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STATE OF THE PHARMACEUTICAL INDUSTRY 2014

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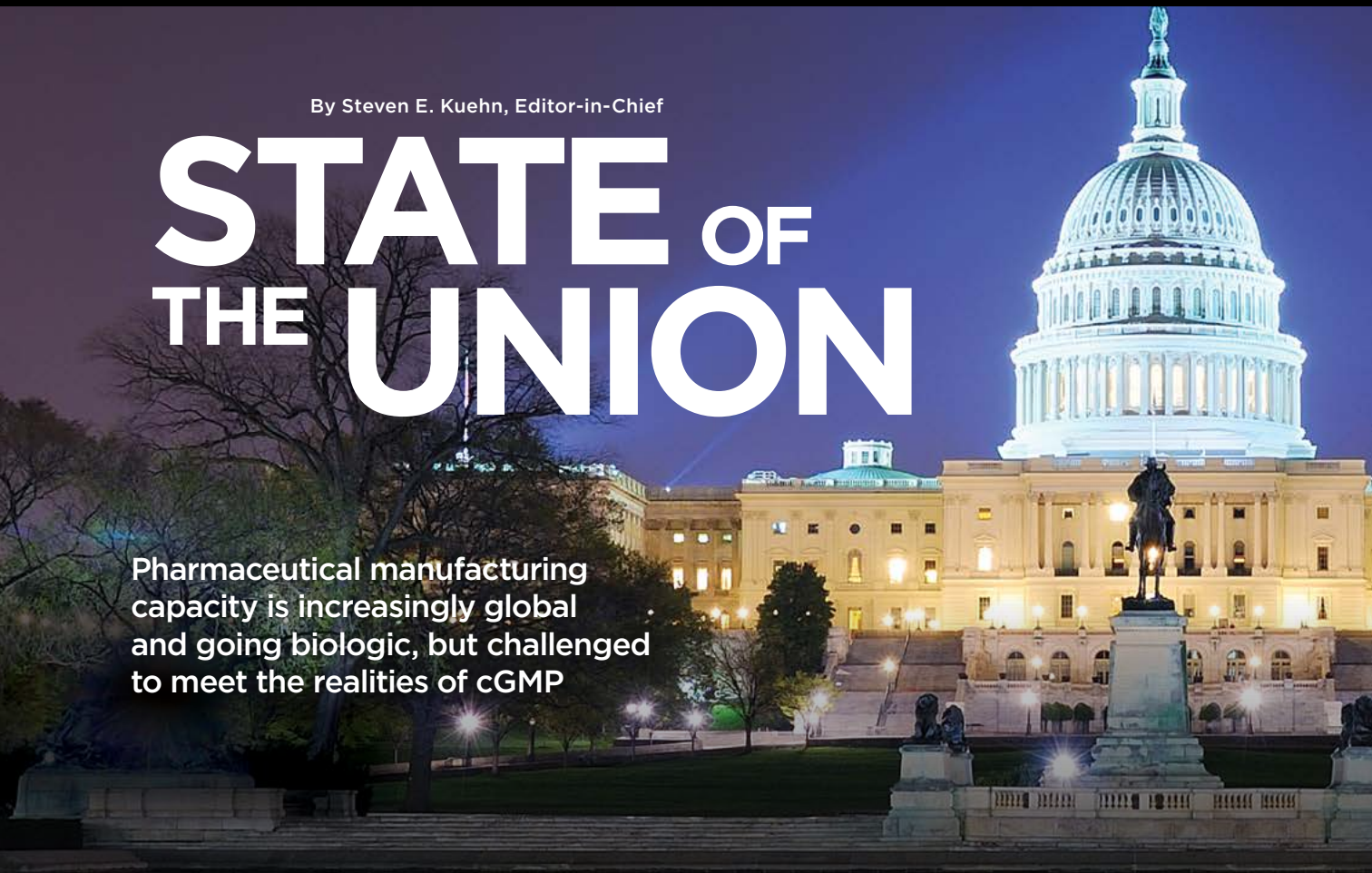


By Steven E. Kuehn, Editor-in-Chief

STATE OF THE UNION

Pharmaceutical manufacturing capacity is increasingly global and going biologic, but challenged to meet the realities of cGMP

IT'S BEEN said that a rising tide lifts all boats. But considering the state of pharmaceutical manufacturing in 2014, some boats are being lifted higher than others. Although the state of the pharmaceutical manufacturing union is strong, the continuing growth in the global demand for affordable prescription and over-the-counter drugs is challenging the industry in new ways to be able to manufacture enough safe, high quality drugs cost effectively and efficiently to meet demand. Similarly, the prominent western economic powers, traditionally North America and Europe, are imposing quality standards on companies selling pharma products in their countries. Both China and India are playing their own major role in contributing to worldwide global drug production capacity in the face of a globalizing industry and demand for drugs, but are facing increased pressure to assure they are making therapies, APIs and excipients to global standards of quality.

DEMAND ON THE RISE

According to the IMS report "The Global Use of Medicines: Outlook through 2016," until recently the industry experienced several years of slowing growth, but certainly not any net decline. For example, the global market for medicines was expected, and reached a low point of 3-4 percent growth in 2012. However, IMS analysts forecast it to jump to a 5-7 percent growth rate by 2016. Total spending on medicines globally is projected to rise to $1 trillion in 2013 and to $1.2 trillion by 2016, says IMS Institute for Healthcare Informatics. In the report "Generic Drugs: World Market 2013-2023," pharma industry analyst firm Visiongain predicts markets for generic drugs will reach $156.9 billion by 2016, reflecting a compound annual growth rate of 5.5%. Visiongain set the U.S. market at $43.1 billion for generics in 2011, making it the world's largest national market for generics, followed by Germany, a distant second, at $8.6 billion. Visiongain says "the generics market is expected to achieve significant revenue growth over the forecast period owing primarily to the greater demand for cost-effective generic medicines."

It's by now well known that patent expiries peaked in 2012. According to IMS, the industry experienced its lowest annual growth during that period. Murray Aitken, executive director, IMS Institute for Healthcare Informatics noted that, "The trillion-dollar spending on medicines we forecast for 2016 represents a rebound in growth that will accentuate the challenges of access

and affordability facing those who consume and pay for healthcare around the world."

IMS Institute identified a number of dynamics that are indeed playing themselves out as their analysts revealed in 2012, including the slowing of spending by developed economies. In 2014 the global pharmaceutical market continues to experience the impact of patent expiration. Global pharmaceutical manufacturing production is shifting from branded to generic as blockbuster drugs lose patent protection. Generic drugs now account for more than 70% of all prescriptions issued in the United States. Like branded pharma, these manufacturers are also facing challenges from increased government price controls in many parts of the world. Also affecting global production capacity is the rise of contract manufacturing organizations' (CMOs) prominence in the global drug manufacturing universe.

Patheon, now currently operating as NewCo after merging with DSM, is a case study of how market forces are affecting CMOs and the biologic portion of the industry. Harry Gill, senior vice president, quality and continuous improvement, for (then) Patheon, notes: "We are observing a shrinking fixed asset base among large Pharma, as there has been 4% compound annual growth rate (CAGR) decline since 2007."

In 2012, says a recent 2013 Frost & Sullivan report "Global Pharmaceutical Contract Manufacturing Market," the global pharmaceutical contract manufacturing market generated $13.43 billion in revenue and a CAGR of 6.6% through 2017. Solid dose formulations comprise the largest segment, says Frost, constituting 49.8% of the total CMO market. However, injectable dose formulations are identified as a primary outsourcing growth driver through the forecasted period with a strong 13% CAGR.

Ajinomoto Althea, a specialist in cGMP-compliant manufacturing and aseptic filling of sterile injectable therapies, is also producing protein delivery technologies for recombinant protein and parenteral products. According to Ajinomoto Althea's Jack Wright, vice president sales and marketing, "One of the biggest market trends that will impact … our business specifically in the years to come, is the increase in outsourcing by Pharma and Biotech companies. The improvements in the CMO market environment stem primarily from new drug approvals, greater funding of biotechnology companies and demand for new services."

Despite the highest number of patent expiries in history (some 40 in 2012), spending in the U.S. will grow by $35-45 billion over the next five years, representing an average annual growth rate of 1-4%, as newer medicines that address unmet needs are introduced and patient access expands in 2014 due to implementation of the Affordable Care Act, explains IMS. In Europe, growth will be in the -1 to 2 percent range due to significant austerity programs and healthcare cost-containment initiatives.

Health systems in pharmerging markets are also increasing spending on drugs, driven by rising incomes, better access to cost-controlled drugs and the effectiveness of government-sponsored programs aiming to increase treatment access — by limiting patients' exposure to costs and encouraging greater use of medicines. Most analysts agree Pharma manufacturers will see flat growth in branded products through 2016. However, as noted, small molecule generics manufacturers are experiencing accelerating growth. Treatments for global priority diseases, such as malaria, tuberculosis and neglected diseases are also expected to improve and drive global pharmaceutical capacity expansion.

MORE DEMAND, BETTER PRODUCTION

Biologics manufacturers are also benefiting and reacting to expanding market opportunity. Biologics are expected to account for about 17 percent of total global spending on medicines by 2016, says IMS: "Seven of the top 10 global medicines by spending will be a biologic within five years." The biopharma industry's continued focus on process efficiency is being fueled by advances in biosimilars, smaller volume drugs, shorter drug lifecycles (faster trials, development cycles), and high-volume product manufacturing issues.

To evaluate the trends that are shaping the bioprocessing segment today, BioPlan Associates recently surveyed 450 global subject matter experts and senior participants on its Biotechnology Industry Council panel of bioprocessing

professionals and asked them to identify the most critical factors and trends they expect will need to be addressed over the coming year. While "process efficiency" was a unifying thread, three clear sub-topics emerged: downstream processing; analytical methods development; and single-use system integration. This year, the industry will see an increase in multi-product facilities, selective single-use adoption (both in clinical and commercial stage), a ramping up of continuous processing, and more advanced automation and monitoring. With downstream processing continuing to lag improvements in upstream, the industry will continue to look for better performing chromatography resins and consider alternatives to protein A.

Pharmaceutical manufacturers are responding to competition and change by decreasing manufacturing costs, primarily by increasing outsourcing to contract manufacturing organizations, onshore and off. Although they have closed many manufacturing plants, pharmaceutical manufacturers are building new capacity throughout the world, particularly bio-pharm plants, in high growth regions, using modular technology and disposable process equipment to reduce cost and risk.

In February, the FDA released "Guidance Agenda: New & Revised Draft Guidances CDER is planning to Publish during Calendar Year 2014." Under the category, "Quality: Facility, Production and Process Control" FDA listed their agenda, which includes intended guidance on CMO Quality Agreements, GXP considerations for outsourced IT (cloud computing), and most notably for manufacturers "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice."

Since its inception 14 years ago, cGMP implementation has been executed by Pharma manufacturers with varying degrees of success. International regulators, especially the FDA, are pressing this agenda and remain committed to it, increasing their budgets and seeking revenues to help the entire global industry move toward its goals of drug quality and safety through manufacturing and process excellence. In her February 14 Blog, FDA director Margaret Hamburg noted after her visit to India, "In my talks with regulators and companies here in India, I have placed a great deal of emphasis on why quality matters. As I explained, quality is linked to product safety, and without a direct focus on quality, the potential for patient harm increases significantly. In recent years the FDA has identified significant lapses in quality by some companies operating in the U.S. and around the world. As a result, American consumers have had to endure greater risk of illnesses, recalls and warnings about the products many of them rely on each day. This is unacceptable. Consumers should be confident that the products they are using are safe and high quality, and when companies sacrifice quality — putting consumers at risk — they must be held accountable."

In his recent blog post on pharmaevolution.com, Girish Malhotra, PE, president, EPCOT International, notes that despite ongoing product-quality issues, drug companies remain profitable. Malhotra explains that since profits are still being achieved with the current inefficient practices, leadership will remain resistant to improving its product development, business and manufacturing practices.

Malhotra predicts that over the next 5 to 15 years, that instead of becoming "process-centric," as regulators hope, Pharma will stay "regulation-centric," and "hedge in adopting many of the internal changes (manufacturing methods, technology and supply-chain improvements) that could improve profitability and move from the current quality by analysis/aggravation to a quality by design approach (QbD)."

Noting that this is due to regulatory constraints, Malhotra explains short patent lives for the ethical (brand) drugs are likely to impede innovation in manufacturing technologies. "Process-centricity, if adopted," says Malhotra, "would allow companies to exceed regulatory requirements, which could also avoid many issues that have created public relations and financial headaches. Current regulatory guidelines and requirements discourage change. Since changing an existing process requires approval, it is still perceived to be a long and expensive step, and something to be avoided."

Malhotra offers that because, in his view, not much is forthcoming from the industry to improve its

manufacturing and business practices; regulatory bodies will pursue regulatory agendas that will force the industry to adopt better practices. "This tug of war will continue unless the industry takes the lead," he says.

Although Malhotra is pointing a well-earned finger at generics manufacturers (one look at recent headlines concerning quality issues coming from India's generics industry supports his assertion) not every generics producer is bereft when it comes to pursuing a regulatory approved quality agenda. Uri Hillel, head of R&D Quality and Corporate Quality & Compliance for Teva Pharmaceuticals, explained in an exchange with *Pharmaceutical Manufacturing* that Teva has worked on implementing guidelines defining Quality by Design (QbD) guidance and has adopted the QbD philosophy in its development of generic products. "For Teva, this means understanding the products, formulations and processes in depth, and submitting appropriate applications to the authorities using a more systematic development approach."

> Pharma manufacturers are responding to competition and change by decreasing manufacturing costs, primarily by increasing outsourcing to contract manufacturing organizations, onshore and off.

Achieving appropriate quality outcomes is the generally understood goal of prevailing regulatory guidance, and those companies that adopt both QbD and (ICH Q10) Pharmaceutical Quality Systems will achieve the "desired state" of pharma manufacturing. And Hallel agrees: "By implementing QbD (ICH Q8, 9) together with ICH Q10 (which is an integrated part of QbD implementation), we can reach the ultimate goal: providing uninterrupted supply of affordable, high-quality medicines to our patient. This is the desired state for the customer and for the industry, while enhanced product and process understanding will facilitate substantial efficient tech transfers, higher rates of successful validation and timely introduction of new medicines to the patients."

The manufacturing of pharmaceutical tablets is moving from its traditional batch process to continuous processing. While chemical and other industries have successfully implemented continuous manufacturing for many years, the drug industry has been slow to change due to the impact of FDA regulation.

Emerson's Jim Lustri explains that for pharmaceutical the financial driver for the move to continuous manufacturing is a significant reduction in capital and operating costs. A batch process typically will have capacity utilization of 35%. This is caused by a significant amount of equipment usage lost to preparation, cleaning and scheduling.

"On the other hand," says Lustri, "a continuous process can have a capacity utilization of over 80%." Emerson says this means a continuous process can make the same amount of production in much smaller equipment. Additionally, continuous processes require less human activity to transport materials between units, so there is a savings in manpower as well.

TOWARDS A BETTER STATE

As demand for safe effective, high quality drugs at lower prices continues unabated, drug manufacturers and their financiers will respond because these are the market conditions in which the industry exists. Some companies will thrive and be profitable because they are adept at implementing change and instituting processes and procedures to improve the cost effectiveness and efficiency of their manufacturing operations. Others won't be as successful and they are already being shaken out of the Pharma universe. Regulators and politicians are adding their own pressures, but ultimately, pharmaceutical manufacturing will achieve a better state because so much is riding on the fact that they do.

KEEPING CALM & CARRYING ON

PhM's 2014 Reader Survey reveals respondents are recognizing relative stability amidst ever-present change and challenging market conditions

By Steven E. Kuehn, Editor-in-Chief

SINCE ITS inception, *Pharmaceutical Manufacturing* has been surveying its readers annually to get a sense of how they are feeling about their jobs and the usual pressures of being employed by the pharmaceutical industry. We've asked about who they are as professionals, where they fit in their organizations and about their attitudes regarding job satisfaction and dissatisfaction. *Pharmaceutical Manufacturing* 2014 Reader survey continued the tradition asking readers to respond to 23 questions in an attempt to better understand ourselves within the context of the profession and provide a mirror to reflect common themes shared by all those serving the industry in 2014. Response to this year's survey remained robust; readers did not have to answer every question, but there were generally no less than 360 readers responding to every question in the survey.

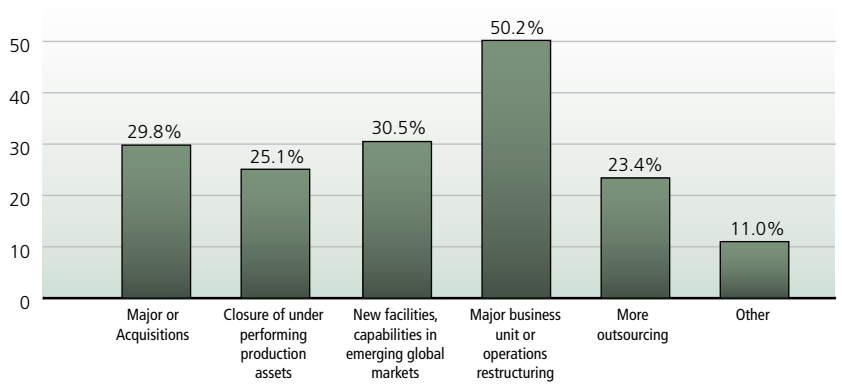
Before we jump a little deeper into what respondents are feeling and trends they are being exposed to over recent times, let's take a quick look at the demographic profile PhM's responding readers provided by their responses. For the most part, respondents were predominately male (82.7% of 365 responses), a majority ranging in age from 30 to 55 and older, with a Bachelor's or Master's degree in either chemical engineering, chemistry, biology or mechanical engineering. Most fill operational roles (66.5% of 367 responses) across manufacturing, quality assessment, plant engineering and R&D categories. A solid 2/3 of respondents hold management roles (have staff to supervise), with the remainder occupying "individual contributor" roles (in the parlance of HR departments of large-scale technical enterprises). For the most part, these folks, and that includes the third of responding women) have been working in the industry from 11 to 20, to more than 20 years (37.1 and 36.5%, respectively) with next largest chunk (11.4%) toiling for Pharma from 7 to 10 years. In other words, most of PhM's respondents continue to enjoy long-term careers in Pharma, and salaries reflect the career maturity of those responding with most (29.2% of 364 respondents) making salaries between $100,000 and $150,000. For others, 17.1% have salaries ranging from $80,000 to $100,000, 13.8% claim annual salaries over $150,000, 11.35% over $200,000.

READERS INCREASINGLY GLOBAL

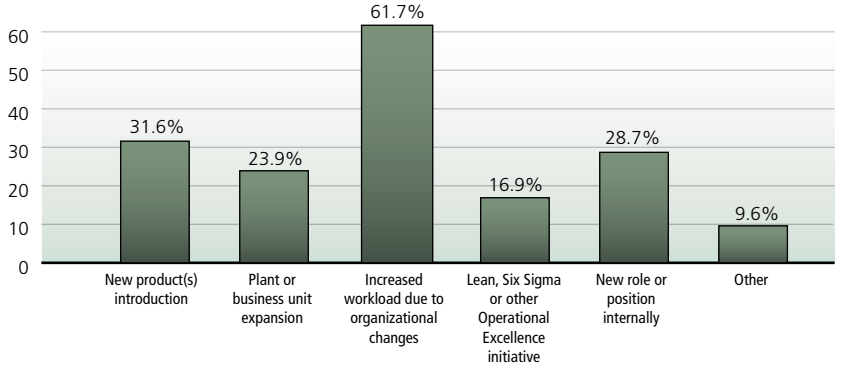
Meanwhile, 73.3% of 367 respondents hail from North America, which is lower by about 10 points than 2013. Apparently making up the difference were respondents from other major regions with a five-point bump from India and three-point bump in respondents from China. What kind of companies are our increasingly global respondents working for? Of the 367 respondents, 23.7% work for a "traditional" Big Pharma company, 17.2% at a "small or mid-sized specialty pharmaceutical manufacturer" followed by generics manufacturers (15%), biopharmaceutical manufacturers (9.5%), vendor/solutions providers (9.5%) and contract manufacturers (9%). Consultancies and "other," which included regulators, academics, OTC makers and excipient manufacturers.

Of all the things we queried our readers about, the second highest number (416) responded to rate their level of job satisfaction. Though 40.6% rated their job satisfaction "okay," 35.8% rated it "high" and another

How have market and competitive forces affected your company recently?



What are the biggest changes that you've had to face in the past year?



10.1% rated it "very high." That left only 13.5% rating it "poor" or "very poor." What was great, and affirming for the profession is that when asked, "What is most important to you for job satisfaction," 30.2% selected "challenging work." Not surprisingly, "salary and benefits" at 23.7% was the next biggest contributor to job satisfaction, followed by "opportunity for advancement" coming in third at 17.5%. Job security, at 13%, was less of a concern in the context of job satisfaction.

What things are making PhM's readers dissatisfied? For starters, slightly fewer comments were received regarding negative forces impacting job satisfaction. This is often rare, because surveys such as these tend to attract people needing a place to vent their frustrations.

Although PhM's survey structure and format do not necessarily support statistically rigorous comparisons and subsequently robust trend conjecture, notable is the fact that, among last year's 398 respondents, 63.1% were concerned with job security while this year (416 total responses) 55.5% were concerned about job security. For those concerned, 114 respondents (50% of the 228 responses to this question) identified "internal cost-cutting measures" as the biggest boogie man when it comes to Pharma personnel's fears concerning their job security.

IN THE FACE OF CHANGE

Pharmaceutical Manufacturing asked readers, "What are the biggest changes that you have had to face in the past year?" And their responses reflected trends affecting the Pharma universe and the dynamics that are impacting operations, including merger activity, new product introductions and capacity changes. Of the 415 responding, 61.7% felt the biggest change they were facing was "increased workload due to organizational changes," which to a certain extent reflects the extra work associated with transacting mergers and acquisitions and structural changes to operations in response to recent market forces. Regarding products, 31.6% said that "new product introduction(s)" was the biggest change they were facing, followed by 28.7% dealing with a new role within their organization. In the "other" category, readers could write in what change was affecting them; comments ran the gamut, but "increased regulatory scrutiny" was mentioned several times as was "shutdown of a facility," and "project disruption due to merger."

Not surprisingly, when asked directly, "How have market and competitive forces affected your company recently?" respondents (410) replies again reflected major trends impinging change on Pharma's operations. For example, 50.2% selected "major business unit or operations restructuring as the elephant in the room, followed by 30.5% noting that "new facilities, capabilities in emerging global markets," were keeping them busy. Garnering similar numbers were "major acquisitions" (29.8%), "closure of underperforming production assets," (25.1%) and "more outsourcing" (23.4%). In the "other" category, respondents wrote in a variety of things affecting their companies including "lower margins," "loss of patents," and on a hopeful note: "sales grew 20%."

INSIGHTS ON INDIA

Challenging conditions to continue in 2014

By Cher Boon Piang, Pharmaceuticals & Healthcare Analyst, Business Monitor International

2013 WAS a challenging year for pharmaceutical firms operating in India. Data from primary research firm AIOCD Pharmasofttech AWACS showed that pharmaceutical sales grew by an average 5.7% in 2013, a far cry from the average growth of 15.3% recorded in 2012. A number of factors have led to the decline in attractiveness of the Indian pharmaceutical market.

DRUG PRICE CONTROL ORDER (DPCO) 2013

In May 2013, India's Department of Pharmaceuticals released a Drug Price Control Order (DPCO), reducing the prices of 348 drugs included in the essential drug list as part of the government's aim to make healthcare affordable for the country's vast 1.2 billion population. The DPCO was cited by Wockhardt, Ranbaxy and Dr Reddy's Laboratories as a challenge to their financial performance. Furthermore, in January 2014, Alok Sonig, senior vice president and India Business Head (Generics) of Dr Reddy's, stated that the firm's revenues for 15 to 20 drugs will be affected by the DPCO, leading to a 5% overall decline in the firm's revenues in the country.

CLINICAL TRIALS HALTED

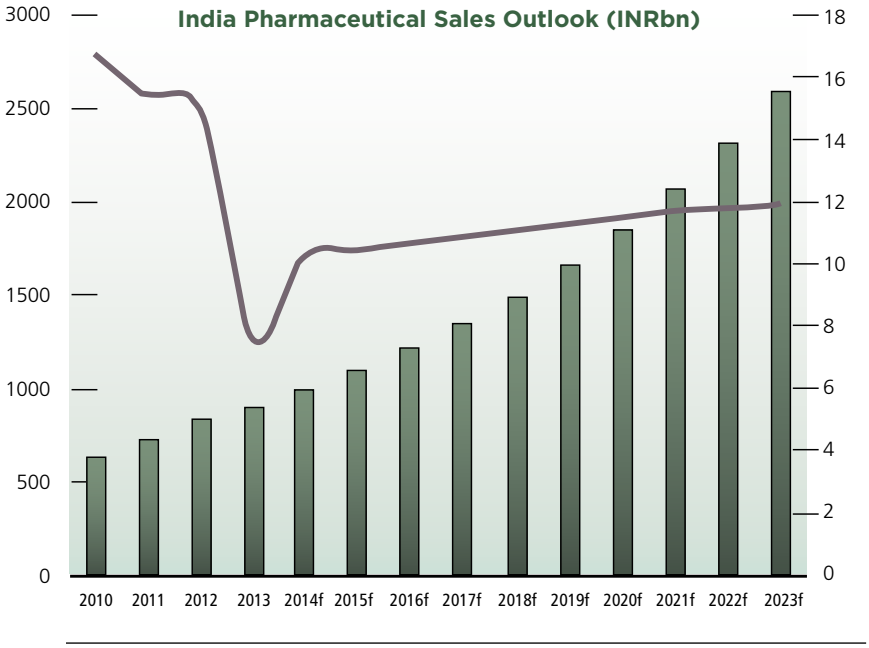
The stopping of clinical trials has been partly due to lax regulations, deaths and other serious adverse reactions, which were not properly reported. Between 2005 and 2012, a total of 2,868 deaths were linked to clinical trials, with 89 of the cases attributed directly to trials — although compensation was only paid to 45 of these victims. Amendments were subsequently made in January 2013 to the Drug and Cosmetics (Third Amendment) Rules 2013 to safeguard patient safety in clinical trials. Following this, in September 2013, the Supreme Court halted clinical trial approvals in the country, stating that there were no comprehensive rules available to regulate the sector. At the time of writing, the country has yet to approve any new clinical trials.

This essentially means that India has halted approval of clinical trials for approximately a year. This has a significant negative impact on pharmaceutical firms that are looking to launch new drugs in the country, affecting revenues and overall sentiment towards this once very promising emerging pharmaceutical market.

2013 was a confusing year in terms of understanding India's position on intellectual property protection. In March 2013, the country rejected Novartis' appeal for patent protection for Gilvec (imatinib), ending a seven-year patent conflict. However, in the following months, it rejected compulsory license applications for various drugs, including Roche's Herceptin (trastuzumab) and Bristol-Myers Squibb's Sprycel (dasatinib), as well as upholding the patent granted for the original compound, laptinib, of GlaxoSmithKline's Tykerb. The country's less aggressive stance on patent protection spells good news for multinational pharmaceutical companies, although the situation may reverse, given the high cost of innovative drugs.

INTERNATIONAL MARKETS FOR GROWTH

Business Monitor International finds that several domestic pharmaceutical companies are well placed to limit the negative impact of uncertainties in the domestic pharmaceutical market, given that the majority of their revenues are generated overseas — particularly in developed states in the U.S. and Europe. However, even the international market is



proving to be challenging for some Indian domestic companies, due to disparities in manufacturing standards. This is particularly so for Ranbaxy; the company's conflict with the U.S. Food and Drug Administration (FDA) places it at the center of the issue:

January 2013: The U.S. Department of Justice (DoJ) filed a consent decree of permanent injunction against Ranbaxy. The decree required the firm to comply with detailed data integrity provisions and prevented Ranbaxy's drugs from entering the U.S. market. The generic drugs in question were manufactured at Ranbaxy's facilities in Paonta Sahib and Dewas, India, including drugs such as Sotret (isotretinoin), gabapentin and ciprofloxacin.

May 2013: The firm pleaded guilty to felony charges relating to the manufacture and distribution of certain adulterated drugs made at two of Ranbaxy's manufacturing facilities in India. Ranbaxy also agreed to pay fines totaling $500 million. The investigation dated back to the period immediately before Ranbaxy was acquired by Daiichi Sankyo, in mid- 2008.

September 2013: The FDA issued an import alert on products manufactured at Ranbaxy's Mohali

plant in India until the company complies with U.S. current GMP standards. The agency identified "significant cGMP violations" at the facility during inspections in September and December 2012, including the firm's failure to "adequately investigate manufacturing problems." During the inspections, the FDA found a black fiber in a tablet that could be a human hair.

Despite promises by Ranbaxy and its parent company, Daiichi Sankyo to improve manufacturing standards, in January 2014, the FDA issued Form 483 to the firm, indicating that its investigator(s) have observed potential violations of the U.S. Food Drug and Cosmetics Act at its active pharmaceutical ingredient (API) plant at Toansa, India.

In addition to the FDA actions against Indian pharmaceutical firms, the European Medicines Agency (EMA) is increasing its scrutiny of potential manufacturing non-compliance in firms producing generic drugs. In December 2013, the FDA announced that the EMA, France, Germany, Italy, the Netherlands and the UK will work together on joint inspections globally to ensure that generic medications are safe and effective. Given that India is a global powerhouse for generic drug production, the country will see increased scrutiny in its drug manufacturing process. Companies that are unable to fulfill criteria laid out by the two regulatory authorities will lose out on the rising demand for generic drugs in the United States and Europe.

Business Monitor International holds a relatively neutral view on India's domestic pharmaceutical sector, given that pharmaceutical growth rebounded from negative territory (between September and October 2013) to relatively healthy numbers in November (+6.9%) and December (+8.2%). This potentially suggests that the effects of the DPCO 2013 will wean off slightly in 2014. However, extensive bureaucracy remains a key downside risk to the pharmaceutical industry's growth potential.

By Steven E. Kuehn, Editor-in-Chief

THE ROAD AHEAD FOR CONTRACT SERVICE EXCELLENCE

Leading contract service organizations discuss operations and strategies driving success

SAY WHAT you will about contract manufacturing and services companies, but the operations they've got out on the road these days are driving more and more of the industry's strategic successes — and that's pretty exciting. While The Maybachs, Rolls-Royces and Cadillacs of Big Pharma were cruising rough roads, finding new strategic routes past cGMP construction zones and patent-cliff detours, The Aston-Martins, Porsches and Maseratis — Contract Pharma's Grand Tourers — started downshifting, not only to better compete for the growing business opportunities that their executive-class clients were offering, but also to accelerate their own strategic ambitions as independent pharmaceutical manufacturing concerns.

Whether CMO, CDMO, CRO or some combination of all three, Contract Pharma is taking advantage of lighter, better handling operational platforms, high performance quality regimes and new sport-tuned process and information technologies to accelerate their capabilities and keep pace with the demand for their services.

Last summer, Catalent opened its new biomanufacturing facility in Madison, Wis. The new plant features state-of-the-art disposable technology and an efficient process layout that supports sterility and throughput.

ON INDUSTRY TRENDS

Patheon's Harry Gill, senior vice president, quality and continuous improvement, finds that for the customer market, "We are observing a shrinking fixed asset base among large Pharma, as there has been 4% CAGR decline since 2007." He notes that more mid-sized and specialty pharmaceutical companies are maintaining core competencies in research and commercialization while outsourcing the rest. "Additionally," says Gill, "we are noticing that more emerging biotech companies are using

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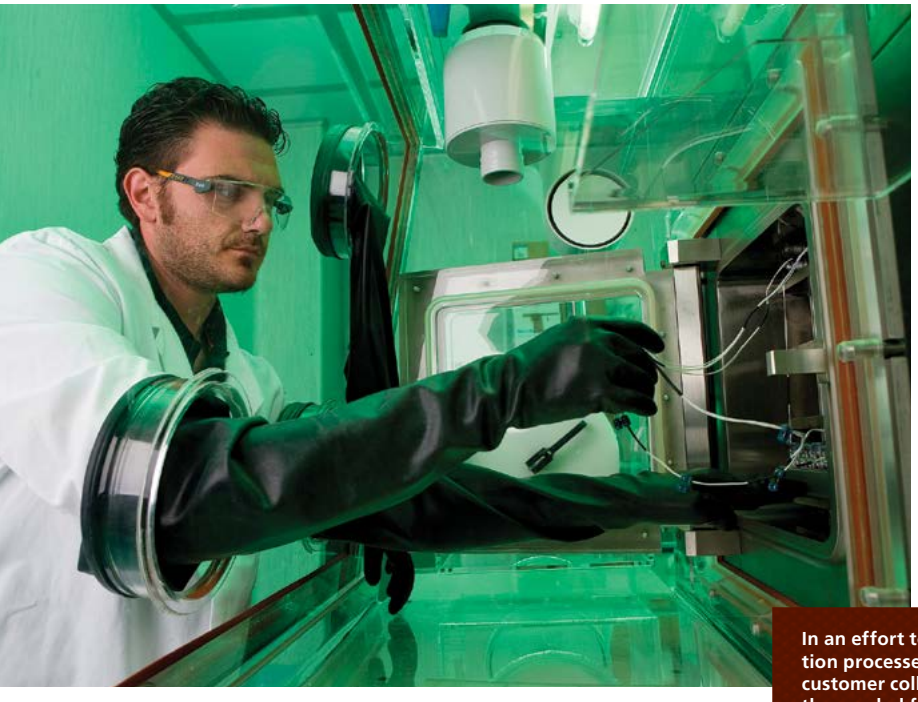

In an effort to utilize technology to improve communication processes with its customers, Patheon established a customer collaboration strategy and platform that provides the needed framework for information exchange and enables the company to share information electronically with its customers.

virtual outsourcing models and generic companies are outsourcing more of their complex products."

In 2012, says the August 2013 Frost & Sullivan report "Global Pharmaceutical Contract Manufacturing Market," the global pharmaceutical contract manufacturing market generated $13.43 billion in revenue and a CAGR of 6.6% through 2017. Solid dose formulations comprise the largest segment, say Frost analysts, constituting 49.8% of the total CMO market, but point to injectable dose formulations as a primary outsourcing growth driver through the forecasted period with a strong 13% CAGR. Frost & Sullivan's study points to several key drivers of this growth, including increasing demand for safe effective solid-dose generics and sterile products and increased focus on complex disease therapies answered by lyophilized and sterile cytotoxics for oncological disease management. Behind it all: "Because of Big Pharma's increased outsourcing, the pharmaceutical contract manufacturing market is expected to show consistent growth."

Ajinomoto Althea, which says it specializes in cGMP-compliant manufacturing and aseptic filling of sterile injectable therapies, is also producing protein delivery technologies for recombinant protein and parenteral products. According to Ajinomoto Althea's Jack Wright, vice president, sales and marketing, "One of the biggest market trends that will impact … our business specifically in the years to come, is the increase in outsourcing by Pharma and Biotech companies. The improvements in the CMO market environment stem primarily from new drug approvals, greater funding of biotechnology companies and demand for new services." Biologics hold great potential, he says. "In an effort to cut costs, many biopharmaceutical companies are choosing to outsource the manufacture of their drugs instead of investing in [the] … facilities suitable for

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DSM has integrated its own innovative and proprietary technologies including XD process technology and its RHOBUST direct capture downstream technology that optimizes bioprocess manufacturing processes, driving down cost and processing times at its new Brisbane facility.

manufacturing the drugs themselves."

Biologics (as do opportunities from complex solid dose formulations) do hold great potential for CMO business, and to better meet such demand, companies are merging and acquiring new capabilities to meet it. Case in point is the November 2013 announcement from Royale DSM that DSM Pharmaceuticals, its finished dosage business, was being combined with Patheon to form a yet-to-be-named (dubbed NewCo in the press release) company that will create an "industry leader" custom development and manufacturing organization (CDMO) for the pharma sector. According to DSM, the creation of NewCo will take DSM from being one of the smaller units of the larger parent to that of a dedicated CDMO with Patheon, and in the process promulgate $2 billion in sales from the work of 8,300 employees worldwide with capabilities for the manufacture of small molecule API and intermediates, biopharmaceuticals via mammalian cell cultures and microbial fermentation. Comprehensive dose form capabilities ranging from oral solid dose to sterile injectables are also on the menu as well.

A merger, no doubt, that's a strategic response to market trends. DSM's Hank Nowak Sr., director, business development & account management notes that analyses of pharmaceutical product pipelines clearly show evidence of an increasing trend towards two major growth areas: molecules more cheaply and efficiently. If a better, more cost effective synthetic route can be devised, particularly if the IP is protected in some way, this can enable CMOs to gain advantages in the manufacture and supply of individual APIs to secondary manufacturers."

Whether through research, survey or anecdotal evidence, there is plenty of data supporting Holton and Bottomley's assertion that CMOs are the engines revving development and manufacturing innovation, something backed up by the CMOs queried for this look across the CMO fleet. "Customers come to DSM Pharmaceuticals for support of complex drug product development," says DSM's Nowak. "As a traditional contract manufacturing organization DSM must continually innovate its processes and technologies to stay ahead of the ever-changing and complex requests made by our customers. Pharma companies will continue to increase their demands for flexible, reputable and high-quality CMO partners. Many Pharma companies will co-invest to build out particular technologies, processes and capacity. Some CMOs will begin to assume more risk during the product-development phases, and in turn, will expect to receive milestone payments."

Elliott Berger, Catalent's Vice President, Global Marketing & Strategy explains that with a high proportion of drugs in development suffering from poor solubility and/or permeability, customers are increasingly looking for partners to help improve the bioavailability of their development products or to optimize the treatment to patients. "Formulations vary significantly,

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so it is helpful that Catalent is able to offer a variety of technologies that improve the effectiveness of pharmaceutical products for certain patient groups; for example, those who have difficulty swallowing, to alter the release profile of an API into the bloodstream, perhaps making the dose more convenient or minimizing side-effects — that is, to delay or pulse release, or to combine multiple APIs in one convenient dose form — to prevent abuse or redirection, and ultimately to make better treatments that are clearly differentiated from a patient and payer perspective."

Vetter's Soelkner finds that the ability to innovate in response to a customer's technical roadblocks is really the stock-in-trade of successful CMOs. "As a strategic partner for (bio-) pharmaceutical companies in today's complex environment, we are continually being challenged to develop new services and products in order to support them in the best possible way." He explains that state-of-the-art technology, while critical to the process, is not the only requirement that it takes to be successful. "This is particularly true when considering the ever-growing share of more and more complex molecules and sensitive drug substances. Experience-based solutions that conclude in innovative and product-specific approaches in development and commercial manufacturing are equally important and are playing an ever-increasing role in realizing successful outcomes."

Ajinomoto Althea's Wright notes that innovation in Pharma is characteristically different than other industries. "While many other industries are made up of individual innovations that can be differentiated, the Pharma industry as a whole represents innovation. The mere nature of the industry is comprised of continuous advances that strive to push the frontiers of medicine and bring life-saving medicines to those in need. In an industry as complex as pharmaceuticals and life sciences, there are many challenges to overcome, and a single solution to a challenge helps push the entire industry forward."

As a whole, the industry is now less able to sustain the research and development budgets of years gone by, says Catalent's Berger. "If innovation were ever proportional to R&D activity, then it would naturally have declined unless new models of research and development were found.

Innovation is becoming more challenging for pharma because of the more difficult molecules coming through their pipelines — often for rare disease states and specialty treatments. "We believe innovation is ramping up of late, taking advantage of better economic and funding environments," says Berger. "We partner with customers in helping to drive this innovation with advanced drug delivery technologies that help take these molecules from 'desired drug delivery profiles' into 'successful treatments,' facilitating a less difficult road from lab to patient."

Vetter finds that the ability to innovate in response to a customer's technical roadblocks is really the stock-in-trade of successful CMOs. As a strategic partner to companies in today's complex environment, CMOs are continually being challenged to develop new services and products in order to support customers in the best possible way.

For biopharmaceuticals it's well established that the process is the product, but it might be fair to say that for CMOs — regardless of small or large molecule production — process is their true product, and strategically the means in which these companies excel and differentiate themselves by creating and sustaining the value (and hence profitable sales) for their services. "In regards to DSM's high-value offerings," says

CONTRACT SERVICE EXCELLENCE

Nowak, "we were the first Safebridge Certified cytotoxics sterile production site globally. We also have the largest lyophilization capacity in the North American CMO industry category."

One notable challenge within Pharma, notes Wright, is the difficulty of getting certain complex proteins to express accurately and with high purity. Low yields, protein degradation, aggregation, and timely purification processes are common frustrations with protein expression in microbial systems. "Through its patented and novel expression technology, Corynex, Ajinomoto Althea can provide the industry a solution to many of these problems, says Wright. "Using the bacterium strand *Corynebacterium glutamicum*, Corynex is able to secrete fully active and folded proteins, with high initial purity, directly into the cell medium. This eliminates many of the costly and time-consuming purification steps required with traditional expression systems."

Last October, DSM Pharmaceutical Products officially announced opening of its new cGMP facility for biopharmaceutical contract manufacturing in Brisbane, Australia. The Brisbane facility serves DSM's blueprint for its future. Not only does the facility field current industry standard technologies, DSM has integrated its own innovative and proprietary technologies including XD process technology and its RHOBUST direct capture downstream technology that optimizes bioprocess manufacturing processes, driving down cost and processing times. DSM's proprietary techniques and technologies, says the company, can cut out several processing steps. According to DSM, its XD cell culture technology achieves 5 to 25 times higher product output than standard processes, producing very high cell densities while retaining high cell viability and consistent quality.

Catalent continues to make significant investment into drug delivery technologies, capabilities, as well, maintaining the presence necessary to help Pharma's innovators bring better products to market. "In fact," says Berger, "around $1 billion has been invested globally over the last five years. Catalent's strategy has, for some time, been to build deep expertise in those segments in which we operate, and we have invested on a major scale in quality people and processes to ensure reliable global supply." Speaking of reliable supply, last summer Catalent opened its new biomanufacturing facility in Madison, Wis., that features state-of-the-art disposable technology and an efficient process layout that supports sterility and throughput. "We don't compromise on quality. We maintain a single Quality Management System and our inspection outcomes are three times better than the industry average, and we are approved to ship to over 80 countries," says Berger.

Catalent counts among its value leaders a number of innovative offerings including advanced SMARTag ADC technology in partnership with Redwood BioSciences, an advanced oral dose form development and supply including OptiMelt hot melt extrusion technology in Europe, expert development to final dose scale up and manufacturing in the U.S., as well as OptiDose tableting technologies for sophisticated drug delivery profiles including combination therapies, complex timed delivery and pulsatile release. Catalent says it also offers oral delivery of macromolecules with its new industry-leading technologies OptiGel Bio and Zydis Bio.

Irvine Pharmaceutical Services says supporting its value to customers is the company's ability to accelerate its processes to meet customer's needs. "We believe our manufacturing turnaround time, typically less than 25 days, is among the best in the CMO space," says Ruby. "We can accomplish this task because we have invested in experienced operators and talented scientists."

INFORMATION SHARING AND COLLABORATION

A key area in which Catalent is making rapid advancement in data and information sharing is with its global Clinical Trial Supply business focusing on digital solutions for advanced Clinical Supply Management, inventory and supply transparency and customer data access. Irvine is currently in the process of moving its IT infrastructure to a secure and compliant cloud-based system. "With well established systems and contingency plans," says Ruby, this update in infrastructure allows Irvine to have even stronger data security and system reliability.

We are also implementing secure, Web-based client access to real time data and project status updates."

With broad geographic operations, Patheon's systems landscape is complex, which can make collaboration and information sharing tough. "As a global CMO," explains Charlie Lickfold, Vice President and head of IT, "We have specific challenges that we use information technology to help resolve. In an effort to utilize technology to improve communication processes with our customers, Patheon established and utilizes a customer collaboration strategy and platform. This platform provides the needed framework for information exchange, which enables us to exchange and share information electronically with our customers." This electronic collaboration solution, says Patheon, allows the company to expedite supply chain processes and simplify the means of information exchange by providing a single integration point for all of Patheon's sites to its customers.

LAST WORD

"Innovation comes from many sources," explains Catalent's Berger, "and through effective collaboration between those engaged in the improvement of medicines, improved clinical outcomes can be found." Berger says that is why his company established the Catalent Applied Drug Delivery Institute with the aim of "harnessing the knowledge of the world's leading experts; partnering with pharmaceutical companies; facilitating mutually beneficial collaborations; and sponsoring, educating and counseling to advance the adoption of emerging technologies."

The Current State of Pharmaceutical Industry Research and Development

Prepared by the Frankel Group LLC Advisory Board

An innovation drought has significantly affected the viability of the current pharma business model.

An industry dependent on innovation is losing the ability to innovate. And, there is an increasing clustering of development in niche areas and away from the core primary care indications, where longer term success will be dependent on premium pricing for follow-on drugs in niche indications (and across the larger indications) which may not be sustainable.

This appears to be due to a number of factors, which are described in some detail in "The Current State of Pharmaceutical Industry Research and Development."

1. Insufficient focus in the current business model ... be it highly innovative or re-engineering, internal or external source of innovation ... and not grafting on ultimately disruptive innovation that can cycle between platform and therapeutic areas.

2. A project measurement gap exists that affects the efficient deployment of capital, which challenges measurement of the risk/return of complex, often hard to predict development projects ... and therefore creating sub-optimal organizational structures and incentives.

3. Cost and organizational challenges are relatively widespread, reducing R&D productivity, spreading beyond R&D organizations to commercial post launch requirements (e.g., safety monitoring).

4. Fundamentally, insufficient investment in translational research, hampered by current deal structures, non-creative deployment of development assets, and need for novel internal/external organizational structures.

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VIDEO

The Future of the Biopharmaceutical Industry

Rutgers Business School's Annual Healthcare Symposium

Presented by Blanche and Irwin Lerner Center for the Study of Pharmaceutical Management Issues at Rutgers Business School, this event provided the opportunity to share the knowledge of the biopharma industry experts. Take away from those who attended was the exchange of ideas and knowledge of the growth of the biopharma industry and networking.

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