3 million square feet of best-in-class capacity. With three facilities in the United States, three in Canada and four in Europe (including two in Italy, one in France and one in the United Kingdom) the North Carolina-based company can meet the international requirements of customers.

Patheon's development and manufacturing capabilities encompass prescription products in solid, semi-solid and liquid dosage forms. The company also has specialized capabilities in high-potency, cephalosporin, controlled/sustained release and sterile manufacturing such as aseptic filling and lyophilization.

Patheon's **Pharmaceutical Development Services** (PDS) group offers contract pre-formulation, formulation and analytical development, clinical trial materials (CTM) manufacturing, clinical packaging and scale-up services for pharma products of essentially all kinds, including biopharmaceuticals.

Founded during 1974 and publicly traded since 1993, the company has always solely concentrated on outsourcing. Patheon proudly serves 300-plus customers including many of the world's leading pharma, biotech and specialty pharma companies.

Patheon provides fully integrated contract manufacturing and development solutions to customers from early development through to high-volume commercial manufacturing and packaging. Offering world-class facilities and expertise as well as an unwavering concentration on service quality, the company is uniquely positioned to serve as the pharmaceutical industry's preferred strategic partner.

During June 2010, Patheon signed an expanded contract manufacturing deal with Merck & Co.

"We have developed a great partnership with Merck and are very pleased that they have chosen to expand it with this contract manufacturing agreement," commented Wes Wheeler, CEO and president of Patheon. "We are 100 percent focused on being the best service provider to our clients. This expanded contract with Merck validates that we are making great progress towards meeting this goal."

The expanded pact solidifies Patheon as a key preferred supplier to Merck. Patheon's projects and services are delivered to Merck from eight global facilities of Patheon.

**Orexigen Therapeutics** Inc. and Patheon announced a long-term deal during March 2010 for commercial manufacturing of **Contrave** (naltrexone HCL sustained release (SR)/bupropion HCL SR) as well as development of future forms of Orexigen products.

"Patheon's manufacturing capabilities provide us a proven platform to help ensure successful market entry and stable commercial supply of Contrave in the event it is approved," says Mike Narachi, Orexigen president and CEO. "This relationship also provides the means to accelerate the development and commercialization of next generation formulations of Orexigen products."

According to Mr. Wheeler, "We have crafted a strategic, long-term partnership predicated on a shared commitment to maximizing the potential of Contrave and **Empatic** and to the mission of addressing the significant health issue of obesity."

Orexigen is a biopharma company concentrated on treating obesity. Orexigen's lead investigational product Contrave has completed Phase III trials. The drug was studied for its ability to help people with obesity initiate and sustain weight loss of at least 5% of their starting body weight in one year.

The product was filed for U.S. regulatory approval during March 2010. The original filing was based on multiple clinical studies that evaluated Contrave in more than 4,500 patients. Orexigen received a Complete Response letter from U.S. regulators on Jan. 31, 2011.

Empatic has completed Phase II clinical development. Both product candidates are designed to act on a specific group of neurons in the central nervous system with the goal of achieving appetite suppression and sustained weight loss via combination therapeutic approaches.



Building upon its strong industry reputation, Patheon released plans for a new corporate strategy during September 2011. The strategy includes: reassessing Patheon's worldwide footprint to enhance capacity use and efficiently focus continuing capital investment on core, strategic businesses; accelerating operational excellence programs in the Commercial and PDS businesses to increase efficiency, lower cost and better serve Patheon's customers; evolving the existing commercial sites to function as centers of excellence that will concentrate on specific technologies or production types; and investing in the PDS business and expanding its presence in early drug development services.

As part of the strategic worldwide footprint review, the company is considering strategic alternatives for the Swindon, United Kingdom, commercial business. Patheon has received indications of interest for the site. The company's U.K. PDS operations are not expected to be part of any potential deal.

The company is in the process of transferring its Zug, Switzerland European headquarters operations to Patheon's continuing U.K. operations. Patheon intends over time to consolidate its Burlington, Ontario lab facility into the company's Toronto operation.

In connection with the Burlington consolidation, the company plans to seek strategic alternatives for its clinical packaging operation that operates out of this

facility. These initiatives are anticipated to result in additional cost reduction. Costs related to the Zug transfer and Burlington consolidation are not expected to have a material impact on the company's financial results.

"The development of a comprehensive strategy to stimulate growth and increase profitability included a thorough review of our markets, our market position, and our prospects for the future," says James C. Mullen, CEO of Patheon. "Our review confirms that we have built a leading position in our industry and that macro trends are working in our favor. But to capitalize on this position, it is clear that we must aggressively improve the performance of our core operations.

"This is being accomplished by a combination of our existing team and outside consulting support. We will create the premier, customer-focused, contract pharmaceutical development and manufacturing organization in the world. This should enable attractive earnings and cash flow to reinvest in the business and grow over the long-term."

Gross profit for Patheon's third-quarter 2011 (ended July 31, 2011) was \$27.4 million versus \$34.4 million for the same period ended in 2010. The change in gross profit was mainly due to unfavorable foreign exchange impact related to the weakening of the U.S. dollar, higher supplies and maintenance and a reduction of take or pay revenue in the United Kingdom. This was partially offset by the prior years' R&D

investment tax credits in the third quarter, and impact of higher volumes.

PDS revenue during third-quarter 2011 totaled \$34 million compared with \$33.1 million for the same period of 2010. Had the local currency rates remained constant to third-quarter 2010, PDS revenue for the three-month period ended July 31, 2011 would have been \$0.1 million lower than during the 2010 third quarter.

The company expects results from operations during fourth-quarter 2011 to be stronger than those of the third quarter, but will be impacted by continuing consulting expense related to the implementation of Patheon's strategic plan and operating efficiency initiatives.

## PFIZER INC./ PFIZER CENTRESOURCE (PCS)

PCS is a supplier of steroid products and a pharma contract manufacturer that offers a variety of GMP-compliant outsourcing services to meet pharm production requirements. PCS is a separate operating unit within Pfizer Inc., the world's leading research-based pharma company that has extensive capabilities and experience in API and dosage-form manufacturing. A worldwide-networked business, PCS markets APIs, fine chemical intermediates, finished dosage forms and provides analytical and regulatory support.

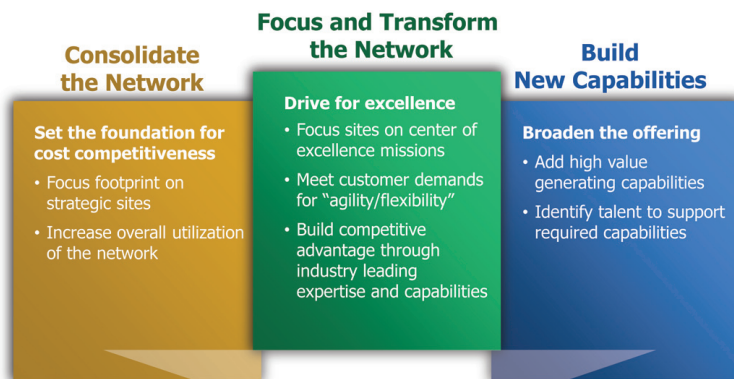
PCS is a part of **Pfizer Global Manufacturing** (PGM), one of the world's pre-eminent supply organizations and an integral part of Pfizer Inc. PCS provides customers with access to PGM's capabilities in steroid active pharmaceutical ingredients; steroid intermediates; custom fermentation; and aseptic/sterile dosage-form manufacturing.

According to the company, PCS offers customers a consistent, reliable and experienced resource for the contract manufacturing of high potency oral solid forms and sterile injectables; custom fermentation and bioprocessing services. PCS is a respected, established contract manufacturer with access to state-of-the-art capabilities and the expertise to handle complex formulations and requirements. The business services concentrate on high-value products with a technology and quality requirement differentiation.

A factor that sets PCS apart from other aseptic filling contractors is the company's access to the advanced technology infrastructure and broad technology

## The CMO Strategy Builds on Three Pillars

### The CMO Strategy



Source: Patheon

Exceed customer requirements for reliable quality, flexibility and speed, at competitive prices

portfolio of PGM. PCS can manage complex projects efficiently with the support of skilled and experienced teams at different PGM sites.

Aseptic/sterile production and injectable manufacturing processes require a significant investment in terms of expertise, equipment, process, technology and quality control. Pfizer facilities and expertise can create a cost-effective solution. PCS can accommodate many sterile project types ranging from lyophilized (freeze-dried) and aseptic filling to different vials, including **Act-O-Vial**, and pre-filled syringes to blow/fill/seal services. PCS offers development-scale and commercial-scale production capabilities.

With access to Pfizer's extensive plant network, PCS says it makes a high-quality sterile manufacturing partner. Pfizer's state-of-the-art capabilities, full technology transfer, process optimization and validation, demonstrated quality standards, competitive costs and dedicated technical and customer service teams enable PCS to handle complex pharma and biopharma formulations.

Throughout the extensive network of PGM sites, PCS offers an extensive array of common technologies, bioprocess technologies and unique drug-product presentations. As Pfizer invests to develop innovative formulations and state-of-the-art facilities, PCS grows in its ability to offer technological advantages versus competitors.

Beyond standard product formulations, there are many examples including Act-O-Vial, the dual chamber system for lyophilized products developed by Pfizer that tremendously simplify the handling by end-users in emergency situations. Similarly, Pfizer has created **Cytosafe**, an innovative plastic vial designed for toxic oncology products to increase safety use. Pfizer has extensive expertise in Blow/Fill/Seal technology, which enables PCS to offer plastic ampoules and bottles in different sizes.

Pfizer's lyophilization expertise is extremely valuable to PCS customers, according to the company. Through many years of experience, Pfizer's technical experts have demonstrated their ability to optimize freeze-drying cycle times and improve costs for PCS customers. Pfizer's sterile manufacturing infrastructure enables PCS to offer large-volume capacity covering an extensive array of complex pharmaceutical products including ster-

oids, biologicals and highly potent substances.

PCS reported robust demand during January 2011 for the company's suite of highly potent drug product development and manufacturing services. As a technical leader in solid dosage forms, PCS' analytical, technical, regulatory, developmental, manufacturing and packaging support encompasses the specialized arena of highly potent solid oral dose drug products.

According to PCS President Michael Kosko, the breadth and popularity of the company's highly potent drug product services speaks to the worldwide industry trend toward outsourcing and away from capital investment in high containment manufacturing.

"We're seeing strong outsourcing demand across the specialized realm of highly potent solid oral dosage forms, from development, clinical and commercial supplies to scale-up and commercial transfer," Mr. Kosko commented. "There's clearly a need for the collaborative, flexible and expert highly potent drug product services we provide."

PCS offers large-scale GMP fermentation capabilities drawing upon Pfizer's long-standing experience with advanced fermentation processes, a history of manufacturing innovation dating to World War II, D-Day, and the company's efforts to supply Allied Forces with penicillin.

Pfizer was honored by the **American Chemical Society** (ACS) for its development of deep-tank fermentation, which allowed for the mass production of large

quantities of penicillin for use in World War II. The process was designated a National Historic Chemical Landmark in a ceremony held during June 2008 in New York.

The company's early technological advances in applying deep-tank fermentation for citric acid and gluconic acid resulted in significant breakthroughs in manufacturing antibiotics including streptomycin, **Terramycin**, and penicillin. Due to the company's large-scale fermentation capabilities, by March 1944 Pfizer was producing more penicillin in one month than it had in all of 1943. According to the ACS, most of the penicillin that went ashore with Allied forces on D-Day stemmed from Pfizer's facility in Brooklyn.

In keeping with its past innovations in fermentation, Pfizer's Kalamazoo, Mich., facility is the company's Center of Excellence in Fermentation. Leveraging this legacy and expertise in custom GMP fermentation, PCS delivers these services to customers worldwide. The company continues to invest in the know-how, equipment, processes, and quality-control protocols for even the largest, most complex GMP fermentation projects.

On May 18, 2010, Pfizer Global Manufacturing announced plans to reconfigure its global plant network to create a fully aligned manufacturing and supply organization from the combined networks of Pfizer and **Wyeth**. This implementation of the first phase of Pfizer's previously announced Plant Network Strategy consists of recommendations to cease operations at eight manufacturing plants in Ireland, Puerto Rico, and the United States

The screenshot displays the PfizerCentreSource website. At the top, the Pfizer logo is on the right, and the PfizerCentreSource logo with the tagline "Partnering with our customers for a Healthier World™" is on the left. A navigation bar includes links for Home, Library, and Contact Us. Below this is a main menu with tabs for Company, Fine Chemicals, Contract Manufacturing (which is selected), and Working With Us. The Contract Manufacturing section features a sub-header "Contract Manufacturing Capabilities" and a descriptive paragraph. Below the text are three featured services, each with an icon and a "read more" link: "Sterile Drug Product Manufacturing" (with a vial icon), "Custom Fermentation" (with a large fermenter icon), and "High Potency" (with a laboratory flask icon). At the bottom of the page, there is a copyright notice for 2004-2011 Pfizer Inc. and links to Terms of Use, Privacy Policy, and Sitemap.

by year-end 2015, as well as to reduce operations at six other sites in Germany, Ireland, Puerto Rico, the United Kingdom, and the United States.

The intended reductions will increase manufacturing efficiency and lower costs by more effectively using resources and technology, improving plant processes, eliminating excess capacity, and better aligning production with market demand. These changes will amount to a worldwide reduction of about 6,000 jobs in the next few years. Product transfers will expand the roles of various plants in Pfizer's manufacturing network.

The proposals set forth in this announcement are subject to compliance with all local legal and regulatory obligations, including the obligation to inform and/or consult with labor organizations, works councils, trade unions and employee representatives.

"The restructuring of our global plant network is critical to our efforts to remain competitive so that we can continue to meet patient needs and expand the access and affordability of our medicines," says Pfizer Nat Ricciardi, president of Pfizer Global Manufacturing. "Nevertheless, today's announcement is very difficult to make because of its impact on our colleagues.

"We have a tremendous global workforce and some of the best manufacturing facilities in the industry. But we must continue to adjust to the fast-changing and extremely competitive environment in which we operate. That means realigning our network and reducing our manufacturing capacity so that we can position Pfizer for the next phase of growth across biopharmaceuticals and our diversified business portfolio."

The announcement was the culmination of an intense half-year evaluation of plants that manufacture aseptic (injectable), solid dose, and biotech medicines, as well as consumer healthcare products.

As of May 2011, Pfizer intended to discontinue manufacturing operations during the next 18 months to five years at three solid-dose sites that manufacture tablets and capsules: Caguas in Puerto Rico; Loughbeg in Ireland; and Rouses Point, N.Y. Wyeth had previously announced in 2005 that the company would exit and sell the Rouses Point site.

Pfizer intends to phase out pharma solid-dose manufacturing at Guayama,

Puerto Rico. That facility will expand its Consumer Healthcare operations.

Although Pfizer's biotech portfolio continues to grow significantly, the company proposes changes at its facilities that manufacture vaccines and large-molecule medicines to improve efficiencies, capitalize on process and productivity improvements and new technology, and to simplify the supply chain. Pfizer intends to exit operations in Shanbally, Ireland, as well as biotech manufacturing in Pearl River, N.Y. Plants in Sanford, N.C., Andover, Mass., and Havant, United Kingdom, also were expected to see reductions.

Pfizer intends to halt production of consumer healthcare products at its facilities in Richmond, Va., and Pearl River. The Pearl River site remains Pfizer's Center of Excellence for Vaccine Research and Development, as previously announced. Consumer Healthcare R&D will continue in Richmond. In Pearl River and Richmond, research and development jobs will not be affected by the planned manufacturing exits. The timing of specific exits depends upon the complexity of operations, the amount of time necessary for product transfers, and other business requirements.

Pfizer Global Manufacturing operates about 78 plants internationally with a workforce of roughly 33,000 colleagues. PGM is one of the preeminent biopharma supply organizations globally.

Pfizer Manufacturing activities in India are part of PGM. Pfizer's purpose is to continually supply the demand of the company's portfolio of products with the highest regard for quality and to be 'a strategic asset to Pfizer.'

PGM has manufacturing operations at 86 locations around the globe supporting every major market. PGM supports Pfizer's business objective of meeting the demand for Pfizer products and is used as a strategic resource in launching drugs and products quickly after regulatory approval has been attained. Using state-of-the-art equipment and cutting-edge technology, manufacturing colleagues work hand in hand with R&D teams to provide the highest-quality products to the marketplace.

The use of state-of-the-art equipment, machinery and computer systems makes PGM the leader and pioneer of many innovative technological breakthroughs in drug delivery systems. These include the

**GITS** (Gastro-Intestinal Tablet System) technology.

## **PIRAMAL HEALTHCARE LTD.**

A **Piramal Group** company, Piramal Healthcare is a worldwide integrated company that provides solutions to unmet medical needs. The company has had a growth track record exceeding 29% CAGR since 1988. Piramal Healthcare generated consolidated revenue of \$656 million during fiscal-year 2009.

Piramal Healthcare has ranked No. 4 in the Indian market with an extensive product portfolio spanning several therapeutic categories. Piramal Healthcare is one of the largest custom manufacturing companies with a worldwide footprint of assets throughout North America, Europe and Asia.

The company's state-of-the-art manufacturing facilities strategically located worldwide produce quality medicines at affordable prices. Piramal Healthcare's Hyderabad plant is the only one in India to have FDA approval for the entire facility and is also accredited and approved by MCA of UK, TGA of Australia and the European and Canadian Drug Authorities. The company's Pithampur plant is accredited by organizations such as Allergan, **Novartis**, **Solvay** and **IVAX**.

**Pharma Solutions** (PPS), a unit of Piramal Healthcare, is a top worldwide Pharmaceutical Contract Development and Manufacturing Organization offering services across the entire drug lifecycle – from development and commercial manufacturing to off-patent supplies of API and formulations.

## **RECIPHARM AB**

A leading contract development and manufacturing organization, Recipharm has headquarters near Stockholm, Sweden, and has 2,000 employees. Recipharm operates 12 development and manufacturing facilities located in Sweden, France, the United Kingdom, Spain and Germany.

Recipharm is one of Europe's top pharma Contract Development and Manufacturing Organizations. The company's Manufacturing Services supply hundreds of different products in various dosage forms such as solid dose, semi solids, steriles (liquids and freeze dried), beta-lactams, hormones, dry-powder metered



dose inhalers, and oral liquids and granulates. Recipharm 2010 sales totaled SEK 2.23 billion.

The company's Pharmaceutical Development Services group offers services varying from straight-forward clinical supply through to more complex product development and formulation. Formulation development, clinical supplies, analytical development, stability studies, packaging development and raw material selection each serve as core activities. Founded during 1995, privately owned Recipharm has grown organically as well as via acquisition.

According to the company, Recipharm prides itself on the manufacturing expertise offered to customers. With a pedigree including facilities acquired from Pfizer, Solvay and **AstraZeneca**, customers can be assured that their project will be in the hands of some of the best trained and talented individuals.

**RecipharmCobra Biologics** has operated as a specialist division of Recipharm AB. RecipharmCobra Biologics has a proven track record in the development and manufacture of monoclonal antibodies, recombinant therapeutic proteins, viruses and DNA along with cell-based vaccines and therapies for clinical studies and regulatory approvals. RecipharmCobra Biologics has two GMP-approved production facilities from which a comprehensive service is provided, such as cell-line development, process and analytical development, GMP manufacture, coordination of formulation and fill/finish activities, and release to clinic.

RecipharmCobra Biologics and **KAHR Medical Ltd.** announced a continuation of their partnership deal during July 2011. KAHR Medical develops novel drugs based on the **Signal Converter Proteins** (SCP) technology for treating cancer and autoimmune diseases. RecipharmCobra Biologics will continue to advance **KAHR-102** for future preclinical and clinical testing using its **maxXpress** service.

"We are extremely pleased that our development partnership continues with KAHR," noted Peter Coleman, general manager at RecipharmCobra Biologics. "Our partnership with KAHR has strengthened over the years due to the strong working relationship between both technical teams and we look forward to its continuation. It is an endorsement of the working relationship we invest in with our customers."

According to Dr. Noam Shani, CEO of KAHR Medical, "It has been a pleasure working with RecipharmCobra Biologics over the years and we have enjoyed the interaction and responsiveness of its team. We hope to build on our successful partnership with the fast-track development of KAHR-102."

SCP molecules mark a paradigm-shift in protein-based drug development because they integrate two functional sides within one molecule. Unlike conventional biologicals that only have one functional side, the two active sides of SCP drugs enable multi-functionality. These molecules are able to block or induce two cell signals and convert signals sent from one cell to another.

KAHR Medical is a portfolio company of **Hadasit Bio-Holdings**. KAHR develops novel drugs based on the SCP platform technology for treating cancer and autoimmune diseases.

RecipharmCobra Biologics announced on Feb. 2, 2011, that the European patents on its '**Xer-cise**' genetic engineering technology have been granted. Xer-cise allows bacteria to be genetically modified without leaving antibiotic resistance genes on their chromosomes. Xer-cise therefore overcomes problems resulting from the bio-safety risk of potentially spreading antibiotic resistance to pathogens, the restricted amount of available antibiotic resistance genes and the competing use of such genes on plasmids.

Xer-cise uses Xer recombinases, which are naturally present in almost all bacterial species. Genetic modification is attained by inserting a DNA cassette containing an antibiotic resistance gene, so that modified bacteria can be identified by their ability to survive in the presence of the antibiotic. By placing the sites recognized by Xer recombinases (dif sites) on either side of the antibiotic resistance gene, the recombinases excise the gene as cells are eventually grown with no antibiotic present.

Xer-cise has been demonstrated in bacteria such as *Escherichia coli*, *Salmonella*, *Bacillus subtilis* and *Mycobacterium*, and is applicable to many other bacteria.

"Xer-cise has enabled molecular biologists at RecipharmCobra and elsewhere to rapidly construct bacterial strains that are not antibiotic resistant, and are therefore advantageous for the commercial production and delivery of biologics," stated Simon Saxby, VP of biologics at

RecipharmCobra Biologics. "We anticipate that this technology will greatly simplify and accelerate the genetic modification of many species of bacteria."

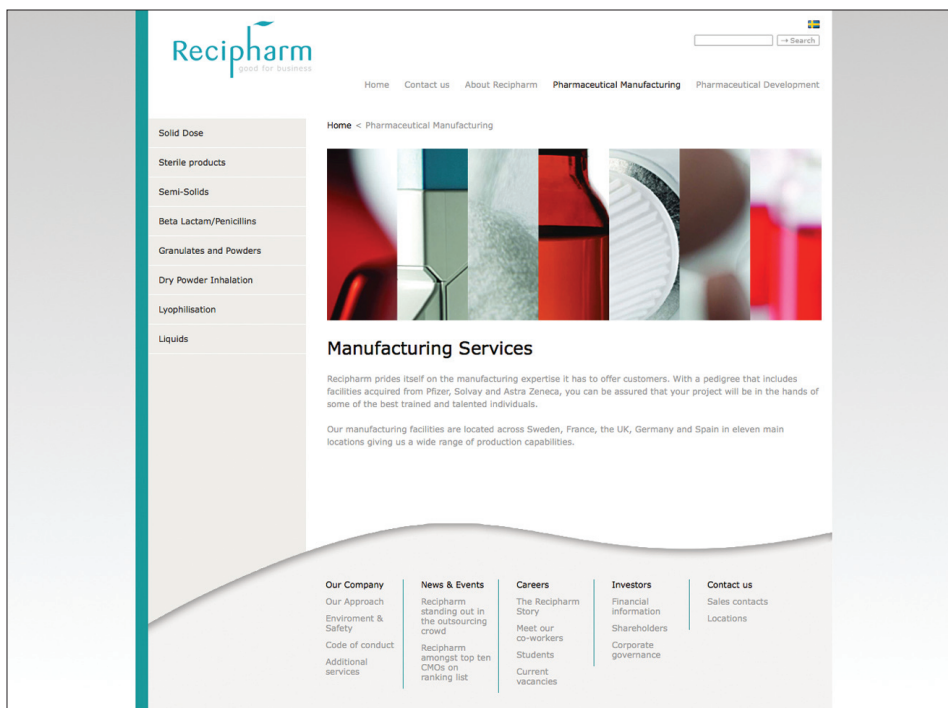
When bacteria are genetically modified, an antibiotic resistance gene is inserted into the chromosome adjacent to the modified region to allow bacterial cells that have undergone the mutation to be identified, as these cells will form colonies on agar plates containing the antibiotic. This can lead to cells that contain multiple antibiotic resistance genes that reduce their versatility for replicating plasmids, which are circular DNA molecules that additionally contain antibiotic resistance genes along with a gene that produces the required protein.

A limited amount of genetic modifications can be undertaken in the same cell due to a restricted number of available antibiotic resistance genes. There is therefore a necessity to remove the chromosomally inserted antibiotic resistance gene. Existing strategies require insertion of another plasmid following the chromosomal modification. This plasmid expresses a recombinase (such as Cre or Fli) that recognizes sites flanking the antibiotic resistance gene and excise it from the chromosome. The plasmid then is required to be removed from the cell. This process therefore introduces more stages, and there are many species of bacteria for which a suitable recombinase plasmid has not been developed.

The Xer-cise technology uses native Xer recombinases that typically function to restore the chromosomal and plasmid dimers created by the enzyme RecA back to monomers. In terms of bacteria, the Xer recombinases are ubiquitous.

An antibiotic resistance gene is flanked by 28 base-pair long dif sites, which in turn are flanked by chromosomal target homology. This cassette is constructed on a plasmid and linearised, or assembled by PCR, and transformed into the target bacterium. Homologous recombination carried out by other enzymes precisely inserts the gene cassette into the chromosome. Gene integration mutants are chosen on agar plates containing the antibiotic. These are then cultured in antibiotic-free medium. The Xer recombinases recombine the two dif sites to one location, thereby excising the intervening antibiotic resistance gene to generate the new mutant strain.

After the successful acquisition of **Co-**



**bra Biomanufacturing** plc, Recipharm announced during February 2010 that the company was combined with the existing Biologics activities based in Sweden. The integrated business became Recipharm-Cobra Biologics.

The combination of the two companies' capabilities created a comprehensive biological service offering spanning cell line development, analytical and process development and GMP production of recombinant proteins, DNA, viruses and cell products for Phase I, II and III studies. This together with fill-finish and formulation capabilities has provided customers with a one-stop shop concept for biologics outsourcing needs.

Then on June 30, 2011, **Cobra Biologics Holding AB** completed the acquisition of Recipharm AB's shares in the operating companies of RecipharmCobra Biologics located in Keele, United Kingdom and Södertälje, Sweden. Cobra Biologics Holding is a new company created for the purposes of further developing this business. The shareholders in the new company consist of the management team, **Zentricity Holding AB** and Recipharm.

"Following a strategic review we have decided to concentrate resources on our core business of pharmaceutical development and commercial manufacturing services for the time being," according to Thomas Eldered, CEO of Recipharm. "In the long term, we still believe the contract development of biologics is an ex-

tremely important business and this transaction will allow us to both retain a stake in and maintain close links with Cobra Biologics. They will continue to be an important partner in this sector and we wish the team every success for the future."

Peter Coleman, previously general manager of RecipharmCobra Biologics and then appointed CEO of Cobra Biologics Holding, noted, "Our new shareholders allow us to remain financially stable whilst focusing on our core business of biologics contract development and manufacturing. We also have the added advantage of continuing our relationship with Recipharm AB."

Cobra Biologics Holding continues to trade under the RecipharmCobra Biologics name.

## ROCHE

Basel, Switzerland-based Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech entity with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. The company is additionally the global leader in *in-vitro* diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management.

Roche's personalized healthcare strategy is intended to provide medicines and diagnostic tools that allow for tangible improvements in patient health, quality of life

and survival. For 2010, Roche had 80,000-plus employees and invested more than 9 billion Swiss francs in R&D. The group generated sales of 47.5 billion Swiss francs.

U.S.-based **Genentech Inc.** is a wholly owned member of the Roche Group and a leading biotech company. Roche has a majority stake in **Chugai Pharmaceutical Co.**, one of Japan's leading pharmaceutical players.

The Roche Group and the **International Chemical Investors Group (ICIG)** entered into a deal during August 2011. ICIG acquired **Roche Colorado Corp.**, which includes Roche's pharma production facility in Boulder, Colorado. ICIG acquired the Roche affiliate company in Boulder with its technical development and small-molecule manufacturing capabilities. Roche Colorado has a workforce of nearly 265 employees.

ICIG is operating the Boulder site – which was renamed **Corden Pharma Colorado Inc.** effective Sept. 1, 2011 – as part of its pharmaceutical business within the **Corden Pharma** organization. Corden Pharma is the pharma arm of ICIG investments. Corden Pharma Colorado is supplying Roche with a number of active pharmaceutical ingredients that the Boulder site was already producing.

"Selling the Boulder site to ICIG will secure a reliable supplier to meet Roche's demand for commercial scale peptides and other medicinal compounds," stated Dr. Georg Wiebecke, head of chemical manufacturing for Roche. "We also are pleased to identify a buyer that will create a sustainable future for the Boulder site."

Roche's Boulder facility is a global leader in producing therapeutic peptide compounds, having pioneered large-scale synthetic manufacturing technologies. The Boulder facility maintains excellent capabilities in the production of complex small molecules and highly potent compounds.

"By purchasing the Boulder facility, we position ourselves for a commanding presence in the contract peptide manufacturing industry," according to Dr. Wolfgang Niedermaier, president of Corden Pharma. "We are excited to expand the market for the Boulder site's unique technical capabilities, attracting additional API production opportunities that will build on its existing portfolio of Roche products and other pharmaceutical contract business."

## ROYAL DSM NV

Royal DSM is a worldwide science-based company active in health, nutrition and materials. By connecting its unique competencies in Life Sciences and Materials Sciences, the company is driving economic prosperity, environmental progress and social advances to create sustainable value for every stakeholder. DSM delivers innovative solutions that nourish, protect and improve performance in worldwide markets including food and dietary supplements, personal care, feed, pharmaceuticals, medical devices, automotive, paints, electrical and electronics, life protection, alternative energy and bio-based materials.

DSM's 22,000 employees deliver annual net sales of about 9 billion euros.

On May 3, 2010, **DSM Biologics** announced the signing of preliminary deals to enter a partnership with the Australian Governments (Queensland State Government and the Commonwealth of Australia) to design, build and operate the first major Australia-based mammalian biopharma manufacturing facility. This site will be based in Brisbane.

DSM Biologics is a business unit of **DSM Pharmaceutical Products** (DPP), a worldwide business providing cGMP custom manufacturing services across all facets of the pharma arena including small-molecule API and intermediates manufacturing, fill/finish of parenteral and solid dosage forms, and large-molecule drug substance production and associated technologies. DPP is a business unit of Royal DSM.

The 70,000-plus-square-foot facility will offer mammalian process development and cGMP clinical and commercial manufacturing services. DSM Biologics will employ its worldwide expertise and portfolio of proprietary technologies to offer Australia and clients from across the globe state-of-the-art, world-class contract manufacturing services.

"We are extremely honored to be selected by and partnering with the Australian Governments, in particular with the Queensland State and the Commonwealth Governments to bring Australia its first major cGMP mammalian contract manufacturing organization (CMO)," according to Karen King, president of DSM Biologics. "This offering will be an important continuation and expansion of the services we currently provide out of our

facility in Groningen, The Netherlands. Clients will have the added advantage of being able to choose between standard technology processes or Royal DSM's proprietary XD and DSP optimization technologies.

"The services offered at the site will support all mammalian cell lines and process technologies including standard CHO-based systems and the **Per.C6** cell-line technology, to which DSM has co-exclusive licensing rights for proteins and mAbs, together with the Dutch biotech company Crucell."

The Australian Governments (the Queensland Government and the Commonwealth of Australia) is providing the full financial funding for the facility, which is part of the Queensland 10-year Biotechnology Strategic Plan. DSM is providing no capital but will provide technological expertise to design and set up the facilities, and will employ the company's proprietary technologies in its operation.

The biotechnology industry in Australia is rapidly growing with 400-plus companies engaged in development activities and an estimated A\$ 60 million in yearly CMO activity fees being exported out of the country because of a lack of a local CMO.

The new biologics manufacturing facility is expected to be commissioned and operational during 2013. The facility is being constructed in Brisbane within the Queensland new **Translational Research Institute**. This one-stop-shop is for discovery, production, clinical testing and manufacturing of new biopharmaceuticals.

**BioPharmaceuticals Australia** (BPA) is responsible for the overall initiative on behalf of the Queensland Government. BPA chose DSM Biologics to operate the facility.

"Royal DSM is the ideal partner for this important initiative," noted David Hughes, CEO of Biopharmaceutical Australia. "We were impressed with the experience, expertise and technologies of DSM Biologics. Their vision of the 'Biologics Plant of the Future' matches ours and Australia's first facility will have state-of-the-art capabilities. Australian biopharmaceutical developers will be able to locally manufacture new drug candidates to international standards in preclinical, clinical and commercial phases. This is an important step for our industry."

"We see the addition of the Brisbane

facility as an important element in our DPP strategy," stated Bob Hartmayer, CEO of DPP. "DPP is committed to providing our clients world-class custom services around the globe. Biologics is an important growth segment of the pharma industry and DSMB will now be positioned to serve its clients at all phases of development and commercialization. We are particularly pleased to be developing and operating the facility in partnership with the Australian Governments (in particular the Queensland State and the Commonwealth Governments)."

DSM Biologics provides and develops technologies that are relevant for optimized mammalian cell culture processes. Examples include the proprietary **XD Technology** for use with mammalian cell lines. The "XD process" leads to very high cell densities within the bioreactor that can result in maximum productivity using readily available equipment. DSM's manufacturing services provides companies with a turn-key biologic manufacturing solution that reduces costs, risks and time to market.

**Crucell Holland NV's** PER.C6 technology platform has been developed for the large-scale manufacture of biopharmaceutical products such as recombinant proteins including monoclonal antibodies. Compared with conventional production technologies, the strengths of PER.C6 technology lie in its excellent safety profile, scalability and productivity under serum-free culture conditions.

DSM Pharmaceutical Products is a worldwide provider of high-quality custom contract manufacturing and development services to the pharma and biopharma industries. DSM contract manufacturing services include: chemical development, registered intermediates, registered starting materials, APIs, mammalian cell production of monoclonal antibodies and proteins, formulation development, clinical-trial manufacturing and finished dose form manufacturing of solids, semi-solids, and scheduled drugs, aseptic liquid and lyophilized products.

DSM Pharmaceutical Products and **Codexis** Inc. (Nasdaq: CDXS) announced an enzyme supply pact during January 2011.

The deal grants DSM rights to use Codexis' custom biocatalysts and services, and secures supply of the company's enzymes for commercialization of sustainable enzyme-based pharma manu-



facturing routes developed by DSM's **InnoSyn** route-scouting services.

Codexis technology allows for the development of new efficient manufacturing processes for APIs and intermediates, which reduce cost and environmental waste. Codexis technology is used at major pharma and chemical companies globally including Merck, Pfizer and Teva.

The DSM InnoSyn route-scouting team provides value creating solutions to its customer by integrating cutting-edge enzyme technology with the full range of advances in synthetic methods. These include homogeneous catalysis, modern organic synthesis and continuous chemistry, for instance micro reactors. The new routes lead to increased efficiency of the manufacturing processes while reducing cost and environmental impact.

"Codexis has a proven track record over nearly 10 years in bringing innovation and manufacturing efficiency to our partners," stated Joseph Sarret, M.D., president of Codexis Pharmaceutical Services and Enzyme Products. "We are pleased to collaborate with DSM in the field of biocatalysis to enable cost-effective manufacturing process at commercial scale."

According to Oliver May, Ph.D., corporate scientist and business manager for DSM's InnoSyn route scouting services, "One important success factor for implementing enzymatic routes is access to a diverse range of biocatalysts. DSM is continuously expanding its unique enzyme collection of more than 3,000 enzymes by in-house developments as well as innovative partnering models. We are very pleased to collaborate with Codexis whose expertise in enzyme development perfectly matches with DSM's capabilities to identify, develop and implement efficient enzymatic routes."

Codexis is a clean technology company that develops optimized biocatalysts. These catalysts make industrial processes faster, cleaner and more efficient. Codexis' technology is commercialized with many top worldwide pharma companies and in development for advanced biofuels with **Shell**. Other potential markets consist of carbon capture, water treatment and chemicals.

Royal DSM agreed in December 2010 to acquire all the outstanding shares of common stock of health nutrition company **Martek** for \$1.09 billion. The deal is expected to provide DSM with new oppor-

tunities in the infant nutrition segment as well as food and beverage and dietary supplements. The acquisition provides a platform for DSM to enter the growing Omega-3 and Omega-6 arena through Martek's microbial DHA and ARA products.

DSM anticipates leveraging its worldwide nutritional infrastructure to channel and accelerate the growth of these products into other regions, applications and market segments beyond Martek's existing U.S.-based position in infant formula ingredients and growing position in food and beverage and dietary supplement applications.

DSM and Martek have had a long-standing relationship. DSM supplies Martek with the key base material for its ARA product.

DSM has complementary intellectual property to the wide array of patents and intellectual property Martek owns. This will additionally extend the competitiveness of the joint company's proprietary products.

DSM should benefit from Martek's acquisition of **Amerifit**, a consumer business for branded dietary supplements. This will be used as an additional marketing channel for Martek as well as DSM ingredients.

Martek's algal and other microbial-based biotech platform and its algal technology pipeline that complements DSM's biotech portfolio is expected to deliver new nutritional and non-nutritional (industrial) growth opportunities. The transaction closed during February 2011.

## DSM PHARMACEUTICAL PRODUCTS

As the custom manufacturing and technology resource within Royal DSM, DPP provides and develops technologies for optimizing mammalian cell culture processes. Examples include the proprietary XD Technology for use with mammalian cell lines. The XD process creates very high cell densities within the bioreactor, leading to significant output enhancements of 5 to 15 fold via commercially available equipment.

In the downstream processing area, DSM's proprietary **Rhobust** technology represents the next generation in expanded bed chromatography (EBA), using cross-linked agarose beads with Tungsten Carbide to increase the particle density. Rhobust is applied as a direct

capture and clarification step for mammalian and microbial harvest to increase yields, reduce the amount of unit operations and reduce process cost.

During June 2011, DSM expanded its innovative biomanufacturing technology portfolio with the launch of the **Kremer Method**. This method further optimizes the downstream processing of proteins and monoclonal antibodies.

"DSM is continually innovating to advance the world of biopharmaceutical manufacturing to the next level," Ms. King noted. "We are pleased to announce the introduction of the new DSP optimization technology, the Kremer Method. The combination of the Kremer Method with our other proprietary technologies significantly reduces the overall costs and processing times of biopharmaceuticals while maintaining high product quality."

Rolf Douwenga, VP of Global R&D for DSM Biologics, added, "The Kremer Method is a valuable addition to the platform of DSM's technologies addressing the full range of mammalian cell culture systems for protein and monoclonal antibody production. The method uses in-line dilution to streamline the purification and polishing of mAbs into one single continuous step in a flow-through mode. This eliminates the need for storage and reduces the amount of material usage such as buffers and resins. The Kremer Method reduces processing and preparation times, labor requirements and the cost of goods and presents an ideal solution to achieving cost effective processing."

After the capture step in conventional downstream processes, additional purification and polishing of proteins are traditionally performed as two separate batch unit operations. With the Kremer Method, these steps are streamlined to work as a single unit operation. Using this method; Host Cell Proteins (HCPs) were removed to a level below the limits of detection; complete aggregate removal was observed comparable to current state-of-the-art processes; and recoveries of 90% were attained. Several patent applications have already been submitted.

XD and Rhobust are registered trademarks of DSM.

During February 2011, DSM Biologics announced the signing of a contract with **NKT Therapeutics Inc.**, a biotech company that concentrates on developing therapeutics based on unique immune cells called natural killer T (NKT) cells.

The contract covers the process development and cGMP manufacturing by DSM of the company's lead product **iNKT mAb**. NKT cells serve as a focal part of the human immune system. Upon exposure to microbial and viral pathogens, NKT cells secrete high levels of specific cytokines that stimulate the immune system to eliminate pathogens.

"We are delighted to be working with NKT Therapeutics, based in the US, from our European biomanufacturing operations located in Groningen, the Netherlands," Ms. King stated. "We are truly honored to be supporting their first clinical program from our cGMP operations. With a range of mammalian bioreactor sizes from 50 liters up to 1,000 liters and, process and analytical development capabilities, DSM offers development and production flexibility combined with economy."

According to Dr. Robert Mashal, president and CEO of NKT Therapeutics, "For NKT, advancing our lead program into cGMP manufacturing marks a significant milestone for the company, and we are certain we have found the right partner in DSM."

NKT Chief Scientific Officer Dr. Alem Truneh said, "Manipulation of NKT cells is an exciting new therapeutic strategy. Following on the heels of our successful studies in primates, we are on track to file an IND next year. DSM provides us with numerous options and flexibility in our manufacturing programs."

Financial terms of the deal were not disclosed.

NKT Therapeutics is a privately held biotechnology company concentrating on developing therapeutics based on unique immune cells called natural killer T (NKT) cells. The corporation's mission is to use its expertise to develop a pipeline of first-in-class NKT-based therapeutics. These therapeutics are intended to treat asthma, cancer, infectious diseases, autoimmune diseases, and dermatitis.

#### THERAPURE BIOPHARMA INC.

Therapure is an integrated biopharma company that develops, manufactures, purifies and packages therapeutic proteins. Therapure applies scientific, manufacturing and downstream purification expertise with an intimate understanding of advanced biology, complex proteins, and regulatory processes to develop effective and innovative solutions to ad-

vance products from discovery to market for its clients.

The contract development and manufacturing organization (CDMO)'s Health Canada-licensed 130,000-square-foot facility includes manufacturing, research and quality control labs and a cGMP warehouse. The facility is built to FDA, EMEA, MHRA and Health Canada standards for the aseptic handling and purification of proteins.

On July 15, 2010, Therapure inked a deal to provide fill/finish services for **OPK Biotech LLC**, a biotech company located in Cambridge, Mass. Therapure is providing fill/finish services to support development for one of OPK's therapeutic products, which is used to increase oxygen transport.

OPK develops and brings to market innovative products in the class of oxygen therapeutics. Using proprietary technology, two products have been developed and manufactured: Hemopure (HBOC-201) (hemoglobin glutamer - 250 (bovine)) for human use and Oxyglobin (HBOC-301) (hemoglobin glutamer - 200 (bovine)) for veterinary use.

"We are proud to have been chosen by OPK as its partner to provide fill/finish services," says Thomas Wellner, president and CEO of Therapure. "Not only does Therapure have a deep understanding of the HBOC market, it also has demonstrated market leading expertise with fill/finish services."

According to Zafir Zafirelis, COO of OPK, "OPK was seeking a service provid-

er with scientific expertise in oxygen therapeutics. This project is important to OPK's product line and we are confident in Therapure's ability to meet our needs."

On June 30, 2010, Therapure announced an accord under which the company will provide development services for **DiaMedica Inc.**, a biopharma company based in Winnipeg, Manitoba, Canada. Therapure will provide cell line development and protein production services to support clinical development for one of DiaMedica's products. The protein may be used for treating diabetes and neurological disorders.

DiaMedica concentrates on developing treatments for diseases with significant unmet need such as diabetes and neurological diseases. The Canada-based biopharma company has several compounds in various stages of development. DiaMedica was chosen as one of Canada's Top 10 life science companies in 2007/2008 and 2008/2009 by the **Ottawa Centre for Research and Innovation (OCRI)**.

"We are proud to have been chosen by DiaMedica as its partner to provide cell line development and protein production services" Mr. Wellner says. "Therapure has performed similar services for a number of clients and has demonstrated market leading expertise."

DiaMedica CEO Rick Pauls stated, "DiaMedica was seeking a cell line developer with the scientific expertise to handle this specialty product. This project is important to DiaMedica's future success

### Global societal trends drive DSM's markets



Source: Royal DSM



and we are confident in Therapure's ability to meet our needs."

On June 21, 2010, Therapure agreed to provide manufacturing services for **ProChon Biotech Ltd.**, a specialty pharmaceutical player located in Israel with an executive management team situated in Woburn, Mass. Therapure is providing services to support clinical manufacturing for one of ProChon's products, which may be used for articular cartilage regeneration.

Privately owned ProChon is concentrated on providing products for articular cartilage regeneration. The biotech company's expertise in modulating the fibroblast growth factor (FGF) allows ProChon to create more effective solutions for tissue regeneration.

"We are pleased to have been chosen by ProChon as its partner to provide clinical manufacturing services" Mr. Wellner says. "Therapure has performed these services for a number of clients and has demonstrated market leading expertise."

According to ProChon CEO Patrick O'Donnell, "We believe that Therapure has the most relevant expertise for successful implementation of our manufacturing requirements."

Therapure announced a contract with **Viron Therapeutics Inc.** of London, Ontario, Canada to provide fill/finish services. Therapure is providing two fill/finish runs for development-stage products in support of continuing clinical trials being conducted by Viron.

A clinical-stage biopharma company, Viron is pioneering the development of viral proteins to treat and prevent human inflammatory disorders. Viral proteins represent a revolutionary new class of medicines. By harnessing the evolutionary power of viruses and other pathogens to evade the human body's protective inflammatory response, Viron can identify and develop powerful protein therapeutics that have distinct advantages in potency and efficacy versus conventional drug therapy.

"We are pleased to be selected by Viron to provide fill/finish services in support of their clinical program," Mr. Wellner says. "Therapure's Health Canada licensed facility was designed and built to handle biologics and proteins. We look forward to expanding our relationship with Viron going forward."

Viron CEO James Rae noted, "Viron is the first company to successfully advance

a viral protein drug into human testing and we look forward to working with Therapure as we advance the clinical development of our products. Our pipeline of additional compounds in preclinical development, combined with a robust discovery program, strongly positions the Company to be a leader in the discovery and commercialization of bio-therapeutics to treat inflammatory-based diseases. Therapure has demonstrated that they have the capabilities to support our commercialization efforts."

Therapure and **LFB Biomedicaments**, a wholly owned subsidiary of the French biopharmaceutical company **LFB S.A.**, announced on Feb. 1, 2010, the signing of a toll manufacturing deal. Therapure will manufacture key plasma proteins to support an expansion by LFB into plas-

ma-derived medicinal markets around the world.

Therapure is responsible for the manufacture of two major plasma proteins. LFB remains responsible for worldwide regulatory approvals and marketing of these products. Therapure is retrofitting the company's Health Canada-licensed manufacturing facility to accommodate the installation of LFB proprietary technology and processes necessary to meet manufacturing obligations.

The companies expected the facility to be finished during 2011. Qualification and validation process, including regulatory batches, will be conducted in 2012 to complete the regulatory approval process during 2013.

The worldwide market for plasma proteins is projected to increase at a rate of

## Therapure Biomanufacturing Services

### Overview

Therapure is an integrated global Contract Development and Manufacturing Organization (CDMO) offering a complete range of therapeutic protein development and manufacturing services. The company has the ability to provide these services in a fully scalable manner at every stage of the development process.

Therapure has significant scientific expertise and a thorough understanding of advanced biology and complex proteins. This expertise is particularly valuable for solving the technical challenges that smaller biotech companies typically encounter in the manufacture of complex biological products.

### Capabilities

#### Technology Transfer & Process Development

Therapure's technology transfer program is designed to quickly and effectively transfer materials, methods and critical product knowledge from the customer's team to Therapure's. The company's process development expertise will enhance current process or address the requirements of process scale-up.

#### Analytical Development & Testing

With Therapure's fully equipped analytical labs, the company is able to perform in-process and release testing as well as develop product specific analytical assays.

#### Scale Up & cGMP Manufacturing

Therapure has experience manufacturing biologic products from a variety of sources including blood, mammalian and primary cell culture. Therapure has the experience and capability to scale protein production from milligrams to kilograms.

#### Aseptic Fill/Finish & Lyophilization

Therapure is approved by Health Canada for the aseptic fill/finishing of vials. Therapure also performs aseptic filling of preformed IV bags and prefilled syringes in addition to lyophilization at clinical and commercial scale.

#### Support Services

Therapure offers a variety of services from warehousing and distribution to validation support and stability testing that enable customers to start and stay with the company as the project evolves.

*Source: Therapure Biopharma*



6% during the next several years. These proteins extracted directly from human plasma include clotting factors crucial to patients with congenital or acquired bleeding disorders that should be made widely available to these communities.

Even though there are sometimes recombinant alternatives to a selection of these proteins, significant investments of time and money are necessary to bring new sources of supply to the marketplace. Therapure will produce these plasma-derived products through LFB's existing technologies, shortening in this manner the time required to bring the increased supply to market.

"We are proud to have been chosen by LFB as its contract manufacturer to support this important market expansion," Mr. Wellner says. "We will be making a substantial investment in manufacturing capacity to meet LFB's needs and to provide them with a more globally diversified and secure supply chain for these life-saving products."

Pierre-Francois Falcou, head of International Operations for LFB, said, "LFB is engaged in rare diseases management and is developing its manufacturing capacities to provide patients with the specific medicines they need."

According to Christian Béchon, president and CEO of LFB, "Their commitment of time and capital to retrofit their Toronto, Canada facility has made us confident that Therapure will be well positioned to significantly contribute to the global expansion of LFB which include North America for added value proteins."

## UPM PHARMACEUTICALS INC.

Baltimore-based UPM is an independent drug development and contract manufacturer serving the pharma and biotech industries. UPM provides high-quality pharma drug development services such as formulation development, cGMP manufacturing, analytical methods development and stability testing. UPM's history includes successful collaborative interactions with virtual to multi-million dollar companies, providing them with customized product development services and solutions. The company concentrates on drug development for dosages with oral routes of administration, in solid dosage forms including capsules and tablets.

UPM's drug development services are characterized by a core commitment to

meeting clients' objectives with the highest quality while maintaining the most efficient use of time and controlling costs. According to the company, UPM takes enormous pride in supporting pharma companies at every stage of the drug development process.

On Sept. 22, 2011, the company announced plans to expand its existing manufacturing capacity, including an OEB 4 processing room, a low humidity processing suite as well as a unique dedicated **Xcelodose** production facility. The overall expansion will add almost 50% more manufacturing space for existing production.

"To meet our client's growing needs, UPM is making a major capital commitment to enhance client services," stated James Gregory, president of UPM. "In response to an increasing number of requests for production of compounds with more stringent environmental safety requirements, UPM is building a unique suite for handling of manufacturing processes associated with OEB 4 compounds. We are also building a dedicated suite for handling and production of low humidity compounds. Finally, as a leader in providing neat API direct-fill-in-a-capsule services using the latest Xcelodose technology, UPM will be developing a unique segregated four room suite to handle Xcelodose processing and encapsulation activities associated with the 600 and 600S equipment systems. We intend to provide these services under the most strict handling conditions up to and including OEB 4 compounds. With the outstanding service being provided by our skilled R&D, manufacturing, laboratory, and Quality Assurance teams, UPM's business is dramatically growing. This expansion will allow us to keep pace with our clients' needs and continue our commitment to speed and quality in the services we provide."

On Sept. 7, 2010, UPM bought the **Cap-sugel Xcelodose 600 S Powder Micro-dosing System** to meet the growing demand for direct API-in-capsule product requests. The 600 S is a precise powder dispenser able to dose as low as 100 micrograms. With the optional **RH Control Unit** that was additionally purchased, the percentage of relative humidity can be controlled to within 1% of the intended target. This feature allows UPM to process challenging compounds including those that are prone to static, poorly flowing or hygroscopic, while maintaining precise dispensing and product integrity.

Along with the company's previously purchased **Xcelodose 600**, UPM is well equipped for automated, small-scale, low-dose powder handling with minimal waste and shorter drug development delivery times. UPM additionally owns the **MG Planeta 50**, **Bonapace Incap**, **Shinogi Qualifil** and various **Fenton** fillers that provide a wide range and capacity for powder-filling projects.

According to UPM, fully appreciating that time-to-market is critical, the company offers remarkably flexible, affordable and rapid outsourcing services designed to meet clients' specific development and manufacturing needs. UPM clients represent small and large companies within the pharma and biotech arenas as well as academic institutions that concentrate on clinical studies.

## XCELIENCE LLC

Xcelience has provided formulation development, drug preformulation, analytical, and clinical supplies manufacturing to a global client base since 1997. Xcelience is renowned for reliably expediting early development activities to speed potential drugs to clinical trials while applying stage-specific scientific knowledge and experience. According to the company, its unique corporate structure creates project teams that work intensively with each client, bringing an extension of the organization into the Xcelience lab.

On Sept. 7, 2011, the company expanded its clinical-trial supplies manufacturing and packaging capabilities to include four new pieces of equipment and a new fully automated packaging line. To complement existing expertise in matrix tablet delivery systems, the company added a **MG Futura** (capsule-filling machine for powder and pellets), **LCI Multi-granulator MG-55** (extruder), **QJ-230T** marumerizer (spheronizer), and wurster insert (bottom spray) to the existing **Glatt GPCG-3** fluid bed processor. These new additions allow for production, coating and encapsulation of **MUDF** delivery systems.

"The new MG Futura is a great example of our continued commitment to add state-of-the-art technology that delivers real value to our clients," says Theodore Koontz, director of operations for Xcelience. "The MG Futura improves upon production times, increases overall capacity, and expands upon our existing ca-

pabilities for powders, pellets and powder micro-dosing for inhalation systems.”

Xcelience also added a fully automated packaging line (including ink-jet coding) for primary bottling of tablets and capsules. The new packaging line enhances the speed at which batches are packaged, shortens time lines, and enhances the company’s ability to package larger batches of drug product.

Bend Research and Xcelience formed a collaboration that was announced on Aug. 24, 2011. This collaboration provides oral solid-solubilization formulation solutions and expedited clinical supply manufacture in combined programs to advance clients’ best new medicines.

The alliance will deliver superior value to clients with challenging drug-development candidates by joining together Bend’s problem-solving and formulation/processing expertise for delivering poorly soluble compounds with Xcelience’s solid reputation for accelerating early-phase development activities. According to the companies, the collaboration will maximize stage-specific expertise and expand operational capacity in a manner that provides immediate streamlined solutions to clients with tight time lines for producing clinical supplies.

“This collaboration reduces project time lines and transfer risk more than would be possible if the two steps occurred sequentially,” stated Derek Hennecke, president and CEO of Xcelience. “It’s a perfect example of what can happen when two organizations combine to push the boundaries of what it means to deliver great value.”

According to Rod Ray, CEO of Bend Research, “In this collaboration, we are combining Xcelience’s strengths in drug-product development and clinical-supply manufacturing with our company’s expertise in science- and engineering-based formulations for low-solubility compounds and our own drug-product intermediate clinical-supply manufacture. This will enable us to provide our high-quality, innovative solutions for clients in shorter time frames, which can be critical in the development of new medicines.”

Mr. Ray said the collaboration is another significant step in Bend Research’s push to build a worldwide network of collaborators dedicated to delivering solutions to advance new medicines. The network will leverage the company’s expertise to provide clients with optimized solutions to

their pharmaceutical development challenges.

For more than three-and-a-half decades, Bend Research has worked with clients to create value by advancing new medicines that improve human health and to solve their most difficult scientific and technical problems. This success is based upon Bend Research’s ability to develop, advance, as well as commercialize pharma technologies. Bend Research’s innovative drug-delivery solutions grow from a solid base of scientific and engineering fundamental understanding.

The firm provides formulation and dosage-form support, assists in process development and optimization, manufactures clinical-trial quantities of drug candidates in its cGMP facilities, and advances promising drug candidates from conception through commercialization. Bend Research is a leader in novel formulations such as solubilization technologies including spray-dried dispersions and hot-melt extrusion formulations as well as controlled-release, inhalation, and biotherapeutics technologies.

**Critical Outcome Technologies Inc.** (COTI) announced on May 18, 2011, the initiation of a project to develop an optimal oral formulation of COTI-2. This lead oncology product has shown efficacy in tests as a single agent and in combo therapy in various animal models of human cancers. Development of an oral form for use in humans will maximize the amount of an orally administered dose that is absorbed into the body.

Following the completion of a successful private placement in April 2011, Critical Outcome Technologies announced its intention to launch three studies related to the continued development of COTI-2 based on scientific and business feedback from prospective licensing partners. The first study, a pharmacodynamic animal experiment, is being conducted. A deal between COTI and Xcelience to work on the second research study was inked on May 2, 2011. Work on the project is under way.

The third study is the completion of the 28-day Good Laboratory Practice (GLP) toxicity experiments in two species that forms part of the Investigational New Drug (IND) enabling experiments required by U.S. regulators starting clinical trials.

“We are committed to achieving all three of these COTI-2 developmental

milestones and we are pleased with the initiation of the oral formulation optimization project,” noted Dr. Wayne Danter, CEO and president of COTI. “Xcelience is a recognized industry leader with an impressive track record of success in formulating more than 100 development stage small molecules for clinical use.”

Mr. Hennecke says, “We are pleased to be recognized and selected for our strength in formulation development expertise for the COTI-2 program. The partnership that has developed is a great example of the value two companies can create when they work together to achieve program objectives.”

COTI-2 has demonstrated to be highly effective as a single agent and in combination therapy in various animal models of human cancers. Other cancer treatments involve the killing of healthy growing and dividing cells in the body leading to significant toxic side effects. COTI-2 evidently targets and destroys cancer cells only and has shown low toxicity in normal human cells versus human cancer cells.

The combined scientific evidence indicates that COTI-2 is an ideal agent for combo therapy with current standard agents for various cancers. These cancers include small cell lung, non-small cell lung, colon, brain, ovarian, endometrial, triple negative breast and pancreatic.

In scientific terms, COTI-2 is a novel small molecule that acts by inhibiting Akt/PKB phosphorylation that results in caspase-9 activation in cancer cells. This process leads to tumor cell death. COTI-2 has shown greater selectivity as well as an improved safety profile and pharmacokinetics versus other Akt inhibitors. COTI is evaluating partners to share in the development of COTI-2 through a license deal.

A leading-edge biotech company located in London, Ontario, COTI specializes in assisting pharma, biotech and therapeutic companies with the accelerated discovery of small molecules to enable new drugs to be brought to market in a more timely, cost effective and efficient manner.

The company’s proprietary technology **CHEMSAS** uses a series of predictive computer models to identify compounds most likely to be successfully incorporated in disease-specific drug discovery, as well as subsequent optimization and pre-clinical development. These compounds are targeted for different diseases, espe-

cially those for which current treatments are either lacking or ineffective. .

During 2010, Xcelience expanded its solid oral dosage form development and manufacturing capabilities to include a **Vector TFC-220 Roller Compactor** in the GMP Manufacturing area. The addition of this new equipment allows clients to achieve a faster transition from development in the experimental area to GMP production of clinical supplies.

Dry granulation technology represents a significant option for clients faced with development challenges resulting from moisture sensitive APIs. Xcelience has a Vector TFC-Lab Micro Roller Compactor

in the experimental area. The TFC-220 is a natural transition for scale-up to the GMP Manufacturing area and significantly expands the company's processing capacity for dry granulation. The TFC-220 is capable of processing blends at a rate of up to 20 kg per hour.

"Taking a cross-functional approach to dry granulation ensures effective technical transfer and supports improved manufacturing outcomes," Mr. Koontz shares.

COTU in 2010 expanded formulation development and manufacturing capabilities to include a **Piccola B10 Mini-press**. This 10-station table top rotary tablet press allows clients to make an early

assessment of how the developed process and formula will perform in production, which can cut down on development time and result in early identification and resolution of potential formulation issues. The ability to cost-effectively produce small batch sizes in the experimental area and obtain all necessary processing parameters is another advantage.

Equipped with a data acquisition and analysis system (the **Director Software V4 Scalability Program**), the Piccola B10 Minipress provides clients detailed analysis including compaction profiles, strain rate studies, single compaction event investigation and statistical analysis of every production run.

"Adding a bench scale tablet press in the experimental area is consistent with our strategy of providing equipment appropriately scaled to the needs of our clients," commented Paul Skultety, Ph.D., who serves as director of pharma development services. "The Piccola scales nicely to our existing Fette 1200i instrumented press in our cGMP manufacturing area, and helps clients build towards improved manufacturing outcomes in a manner consistent with the FDA's Quality by Design initiative."

On July 12, 2010, **Penn Pharma** and Xcelience entered into a joint-venture pact to provide Capsugel's Xcelodose precision powder micro-dosing system technology on a worldwide basis. The joint venture provides pharma and biotech companies the opportunity to manufacture first in human batches faster and closer to the clinical sites. The companies are operating the largest network of Xcelodose systems globally, guaranteeing immediate manufacturing capacity.

"This joint venture will create a powerful partnership between two leading providers who share a common commitment to quality, innovation, and building client relationships based on trust and performance" Mr. Hennecke shares.

According to Paul Wituschek, global sales and marketing director of Penn Pharma, "Xcelience has more than six years experience in powder in capsule technology and has processed more than 100 clinical supply batches using the Xcelodose technology. Penn will be able to immediately leverage this expertise to provide this important accelerated development option to our clients."

Xcelodose is a registered trademark of Capsugel, which is a division of Pfizer.

#### **XCELIENCE PROVIDES CGMP-COMPLIANT CLINICAL PHARMACEUTICAL MANUFACTURING, PACKAGING AND LABELING SERVICES IN SUPPORT OF SOLID, SEMI-SOLID AND ORAL LIQUID DOSAGE FORMS**

Xcelience is an industry leader in formulation development and clinical supplies manufacturing. The company provides a vast number of services and solutions for a variety of drug manufacturing and packaging needs such as screening, dilution, tableting, solids processing and labeling services. In addition, Xcelience can custom tailor formulation and pharmaceutical manufacturing services to get customers exactly what they need in the shortest amount of time possible.

##### **Xcelience capabilities include:**

- \* Tablet manufacturing, including matching placebo (direct compression, high shear granulation, fluid bed granulation and coating)
- \* Capsules (direct blend, granulated blend, liquid-in-capsule, reference product blinding and placebo)
- \* API in capsule services
- \* Encapsulation and over-encapsulation of tablets, capsules, and other solid dosage forms
- \* Liquids/Ointments/Creams
- \* Reference product blinding
- \* Clinical packaging services, including blister packaging, standard packaging, and blinding kits for clinical studies,
- \* Clinical labeling services for packaged materials
- \* Creation and qualification of blinded reference product
- \* Process definition, qualification and optimization
- \* Process qualification
- \* Technology transfer

##### **GMP Manufacturing Capabilities include:**

- \* Cleaning verification
- \* Dilution
- \* Finishing and Packaging
- \* Dry and Wet Granulation
- \* Milling
- \* Mixing/Transfer
- \* Particle Sizing
- \* Pumping
- \* Screening
- \* Slugging

Source: Xcelience



Penn Pharma is a top provider of fully integrated and cost effective pharma development and custom manufacturing services to the international healthcare arena. The company's services support a fast and effective route from clinic to market. Penn provides unparalleled service offerings developed throughout the company's 30-year trading history. Penn's core services consist of formulation development, analytical development and stability studies, clinical-trial supply – packing and labelling, storage and distribution, clinical and commercial manufacturing, Qualified Person (QP) Release services and commercial product sourcing for clinical trials.

## XCELLEREX LLC

Marlborough-Mass.-based Xcellerex is commercializing turnkey biomanufacturing solutions that transform the speed and economics of producing therapeutic proteins. These proteins include biosimilars and vaccines. Xcellerex's FlexFactory is a complete modular and portable production train based on single-use technologies, advanced process automation, and compact clean room architecture.

FlexFactory enables deployment of GMP manufacturing capacity more rapidly and at greatly reduced costs versus traditional facilities. Through the company's BridgeSourcing services, Xcellerex manufactures a partner's biomolecules while the partner prepares for commissioning of its own new FlexFactory.

When a partner's facility is ready, Xcel-

lerex deploys the company's **TransPlant** process to install, validate and train partner personnel in their own FlexFactory. This parallel path model accelerates time to clinical and commercial manufacturing and enables partners to manage the development and market risks associated with additional manufacturing capacity.

Xcellerex leverages the company's proprietary single-use technologies via the sale of XDR bioreactors, **XDM Quad Mixers**, and related single-use assemblies. More than 20 therapeutic proteins and vaccines have been manufactured for clinical studies that use Xcellerex technology.

Xcellerex is backed by an experienced management team and top-tier venture investors such as **Kleiner Perkins Caufield & Byers**, **VantagePoint Venture Partners** and **SCG Capital**.

On June 28, 2011, Xcellerex introduced the **XDR-10**, a new 10-liter version of the company's industry-leading XDR line of single-use bioreactors. The XDR-10 joins an existing portfolio that includes units with nominal working volumes of 50, 200, 500, 1,000 and 2,000 liters.

According to the company, the XDR-10 shares the same robust design and vessel geometries as the larger XDR models, providing seamless linear scale-up from 10L to 2,000L. The XDR-10 additionally features industrial-grade instrumentation and controls to deliver consistent process performance across the entire product line.

Because the entire XDR family uses the same product contact materials, qualifi-

cation is greatly simplified as a process is scaled-up. Primary application areas include process development, seed trains as well as production process modeling.

"With the XDR-10, we can now offer biologics developers a seamless path from bench top to production," according to Jiyoung Lee, who serves as product manager for bioreactors at Xcellerex. "The product line delivers linear scale-up across all volumes, allowing reliable, predictable results. Taking the step, from bench- to pilot-scale, just got less risky. We gathered extensive marketplace input before designing this system, and we are confident that its combination of award-winning process controls and robust vessel design make the XDR-10 a unique productivity tool that has been missing from the single-use marketplace.

"Of course, the system also comes with the deep process knowledge of the Xcellerex team. Our early development partners have achieved process equivalence in their scale-up runs, both from flask to the XDR-10 and from the XDR-10 to production scales."

"Biopharm customers have enthusiastically embraced the XDR as the best fully integrated, GMP single-use bioreactor available," noted Ken Clapp, senior director of global marketing and product management at Xcellerex. "They have been eager to get their hands on a bench scale version of the system, and we believe they will be thrilled with this new product. The XDR-10 emphasizes our ongoing commitment to define the future of biomanufacturing...now, starting at the bench top."

## Revenue: Global Contract Manufacturing Companies

Company	Total Revenue 2010	Total Revenue 2009
AAI Pharma Services Corp.	\$171,000,000*	N/A
Abbott Laboratories	35,166,721,000	30,764,707,000
Acino Group	169,121,511	209,763,824
Aenova Holding GmbH	331,525,000*	N/A
Aesica Pharmaceuticals Ltd.	238,698,000*	N/A
Alkermes plc	186,640,000 (March 11)	178,281,000 (March 10)
Althea Technologies Inc.	43,900,000*	N/A
Amatsi	26,522,000*	N/A
Aurobindo Pharma Ltd.	920,223,626 (March 11)	724,105,686 (March 10)
Bayer AG	46,530,196,800	41,331,884,800
Boehringer Ingelheim GmbH	16,690,294,600	16,869,318,100
Cambridge Major Laboratories Inc.	50,000,000-60,000,000*	N/A
Catalent Pharma Solutions Inc.	1,640,300,000 (June 11)	1,626,200,000 (June 10)
Cedarburg Hauser Pharmaceuticals	20,000,000*	N/A
Charles River Laboratories International Inc.	1,133,416,000	1,171,642,000
Divis Laboratories Ltd.	29,065,099,534 (March 11)	20,690,334,704 (March 10)
Dr. Reddy's Laboratories Ltd.	1,663,011,558 (March 11)	1,564,690,978 (March 10)
Gallus BioPharmaceuticals LLC	50,000,000-100,000,000*	N/A
GlaxoSmithKline plc	43,871,318,400	43,834,233,600
Hospira Inc.	3,917,200,000	3,879,300,000
Lonza Group Ltd.	2,569,018,405	2,578,604,294
Paragon Bioservices Inc.	10,000,000-20,000,000*	N/A
Patheon Inc.	671,200,000 (October 10)	655,100,000 (October 09)
Pfizer Inc.	67,809,000,000*	50,009,000,000*
Piramal Healthcare Ltd.	558,810,891 (March 11)	806,974,616 (March 10)
Recipha AB	311,256,991	264,013,990
Roche	45,507,093,558	47,019,746,933
Royal DSM N.V.	12,001,205,000	10,431,102,600
Synco Bio Partners	33,152,500-39,783,000*	N/A
Therapure Biopharma Inc.	3,856,640*	N/A
UPM Pharmaceuticals Inc.	12,000,000*	N/A
Xcelience LLC	5,000,000-10,000,000*	N/A
Xcellerex LLC	26,100,000*	N/A

Notes:

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Source: eKnowledgeBase.com

## R&D: Global Contract Manufacturing Companies

Company	Total R&D 2010	Total R&D 2009
AAI Pharma Services Corp.	N/A	N/A
Abbott Laboratories	3,724,424,000	2,743,733,000
Acino Group	N/A	N/A
Aenova Holding GmbH	N/A	N/A
Aesica Pharmaceuticals Ltd.	N/A	N/A
Alkermes plc	97,239,000 (March 11)	95,363,000 (March 10)
Althea Technologies Inc.	N/A	N/A
Amatsi	N/A	N/A
Aurobindo Pharma Ltd.	N/A	N/A
Bayer AG	4,048,583,300	3,641,470,600
Boehringer Ingelheim GmbH	3,252,923,300	2,937,311,500
Cambridge Major Laboratories Inc.	N/A	N/A
Catalent Pharma Solutions Inc.	N/A	N/A
Cedarburg Hauser Pharmaceuticals	N/A	N/A
Charles River Laboratories International Inc.	N/A	N/A
Divis Laboratories Ltd.	355,808,729 (March 11)	251,211,752 (March 10)
Dr. Reddy's Laboratories Ltd.	112,658,997 (March 11)	84,449,719 (March 10)
Gallus BioPharmaceuticals LLC	N/A	N/A
GlaxoSmithKline plc	6,886,956,400	6,344,591,200
Hospira Inc.	300,500,000	240,500,000
Lonza Group Ltd.	94,900,307	98,734,663
Paragon Bioservices Inc.	N/A	N/A
Patheon Inc.	N/A	N/A
Pfizer Inc.	9,413,000,000	7,845,000,000
Piramal Healthcare Ltd.	15,945,924 (March 11)	15,618,634 (March 10)
Recipharm AB	N/A	N/A
Roche	9,610,812,883	9,465,107,362
Royal DSM N.V.	448,221,800	404,460,500
Synco Bio Partners	N/A	N/A
Therapure Biopharma Inc.	N/A	N/A
UPM Pharmaceuticals Inc.	N/A	N/A
Xcellience LLC	N/A	N/A
Xcellerex LLC	N/A	N/A

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Source: eKnowledgeBase.com

## Net Income and EPS: Global Contract Manufacturing Companies

Company	Net Income/(Loss) 2010	Net Income/(Loss) 2009	Earnings/(Loss) Per Share 2010	Earnings/(Loss) Per Share 2009
AAI Pharma Services Corp.	N/A	N/A	N/A	N/A
Abbott Laboratories	4,626,172,000	5,745,838,000	2.96	3.69
Acino Group	5,991,320	44,425,676	1.883	13.964
Aenova Holding GmbH	N/A	N/A	N/A	N/A



## Net Income and EPS: Global Contract Manufacturing Companies

Company	Net Income/(Loss) 2010	Net Income/(Loss) 2009	Earnings/(Loss) Per Share 2010	Earnings/(Loss) Per Share 2009
Aesica Pharmaceuticals Ltd.	N/A	N/A	N/A	N/A
Alkermes plc	-45,540,000 (March 11)	-39,626,000 (March 10)	-0.48 (March 11)	-0.42 (March 10)
Althea Technologies Inc.	N/A	N/A	N/A	N/A
Amatsi	N/A	N/A	N/A	N/A
Aurobindo Pharma Ltd.	132,207,337 (March 11)	117,058,487 (March 10)	0.41 (March 11)	0.37 (March 10)
Bayer AG	1,725,256,100	1,802,169,900	2.08	2.25
Boehringer Ingelheim GmbH	1,177,576,800	2,332,609,900	N/A	N/A
Cambridge Major Laboratories Inc.	N/A	N/A	N/A	N/A
Catalent Pharma Solutions Inc.	-54,000,000 (June 11)	-289,600,000 (June 10)	N/A	N/A
Cedarburg Hauser Pharmaceuticals	N/A	N/A	N/A	N/A
Charles River Laboratories International Inc.	-342,117,000	112,602,000	-5.38	1.74
Divis Laboratories Ltd.	9,697,715,427 (March 11)	7,663,585,985 (March 10)	0.73 (March 11)	0.59 (March 10)
Dr. Reddy's Laboratories Ltd.	245,801,449 (March 11)	23,778,618 (March 10)	1.45 (March 11)	0.14 (March 10)
Gallus BioPharmaceuticals LLC	N/A	N/A	N/A	N/A
GlaxoSmithKline plc	2,524,856,800	8,759,738,800	0.49	1.67
Hospira Inc.	357,200,000	403,900,000	2.11	2.47
Lonza Group Ltd.	272,239,264	152,415,644	5.30	3.04
Paragon Bioservices Inc.	N/A	N/A	N/A	N/A
Patheon Inc.	-5,000,000 (October 10)	-6,800,000 (October 09)	-0.04 (October 10)	-0.18 (October 09)
Pfizer Inc.	8,257,000,000	8,635,000,000	1.02	1.23
Piramal Healthcare Ltd.	2,868,431,658 (March 11)	107,293,223 (March 10)	12.77 (March 11)	0.48 (March 10)
Recipha AB	-5,412,682	985,386	0.15	0.18
Roche	8,522,814,417	8,157,592,025	9.69	8.65
Royal DSM N.V.	672,332,700	446,895,700	4.02	2.67
Synco Bio Partners	N/A	N/A	N/A	N/A
Therapure Biopharma Inc.	N/A	N/A	N/A	N/A
UPM Pharmaceuticals Inc.	N/A	N/A	N/A	N/A
Xcelience LLC	N/A	N/A	N/A	N/A
Xcellerex LLC	N/A	N/A	N/A	N/A

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Source: eKnowledgeBase.com

## Total Assets: Global Contract Manufacturing Companies

Company	Total Assets 2010	Total Assets 2009
AAI Pharma Services Corp.	N/A	N/A
Abbott Laboratories	59,462,266,000	52,416,623,000
Acino Group	457,188,888	436,696,665
Aenova Holding GmbH	N/A	N/A
Aesica Pharmaceuticals Ltd.	N/A	N/A

## Total Assets: Global Contract Manufacturing Companies

Company	Total Assets 2010	Total Assets 2009
Alkermes plc	\$452,448,000 (March 11)	\$515,600,000 (March 10)
Althea Technologies Inc.	N/A	N/A
Amatsi	N/A	N/A
Aurobindo Pharma Ltd.	1,115,268,411 (March 11)	880,389,987 (March 10)
Bayer AG	68,302,106,600	67,686,796,200
Boehringer Ingelheim GmbH	21,526,581,300	19,896,804,400
Cambridge Major Laboratories Inc.	N/A	N/A
Catalent Pharma Solutions Inc.	2,831,200,000 (June 11)	2,727,400,000 (June 10)
Cedarburg Hauser Pharmaceuticals	N/A	N/A
Charles River Laboratories International Inc.	1,733,373,000	2,204,093,000
Divis Laboratories Ltd.	42,436,442,291 (March 11)	36,220,735,935 (March 10)
Dr. Reddy's Laboratories Ltd.	2,115,250,599 (March 11)	1,788,517,243 (March 10)
Gallus BioPharmaceuticals LLC	N/A	N/A
GlaxoSmithKline plc	65,253,796,000	66,230,362,400
Hospira Inc.	6,046,300,000	5,502,900,000
Lonza Group Ltd.	4,580,138,037	4,739,263,804
Paragon Bioservices Inc.	N/A	N/A
Patheon Inc.	808,900,000 (October 10)	790,800,000 (October 09)
Pfizer Inc.	195,014,000,000	212,949,000,000
Piramal Healthcare Ltd.	2,820,311,126 (March 11)	676,094,251 (March 10)
Recipharm AB	303,471,056	181,088,921
Roche	58,493,098,160	71,477,185,583
Royal DSM N.V.	13,897,528,000	12,749,125,400
Synco Bio Partners	N/A	N/A
Therapure Biopharma Inc.	N/A	N/A
UPM Pharmaceuticals Inc.	N/A	N/A
Xcelience LLC	N/A	N/A
Xcellerex LLC	N/A	N/A

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Source: eKnowledgeBase.com

## Shareholders' Equity: Global Contract Manufacturing Companies

Company	Shareholders' Equity 2010	Shareholders' Equity 2009
AAI Pharma Services Corp.	N/A	N/A
Abbott Laboratories	22,476,464,000	22,898,729,000
Acino Group	334,952,969	339,504,144
Aenova Holding GmbH	N/A	N/A
Aesica Pharmaceuticals Ltd.	N/A	N/A
Alkermes plc	392,018,000 (March 11)	412,616,000 (March 10)
Althea Technologies Inc.	N/A	N/A

## Shareholders' Equity: Global Contract Manufacturing Companies

Company	Shareholders' Equity 2010	Shareholders' Equity 2009
Amatsi	N/A	N/A
Aurobindo Pharma Ltd.	572,114,004 (March 11)	426,225,055 (March 10)
Bayer AG	24,974,441,300	25,059,311,700
Boehringer Ingelheim GmbH	8,585,171,400	7,825,316,100
Cambridge Major Laboratories Inc.	N/A	N/A
Catalent Pharma Solutions Inc.	-213,700,000 (June 11)	-262,000,000 (June 10)
Cedarburg Hauser Pharmaceuticals	N/A	N/A
Charles River Laboratories International Inc.	687,423,000	1,375,243,000
Divis Laboratories Ltd.	40,700,745,642 (March 11)	34,333,722,222 (March 10)
Dr. Reddy's Laboratories Ltd.	1,023,950,056 (March 11)	955,486,337 (March 10)
Gallus BioPharmaceuticals LLC	N/A	N/A
GlaxoSmithKline plc	13,732,192,400	15,459,726,000
Hospira Inc.	3,183,500,000	2,623,700,000
Lonza Group Ltd.	2,288,151,840	2,228,719,325
Paragon Bioservices Inc.	N/A	N/A
Patheon Inc.	273,000,000 (October 10)	271,300,000 (October 09)
Pfizer Inc.	87,813,000,000	90,014,000,000
Piramal Healthcare Ltd.	2,641,023,015 (March 11)	375,134,423 (March 10)
Recipharm AB	88,268,358	68,741,066
Roche	11,179,064,417	9,024,156,442
Royal DSM N.V.	7,268,354,100	6,562,868,900
Synco Bio Partners	N/A	N/A
Therapure Biopharma Inc.	N/A	N/A
UPM Pharmaceuticals Inc.	N/A	N/A
Xcellience LLC	N/A	N/A
Xcellerex LLC	N/A	N/A

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Source: eKnowledgeBase.com

## Employees: Global Contract Manufacturing Companies

Company	2010 Employees	2009 Employees
AAI Pharma Services Corp.	855*	N/A
Abbott Laboratories	90,000	73,000
Acino Group	443	419
Aenova Holding GmbH	1,500	N/A
Aesica Pharmaceuticals Ltd.	501-1,000*	N/A
Alkermes plc	600 (March 11)	570 (March 10)
Allthea Technologies Inc.	180*	N/A
Amatsi	175*	N/A
Aurobindo Pharma Ltd.	8,317 (March 11)	8,066 (March 10)



## Employees: Global Contract Manufacturing Companies

Company	2010 Employees	2009 Employees
Bayer AG	111,400	111,000
Boehringer Ingelheim GmbH	42,224	41,534
Cambridge Major Laboratories Inc.	180	N/A
Catalent Pharma Solutions Inc.	8,200 (June 11)	9,200 (June 10)
Cedarburg Hauser Pharmaceuticals	95*	N/A
Charles River Laboratories International Inc.	7,500	N/A
Divis Laboratories Ltd.	N/A	N/A
Dr. Reddy's Laboratories Ltd.	14,923 (March 11)	13,000 (March 10)
Gallus BioPharmaceuticals LLC	100-250*	N/A
GlaxoSmithKline plc	96,500	99,913
Hospira Inc.	14,000	13,500
Lonza Group Ltd.	8,280	8,386
Paragon Bioservices Inc.	20-49*	N/A
Patheon Inc.	4,300 (October 10)	N/A
Pfizer Inc.	110,600	116,500
Piramal Healthcare Ltd.	N/A	N/A
Recipharm AB	1,800	N/A
Roche	80,653	81,507
Royal DSM N.V.	22,000	N/A
Synco Bio Partners	125*	N/A
Therapure Biopharma Inc.	35*	N/A
UPM Pharmaceuticals Inc.	60*	N/A
Xcelience LLC	50-99*	N/A
Xcellerex LLC	120*	N/A

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Source: eKnowledgeBase.com

## Corporate Addresses and Contact Info: Global Contract Manufacturing Companies

### AAI Pharma Services Corp.

2320 Scientific Park Dr.  
 Wilmington, NC 28405, United States  
 Phone: 910-254-7000  
 Fax: 910-815-2300  
 Website: [www.aai-pharma.com](http://www.aai-pharma.com)  
 Email: [info@aaiintl.com](mailto:info@aaiintl.com)  
 Private  
 Year Established: N/A

### Abbott Laboratories

100 Abbott Park Rd.  
 Abbott Park, IL 60064-6400, United States  
 Phone: 847-937-6100  
 Fax: 847-937-1511  
 Website: [www.abbott.com](http://www.abbott.com)  
 Email: [customerservice@abbott.com](mailto:customerservice@abbott.com)  
 Public  
 Year Established: 1888

### Acino Group

Erlenstrasse 1  
 Basel, CH-4058, Switzerland  
 Phone: +41 61 338 60 00  
 Fax: +41 61 338 60 80  
 Website: [www.acino-pharma.com](http://www.acino-pharma.com)  
 Email: [info@acino-pharma.com](mailto:info@acino-pharma.com)  
 Public  
 Year Established: 1836

### Aenova Holding GmbH

Gut Kerschlach 1  
 Paehl, 82396, Germany  
 Phone: +49 88 08 9243 111  
 Fax: +49 88 08 9243 100  
 Website: [www.aenova.de](http://www.aenova.de)  
 Email: [info@aenova.de](mailto:info@aenova.de)  
 Private  
 Year Established: 2008

### Aesica Pharmaceuticals Ltd.

Q5, Quorum Business Park, Benton Lane  
 Newcastle upon Tyne, NE12 8BS United Kingdom  
 Phone: +44 191 218 1960  
 Fax: +44 191 266 9447  
 Website: [www.aesica-pharma.com](http://www.aesica-pharma.com)  
 Email: [info@aesica-pharma.com](mailto:info@aesica-pharma.com)  
 Private  
 Year Established: 2004

### Alkermes plc

Treasury Building  
 Lower Grand Canal Street  
 Dublin 2, Ireland  
 Phone: +353 1 772 8000  
 Website: [www.alkermes.com](http://www.alkermes.com)  
 Email: [mediainfo@alkermes.com](mailto:mediainfo@alkermes.com)  
 Public  
 Year Established: 1987

**Althea Technologies Inc.**

11040 Roselle St.  
San Diego, CA 92121-1205, United States  
Phone: 858-882-0123  
Fax: 858-882-0133  
Website: [www.altheatech.com](http://www.altheatech.com)  
Email: [info@altheatech.com](mailto:info@altheatech.com)  
Private  
Year Established: 1998

**Amatsi**

17 Parc des Vautes  
St. Gely du Fesc, 34980, France  
Phone: +33 4 99 58 38 60  
Fax: +33 4 99 58 38 61  
Website: [www.amatsi.com](http://www.amatsi.com)  
Private  
Year Established: N/A

**Aurobindo Pharma Ltd.**

Plot # 2, Maitri Vihar, Ameerpet, Hyderabad  
Andhra Pradesh, 500 038, India  
Phone: +91 40 6672 5000  
Fax: +91 40 2374 1080  
Website: [www.aurobindo.com](http://www.aurobindo.com)  
Email: [info@aurobindo.com](mailto:info@aurobindo.com)  
Public  
Year Established: 1986

**Avid Bioservices Inc.**

14282 Franklin Ave.  
Tustin, CA 92780, United States  
Phone: 714-508-6100  
Website: [www.avidbio.com](http://www.avidbio.com)  
Owned  
Year Established: N/A

**Baxter BioPharma Solutions**

Bloomington, IN  
Website: [www.baxterbiopharmasolutions.com](http://www.baxterbiopharmasolutions.com)  
Owned  
Year Established: N/A

**Bayer AG**

Bayer-Werk  
Leverkusen, D-51368, Germany  
Phone: +49 214 30 1  
Website: [www.bayer.com](http://www.bayer.com)  
Public  
Year Established: 1863

**Ben Venue Laboratories Inc.**

300 Northfield Rd.  
Bedford, OH 44146, United States  
Phone: 440-232-3320  
Fax: 440-439-6398  
Website: [www.benvenue.com](http://www.benvenue.com)  
Owned  
Year Established: 1938

**Biomay AG**

Vienna Competence Center, Lazarettgasse 19  
Vienna, 1090, Austria  
Phone: +43 1 7966296 100  
Fax: +43 1 7966296 111  
Website: [www.Biomay.com](http://www.Biomay.com)  
Email: [info@biomay.com](mailto:info@biomay.com)  
Private  
Year Established: 1984

**Boehringer Ingelheim GmbH**

Blinger Strasse 173  
Ingelheim, 55216, Germany  
Phone: +49 6 13 277 0  
Fax: +49 6 13 272 3000  
Website: [www.boehringer-ingelheim.com](http://www.boehringer-ingelheim.com)  
Public  
Year Established: 1885

**Cambridge Major Laboratories Inc.**

W130 N10497 Washington Dr.  
Germantown, WI 53022, United States  
Phone: 262-251-5044  
Fax: 262-251-5577  
Website: [www.c-mlabs.com](http://www.c-mlabs.com)  
Email: [info@c-mlabs.com](mailto:info@c-mlabs.com)  
Private  
Year Established: 1976

**Catalent Pharma Solutions Inc.**

14 Schoolhouse Rd  
Somerset, NJ 08873, United States  
Phone: 732-537-6200  
Fax: 732-537-6480  
Website: [www.catalent.com](http://www.catalent.com)  
Email: [info@catalent.com](mailto:info@catalent.com)  
Private  
Year Established: 2007

**Cedarburg Hauser Pharmaceuticals**

870 Badger Circle  
Grafton, WI 53024, United States  
Phone: 262-376-1467  
Website: [www.cedarburghauser.com](http://www.cedarburghauser.com)  
Private  
Year Established: N/A

**Charles River Laboratories International Inc.**

251 Ballardvale St.  
Wilmington, MA 01887, United States  
Phone: 781-222-6000  
Website: [www.criver.com](http://www.criver.com)  
Email: [askcharlesriver@crl.com](mailto:askcharlesriver@crl.com)  
Public  
Year Established: 1947

**Divis Laboratories Ltd.**

Divi Towers, 7-1-77/E/1/303  
Dharam Karan Road, Ameerpet, Andhra Pradesh  
Hyderabad, 500 016, India  
Phone: +91 40 2378 6300  
Fax: +91 40 2378 6460  
Website: [www.divislabs.com](http://www.divislabs.com)  
Email: [mail@divislaboratories.com](mailto:mail@divislaboratories.com)  
Public  
Year Established: 1990

**Dr. Reddy's Laboratories Ltd.**

8-2-337, Road No 3, Banjara Hills  
Hyderabad, 500034, India  
Phone: +91 40 49002900  
Fax: +91 40 49002999  
Website: [www.drreddys.com](http://www.drreddys.com)  
Email: [webmaster@drreddys.com](mailto:webmaster@drreddys.com)  
Public  
Year Established: 1984

**DSM Pharmaceutical Products**

45 Waterview Blvd.  
Parsippany, NJ 07054, United States  
Phone: 973-257-8011  
Website: [www.dsm.com/en\\_US/html/dpp/home\\_dpp.htm](http://www.dsm.com/en_US/html/dpp/home_dpp.htm)  
Email: [info.dsmpharmaceuticalsna@dsm.com](mailto:info.dsmpharmaceuticalsna@dsm.com)  
Owned  
Year Established: N/A

**Famar Health Care Services**

63, Ag. Demetriou Str., Alimos  
Athens, 174 56, Greece  
Phone: +30 210 98 98 500  
Fax: +30 210 98 88 800  
Website: [www.famar.gr](http://www.famar.gr)  
Email: [info@famar.gr](mailto:info@famar.gr)  
Owned  
Year Established: 1949

**Fujifilm Diosynth Biotechnologies UK Ltd.**

101 J. Morris Commons Lane  
Morrisville, NC 27560, United States  
Phone: 919-337-4477  
Website: [www.fujifilmdiosynth.com](http://www.fujifilmdiosynth.com)  
Owned  
Year Established: N/A

**Gallus BioPharmaceuticals LLC**

4766 LaGuardia Drive  
St. Louis, MO 63134, United States  
Phone: 314-426-5000  
Fax: 314-733-3888  
Website: [www.gallusbiopharma.com](http://www.gallusbiopharma.com)  
Email: [info@gallusbiopharma.com](mailto:info@gallusbiopharma.com)  
Private  
Year Established: N/A

**GlaxoSmithKline plc**

980 Great West Rd.  
Middlesex, Brentford TW8 9GS, United Kingdom  
Phone: +44 208 047 5000  
Fax: +44 208 047 7897  
Website: [www.gsk.com](http://www.gsk.com)  
Email: [corporate.media@gsk.com](mailto:corporate.media@gsk.com)  
Public  
Year Established: 2000

**Hospira Inc.**

275 North Field Dr.  
Lake Forest, IL 60045, United States  
Phone: 224-212-2200  
Website: [www.hospira.com](http://www.hospira.com)  
Public  
Year Established: 2003

**Hospira One 2 One**

275 North Field Dr.  
Lake Forest, IL 60045, United States  
Phone: 224-212-2267  
Website: [www.one2one.hospira.com](http://www.one2one.hospira.com)  
Owned  
Year Established: N/A

**Lonza Group Ltd.**

Muenchensteinerstrasse 38  
Basel, CH-4002, Switzerland  
Phone: +41 61 316 81 11  
Fax: +41 61 316 91 11  
Website: [www.lonza.com](http://www.lonza.com)  
Email: [info@lonza.com](mailto:info@lonza.com)  
Public  
Year Established: 1897

**Meridian Life Science Inc.**

3471 River Hills Dr.  
Cincinnati, OH 45244, United States  
Website: [www.meridianlifescience.com](http://www.meridianlifescience.com)  
Email: [info@meridianlifescience.com](mailto:info@meridianlifescience.com)  
Owned  
Year Established: N/A

**Paragon Bioservices Inc.**

UMB BioPark  
801 W. Baltimore St. Suite 401  
Baltimore, MD 21201, United States  
Phone: 410-975-4050  
Fax: 410-605-2028  
Website: [www.paragonbioservices.com](http://www.paragonbioservices.com)  
Private  
Year Established: N/A

**Patheon Inc.**

421 Emperor Blvd., Suite 200  
Research Triangle Park, NC 27709-5145, United States  
Phone: 919-226-3200  
Website: [www.patheon.com](http://www.patheon.com)  
Email: [info@patheon.com](mailto:info@patheon.com)  
Public  
Year Established: 1974

**Pfizer CentreSource**

7000 Portage Road, PORT-041-201  
Kalamazoo, MI 49001, United States  
Phone: 269-833-5844  
Fax: 269-833-4671  
Website: [www.pfizercentresource.com](http://www.pfizercentresource.com)  
Email: [centresource.info@pfizer.com](mailto:centresource.info@pfizer.com)  
Owned  
Year Established: N/A

**Pfizer Inc.**

235 East 42nd St.  
New York, NY 10017-5755, United States  
Phone: 212-733-2323  
Fax: 212-733-7851  
Website: [www.pfizer.com](http://www.pfizer.com)  
Email: [pfizermedia@pfizer.com](mailto:pfizermedia@pfizer.com)  
Public  
Year Established: 1849

**Piramal Healthcare Ltd.**

247 Business Park, A - Wing, 6th floor, LBS marg, Mumbai  
Vikroli (W), 400083, India  
Phone: +91 22 3095 6666  
Website: [www.piramalhealthcare.com](http://www.piramalhealthcare.com)  
Email: [corporate.communication@piramal.com](mailto:corporate.communication@piramal.com)  
Public  
Year Established: N/A

**Recipharm AB**

Lagervagen 7  
Jordbro, SE-136 50, Sweden  
Phone: +46 8 602 52 00  
Fax: +46 8 81 87 03  
Website: [www.recipharm.com](http://www.recipharm.com)  
Email: [info@recipharm.com](mailto:info@recipharm.com)  
Private

Year Established: 1995

**RecipharmCobra Biologics**

Stephenson Building, The Sciences Park  
Keele, ST5 5SP, United Kingdom  
Phone: +44 178 271 4181  
Website: [www.cobrabiomanufacturing.com](http://www.cobrabiomanufacturing.com)  
Email: [info@cobrabiomanufacturing.com](mailto:info@cobrabiomanufacturing.com)  
Owned  
Year Established: 1992

**Roche**

Grenzacherstrasse 124  
Basel, CH-4070, Switzerland  
Phone: +41 61 688 11 11  
Fax: +41 61 691 93 91  
Website: [www.roche.com](http://www.roche.com)  
Email: [investor.relations@roche.com](mailto:investor.relations@roche.com)  
Public  
Year Established: 1896

**Royal DSM N.V.**

PO Box 6500  
Heerlen, 6401 JH, Netherlands  
Website: [www.dsm.com](http://www.dsm.com)  
Public  
Year Established: N/A

**Synco Bio Partners**

Paaschewweg 30  
Amsterdam, 1105 BJ, Amsterdam  
Phone: +31 20 750 3600  
Website: [www.syncobiopartners.com](http://www.syncobiopartners.com)  
Email: [contact@syncobiopartners.com](mailto:contact@syncobiopartners.com)  
Private  
Year Established: 2000

**Therapure Biopharma Inc.**

2585 Meadowpine Blvd.  
Mississauga, ON L5N 8H9, Canada  
Phone: (905) 286-6200  
Fax: (905) 286-6300  
Website: [www.therapurebio.com](http://www.therapurebio.com)  
Email: [info@therapurebio.com](mailto:info@therapurebio.com)  
Private  
Year Established: N/A

**UPM Pharmaceuticals Inc.**

6200 Seaforth Street  
Baltimore, MD 21224, United States  
Phone: 410-843-3700  
Fax: 410-633-4438  
Website: [www.upm-inc.com](http://www.upm-inc.com)  
Private  
Year Established: N/A

**Xcellience LLC**

5415 W. Laurel St.  
Tampa, FL 33607, United States  
Phone: 813-286-0404  
Fax: 813-286-1105  
Website: [www.xcellience.com](http://www.xcellience.com)  
Email: [info@xcellience.com](mailto:info@xcellience.com)  
Private  
Year Established: 1997

**Xcellerex LLC**

170 Locke Dr.  
Marlborough, MA 01752-7230, United States  
Phone: 508-480-9235  
Fax: 508-480-9238  
Website: [www.xcellerex.com](http://www.xcellerex.com)  
Private  
Year Established: N/A