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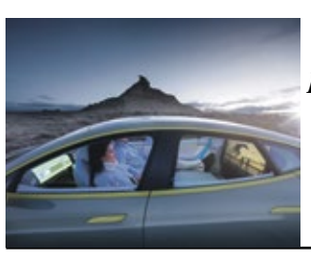

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People:
Dr. Marijn E. Dekkers has been elected as VCI President by the general assembly of the German Chemical Industry Association (VCI).

Dr. Thomas Colacot has been awarded the 2015 American Chemical Society (ACS) National Award for Industrial Chemistry.

Frank H. Lutz has been appointed CFO of Bayer MaterialScience effective October 1, 2014.

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Discovering The Future

How can Pharma Overcome Today's Challenges and Successfully Commit to Innovation Again?

Dramatic changes to the scientific and business environments have made it impossible for pharmaceutical companies to continue operating as they have in the past. A perceived decline in innovation, market competition from generics, skyrocketing R&D costs, increased regulatory hurdles to develop and test new drugs, and key patent expirations on a number of blockbuster drugs – the so-called patent cliff – have all put significant pressure on branded pharmaceutical companies. The pharmaceutical industry (pharma) has responded to these challenges by embarking on a range of initiatives. The vibrant M&A activity in the sector, however, has not helped a lot to increase the output of new drugs. Dr. Magid Abou-Gharbia, a pharmaceutical industry veteran and director of the Moulder Center for Drug Discovery Research at Temple University School of Pharmacy in Philadelphia, discusses the challenges facing the pharmaceutical industry and pharma's responses, focusing on the industry's changing perspective and new business models for coping with the loss of talent and declining clinical pipelines.

Dr. Magid Abou-Gharbia, Director, Moulder Center for Drug Discovery Research, School of Pharmacy, Temple University, Philadelphia

CHEManager International: In a 2012 PricewaterhouseCoopers (PwC) report, a line by Charles Dickens was used to describe the situation that pharma finds itself facing: "It was the best of times, it was the worst of times … ." Does that quote describe the industry's situation adequately?

M. Abou-Gharbia: The quote from Charles Dickens seems very appropriate. Dramatic changes to the business and scientific environments in the pharmaceuticals sector have fundamentally altered how business must operate in order to survive in the 21st century. The industry has seen significant advancement in its ability to conduct scientific research through the development of an amazing array of tools, and revenue from drug sales is at or near an all-time high. Scientifically, it is the best of times. At the same time, however, the industry is faced with numerous challenges that must be addressed in order for the industry to thrive. A perceived decline in innovation, fierce market competition from generics, increased regulatory hurdles and key patent expirations on a number of "blockbuster" drugs – the so-called patent cliff – have all put significant pressure on branded pharmaceutical companies and threatened the future of the industry as a whole. Many companies have downsized, cut the number of research projects, outsourced functions, and undergone mergers and acquisitions in response to these challenges and the economic uncertainty that they create. The industry consolidation that we have witnessed over the past 15 years has dramatically decreased the number of industrial scientists pursuing novel therapies, decreasing the likelihood of success. From this standpoint, it is the worst of times.

In your opinion, which challenges are putting the highest pressure on pharmaceutical companies?

M. Abou-Gharbia: Without a doubt, the pharmaceuticals industry is facing significant challenges. The clearest threat to the branded pharmaceuticals companies is the lack of new products that can replace the products whose patents will expire in the next decade, which will result in a significant loss of revenue. It has been estimated that between 2011 and 2015, over $250 billion in sales of patent-protected drugs will be – or have become – vulnerable to generic competition. In the absence of new products, it is not clear how branded companies will move forward. Ironically, over the last 10 to 15 years, the majority of branded companies have been laying off the scientists and staff responsible for identifying the new drugs that they so desperately need. The ever-changing regulatory environment further complicates the task of bringing new drugs to market. Gaining regulatory approval for new drugs will always be required, but the shifting sands of the regulatory requirements are difficult to predict and sometimes contradictory across multiple jurisdictions. There are many examples of drugs that are FDA-approved but were turned down by the EMA – European Medicines Agency – and vice versa. In summary, the predominant challenge facing the industry is identifying and commercializing novel therapeutics in a changing and challenging environment.

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Bayer to Seek IPO for MaterialScience

Following years of pressure from financial markets to divest its engineering plastics business and focus on life sciences, Bayer has now decided the time is ripe.

On Sept. 18, the German holding's supervisory board greenlighted management's plans to shed the sub-group Bayer MaterialScience (BMS). The board's employee representatives agreed to the move in exchange for a guarantee that jobs in both the plastics and life science operations would be guaranteed up to the end of 2020. Provided the stock market climate appears favourable, CEO Marijn Dekkers said an initial public offering will be sought over the next 12-18 months for BMS, the world's leading manufacturer of polycarbonate and a leader in most global polyurethanes markets.

Alternatively, Dekkers said management would consider spinning off the business to shareholders, as was done ten years ago with the chemical activities that became Lanxess. He also did not rule out a direct sale if an attractive offer was made.

Dr. Marijn Dekkers, Chairman of the Board of Management, Bayer

In an ipo, BMS has been mooted to command anywhere between €8 billion and €12 billion, under the spin-off scenario considerably less, depending on how much debt Bayer decided to saddle the company with. With the recent launch of new pharmaceutical products, the debt-financed pending €10.4 billion acquisition of US Merck's consumer drugs business and the "very successful development" of the crop science business, Bayer's center of gravity has greatly shifted toward life sciences, the Dutch-born CEO explained. Citing one argument for the separation of MaterialScience, Dekkers said as a standalone company the plastics business would have the chance to obtain more funds for capital investment than Bayer, which needed to spend increasing sums on its pharmaceutical and agricultural chemicals businesses, would be willing to supply. In addition to making further acquisitions – analysts suggested that Zoetis, the veterinary products manufacturer spun off from Pfizer would be an attractive target – Dekkers said Bayer also plans to step up R&D spending on HealthCare and CropScience. The group will also continue driving the commercialization of recently launched pharmaceutical products, for which it expects combined peak annual sales potential of at least €7.5 billion.

Dekkers asserted also that a split from Bayer would allow BMS to make its own investment and portfolio decisions, giving it "the best development prospects in a highly competitive market." In the five years from 2009 to 2013, the plastics sub-group was extremely capital-intensive for the holding, which pumped more than €3.8 billion into tangible assets and R&D. Projects included world-scale production facilities in China and Europe, foremostly the new 400,000 t/y TDI plant at Dormagen.

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Merck KGaA to Buy Sigma-Aldrich

In the biggest acquisition in the history of the family-owned company, Darmstadt Germany-based chemicals, pharmaceuticals and laboratory products manufacturer Merck KGaA is opening its well-filled war chest to buy US-specialty life science company Sigma-Aldrich for $17 billion in cash.

The $140 per share offer unveiled on Sept. 22 represents a 37 % premium on the Sept. 19 closing price of the St Louis, Missouri firm, which has annual sales of $2.7 billion and claims to be the world's largest supplier of biochemical and organic chemicals to research laboratories. Buying Sigma-Aldrich – the transaction is expected to be completed in mid-2015 – will expand the portfolio of Merck's laboratory supply subsidiary Merck Millipore in North America and give it an enhanced presence in Asia.

Describing the deal as a "quantum leap" for Merck, CEO Karl-Ludwig Kley said that by offering a much broader product slate, the merged companies would be able to secure stable growth and profitability in an industry driven by globalization trends.

Dr. Karl-Ludwig Kley, Chairman of the Executive Board, Merck KGaA

Merck expects synergies of around €260 million ($334 million) within three years after closing. CFO Marcus Kuhnert said savings would come in part from combining manufacturing capacity and streamlining administrative functions. The portfolio is said to be complementary along the entire value chain of drug production and validation. No information on possible job losses or site closures has been announced. Sigma Aldrich currently has more than 9,000 employees in 40 countries. Its president and CEO, Rakesh Sachdev, called the takeover offer "a clear validation" of its successful transformation into a customer-focused and solution-oriented global organization." Both Sigma-Aldrich's board of directors and Merck's board of partners have signaled their approval. Kley said Merck has secured bridge financing for the cash deal and expects that the final financing structure to be comprised of a combination of cash, bank loans and bonds. The German company acquired US-based Merck Millipore in 2006 for $6 billion, the same year it bought Swiss biopharmaceuticals producer Serono for €10.3 billion ($ 13.3 billion).

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EU Approves Huntsman's Acquisition of Rockwood Businesses

The European Commission has cleared Huntsman's proposed acquisition of a number of Rockwood's chemical businesses in exchange for Huntsman's promise to divest its TR52 portfolio, the company's principal titanium dioxide (TiO_2) grade used in printing ink applications. This follows an in-depth investigation into the current state of the global TiO_2 market. The Commission had previously investigated the market in 2009, when Huntsman acquired Tronox manufacturing facilities in the US and the Netherlands, as well as a 50% share of a titanium ore mining and titanium dioxide manufacturing joint venture in Australia. Other Rockwood businesses being acquired by Huntsman include functional additives, color pigments, timber treatment and wood protection chemicals in North America, as well as water treatment chemicals and the supply of rubber automotive spare parts. Both parties to the current deal are based in the US; however, the EU's competition section said the combination of the two leading suppliers of the TiO_2 for printing ink applications would have created a dominant position for the merged US producer in the European Economic Area (EEA) and allowed it to raise prices.

The Commission said its investigation had also shown that the combined entity would not face sufficient competition from other titanium dioxide suppliers such as DuPont, Tronox, Kronos, eastern European and Asian producers, which it said lack the relevant know-how or incentives to expand on the market.

As the TiO_2 market is characterized by high barriers to entry, mostly linked to know-how and capital expenditure requirements, customers might find it difficult to switch to alternative suppliers, Brussels added. Huntsman's divestment of the global TR52 business, including the brand, technology and know-how, customer arrangements and some key personnel, has assured the EU that the overlap with the Rockwood activities will be removed, enabling the purchaser of the business to operate a viable business in competition with the merged entity and other market participants. The competition authority also examined the competitive effects of the proposed acquisition in the markets for cosmetics, pharmaceuticals and food, synthetic fibers, coatings, plastics and paper, as well as the markets for some byproducts of the titanium dioxide production, including ferrous sulfate and filter salts and concluded that Huntsman here will continue to face significant competition from players such as Kronos, DuPont and Precheza. The companies involved have agreed not to complete the transaction before finalizing a binding agreement for a sale of the affected business to a purchaser approved by the Commission. (dw) ■

Chevron Sells Evangeline Pipeline to Boardwalk

In a deal set to close in the fourth quarter, US oil and petrochemicals producer Chevron plans to sell its Evangeline ethylene pipeline system in Texas to Houston-based Boardwalk Pipeline Partners for $295 million in cash. The 176-mile interstate Evangeline system running from Port Neches, Texas to Baton Rouge, Louisiana is a "great strategic fit" with the Houston company's subsidiary Boardwalk Louisiana Midstream, BLM, which currently has one of the most extensive ethylene distribution systems in Louisiana, said BLM President Kevin Miller. BLM plans to connect Evangeline to its Sulphur Hub storage facilities in the Lake Charles, Louisiana area after the acquisition is completed. (dw) ■

UK Lends Hand to BP in US Gulf Spill Case

The British government has urged the US Supreme Court to review appeals court rulings against BP over the 2010 Deepwater Horizon oil spill on the coast, which killed 11 workers and released millions of barrels of oil into the Gulf of Mexico. The appeal came days after a US federal court in the state of Louisiana court ruled that BP was "grossly negligent" and "reckless" in the spill, a move that could add nearly $18 billion in fines to more than $42 billion in charges. Up to now, the British group has paid more than $28 billion in damage claims and cleanup costs as well as pleading guilty to criminal charges. Throughout the process, it has claimed that it was not chiefly or solely responsible, placing part of the blame on contractor Halliburton and Transocean. The Louisiana court, however, assigned BP 67% of the blame with 30% to Transocean and 3% to Halliburton. In its friend of court brief, the UK said the rulings raised grave international concerns by undermining confidence in the "vigorous and fair resolution of disputes."

BP argues that the decisions, if allowed to stand, will fundamentally alter class action law and discourage companies from settling complex cases. It also contends they will likely discourage companies from investing in the US if they are exposed to liability for losses they did not cause. (dw) ■

Arkema Makes Bid for Adhesives Manufacturer Bostik

French chemical producer Arkema has offered to acquire German adhesives manufacturer Bostik from its former parent company, oil and petrochemicals major Total. Arkema did not say how much it planned to pay for the manufacturer of adhesives and sealants used in products ranging from aircraft components and building materials to diapers. However, news agencies put the price at €1.74 billion. Bostik, which claims to be world's number three adhesives producer – rivals are Henkel and H.B. Fuller – has annual sales of just over €1.5 billion and nearly 5,000 employees. The chemical company said it hoped to finalize the deal, designed to expand its position in a fragmented global adhesive and sealants market, over the next several months. It plans to fund the deal through a €350 million rights issue, the issuance of hybrid securities worth €600-700 million and a senior bond issue for the remainder.

Under pressure from shareholders to improve its cash flow and raise dividends, Total has embarked on a major divestment program. After selling assets of $15-20 billion over the 2012-14 period, the company on Sept. 22 announced plans to divest assets worth an additional $10 billion in 2015-17. (dw) ■

FMC Set to Acquire Cheminova for $1.8 Billion

Danish holding company Auriga Industries is selling its crop protection unit Cheminova to US diversified chemical producer FMC for $1.8 billion. The holding had announced in July that it was considering a sale of the unit, its only business. Following the transaction, expected to close in early 2015, Auriga is to be dissolved. Auriga's shareholders are scheduled to approve the transaction at an extraordinary general meeting in October, and anti-trust authorities also must give their blessing for the deal. Cheminova develops and supplies crop protection products to increase the yield and quality of crops for farmers. The company, operating out of more than 20 countries, claims to have around 2–3% percent of the global market. (dw) ■

Google and Abbevie Partner on R&D for Age-related Illnesses

Calico, an investment firm founded by Google to fund projects aimed at delaying the human aging process, is partnering with US drugmaker Abbevie to develop therapies for age-related diseases of the nervous system, such as Parkinson's, as well as cancer. At the outset of the cooperation, each of the companies will make a financial contribution to the research valued at $250 million. At a later stage, contributions of around $500 million are envisioned, bringing the total to $1.5 billion. (dw) ■

Bayer to Seek IPO for MaterialScience

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At the same time, Asian competitors also spent heavily, widening the oversupply for polycarbonate, which observers identify as another part of the motivation behind Bayer's decision to quit the business. While most commentators saw the exit plastics as a logical step from Bayer's current perspective, some wondered openly about the prospects for a stock market launch of a company the size of BMS, which had nearly 17,000 employees, sales of more than €11 billion and EBITDA of just over €1 billion in 2013. In the past, having the plastics arm offered Bayer protection against hostile takeovers and drug-related lawsuits, such as the expensive settlements with patients affected by the cholesterol treatment Lipobay/Baycol that almost led the group to quit the pharmaceuticals market at the beginning of the millennium. In the meantime, analysts said, the build-up of life science assets makes holding onto MaterialScience unnecessary. HealthCare and CropScience now account for more than two-thirds of Bayer's group sales and almost 90% of earnings. Before the dust settled on the news of the BMS divestment plans, financial markets already were urging Bayer to separate its life sciences assets into two separate companies. ■

LyondellBasell May Add More Shale Gas-fed Ethylene in Texas

Petrochemicals giant LyondellBasell said it is weighing further expansion of its ethylene capacity at Channelview, Texas, potentially adding as much as 550 million lb/y (nearly 250,000 t/y) up to 2017. The Rotterdam-based group said preliminary engineering work is already under way to assess feasibility of the expansion, which would be in addition to the already announced installation of two large gas-fed cracking furnaces at the Channelview site, expected to lift output by 250 million lb/y by early 2105. LyondellBasell is grasping with both hands the chances offered by US shale gas-derived ethane. Tim Roberts, executive vice president, Olefins & Polyolefins Americas, said the group's strategy continues to be "the cost-effective expansion of existing facilities to take swift advantage of abundant supplies of low cost natural gas and ethane from shale production."

Last year, CEO Jim Gallogly said all US assets would be configured to run solely on domestically produced feedstocks, with up to 90% coming from natural gas. Along with the projects at Channelview, LyondellBasell is increasing ethylene capacity at two additional plants in Texas. An 800 million lb/y capacity build-up was recently completed at La Porte, and another 800 million lb/y expansion at Corpus Christi, Texas is due to be completed in late 2015. The three projects together will add 1.85 billion lb/y of ethylene capacity to LyondellBasell's US total, which, as Roberts noted, is the equivalent of constructing a new stand-alone cracking unit. If the plans just announced are realized, the new capacity addition will total 2.4 billion lb/y. (dw) ■

Activist Investor Urges DuPont to Split in Two

Through his hedge fund Trian, US activist investor Nelson Peltz, who has stirred up affairs at a number of other companies, has set his sights on breaking up chemical giant DuPont. Trian is one of the chemical company's largest shareholders, with a stake estimated to be worth $1.6 billion. Peltz, who has acknowledged private discussions with the company, said he could "no longer remain silent" as DuPont continues to destroy value through its conglomerate structure. The hedge fund owner added that the company's share price is 21% lower than its all-time high in 1998, its revenue growth lags its peers and management has lowered or missed its earnings guidance for three consecutive years. Beyond the already planned separation of the performance chemicals business, Peltz urges DuPont to break into two separate, autonomous businesses. A unit called GrowthCo should include agriculture, nutrition & health and industrial biosciences, while another, CyclicalCo, would encompass performance materials, safety & protection and electronics & communications. "We believe the Trian initiatives have the potential to double the value of DuPont's stock over the next three years," Peltz said. (dw) ■

Canadian Beekeepers Sue Syngenta and Bayer Over Neonics

Beekeepers in Canada's Ontario province are suing global chemical producers Syngenta and Bayer for $450 million, alleging that their neonicotinoid-based (neonic) pesticides are responsible for the phenomenon known as Colony Collapse Disorder. The lawsuit claims the companies were negligent in the design, sale manufacture and distribution of the pesticides used on corn, soybeans and many other crops. Neonic pesticide manufacturers contend that rather than the chemical crop protection agents, factors such as viruses, adverse weather conditions and loss of habitat, are responsible. Bayer is currently conducting research to support this argument. Tibor Szabo, vice president of the Ontario Beekeepers' Association, told the Canadian press that beekeepers learned long ago to cope with viruses, and the bee deaths that are gripping his industry are due to the consumption of pollen poisoned by neonicotinoids. The pesticides have been temporarily banned in the EU. The moratorium that went into effect in December 2013 applies to all crops except winter cereals and plants not attractive to bees, such as sugar beets.

Canada is also planning legislation and as a first move is proposing to require commercial growers to apply for permits to use neonicotinoid pesticides. News reports say that all corn and canola and half the soybean seeds planted across the country are coated by the manufacturers with neonicotinoids to make them resistant against grubs, worms and other insects. According to the Toronto newspaper Globe and Mail, farmers organized in the association Grain Farmers of Ontario are rejecting plans to restrict the use of neonics, saying this will hurt them financially and could lead to increased spraying of pesticides that are more damaging to the environment and humans. The organization said the proposal to require commercial growers to apply for permits should be put on hold until various research projects, including a three-year field test of new planting methods adopted last spring, are completed. (dw) ■

Bayer Said to Have Tapped Rothschild for BMS Float

Bayer is said to have chosen investment bank Rothschild to advise on its plan for an initial public offering (ipo) of engineering plastics subgroup Bayer MaterialScience (BMS).

Quoting sources familiar with the situation, the news agency Reuters said a deal could value the unit at about €10 billion. BMS last reported sales of €11.2 billion.

Bayer's CEO Marijn Dekkers said on Sept. 18 that the divestment of the plastics business, which is to be rebranded, would free up money for investment in the healthcare, veterinary drugs and crop protection businesses.

Along with an ipo, the Leverkusen group is also weighing a spin-off of BMS to Bayer shareholders, the procedure used ten years ago to shed the chemicals business now trading as Lanxess.

A flotation on the Frankfurt stock exchange could see about a quarter of the shares being listed, one of Reuters' sources, said, adding that a listing in the US seemed unlikely from the current perspective. (dw) ■

Germany Places Moratorium on Fracking Until 2021

Germany's federal environment ministry has announced plans for a moratorium on commercial hydraulic fracturing, or fracking, above 3,000 meters depth until at least 2021. Exceptions could be made for test drilling, said environment minister Barbara Hendricks. The ministry said it would allow conventional fracking, using chemicals that pose no threat to water supplies, under strict conditions. Hendricks said Germany's rules would be the strictest rules worldwide for unconventional gas exploration, as protecting drinking water and public health remain her "top priority." (dw) ■

Air Products LNG Technology for Freeport Terminal

US-based Air Products, which claims to be the global leader in LNG technology and equipment, has been tapped to supply two sets of its proprietary technology, equipment and process license for Freeport LNG's liquefaction and export project in Texas. The contract includes two of Air Products' main cryogenic coil wound heat exchangers and the associated equipment and technology. The trains are scheduled to be on stream in 2018.

This is the second such contract won by the gases producer. It is also providing the LNG technology and equipment for Dominion's liquefaction project at the Cove Point LNG facility in Lusby, Maryland, USA.

Air Products said most LNG produced worldwide employs its technology. In January 2014, the company dedicated a second LNG plant in the US, at Port Manatee, Florida. Added to its Wilkes-Barre, Pennsylvania, facility, this doubles the company's manufacturing capacity specifically for the manufacture of larger LNG heat exchangers. (dw) ■

Almac Joins Academic and Industrial Partners to Find Green Chemicals

Almac, the contract development and manufacturing organization based at Craigavon, UK, has announced its "high level" participation in a synthetic biology project to develop novel routes to chemicals. Other academic and industrial partners include Bangor University of Wales and Hockley International, a Manchester, England-based manufacturer and exporter of environmental health and industrial chemical products.

The research team has received a grant of £1 million from the UK's Biotechnology & Biological Sciences Research Council and Technology Strategy Board. (dw) ■

DuPont to Lift Output of Ethylene Copolymers in Texas

DuPont is planning to invest more than $100 million in expanding output of ethylene copolymers output at its Texas plants over the next three to four years. Without providing capacity figures, either current or for the increase, the US chemical giant said the build-up, about a third of which is to be completed by the end of next year, was in response to increasing demand for the products used mainly in food packaging and automotive, but also in industrial applications. DuPont said the investment will support growth for its specialty resins, including Surlyn ionomer resin, Nucrel ethylene acid copolymer resin, Elvaloy ethylene copolymer resins, Vamac ethylene acrylic elastomers and special grades of Elvax EVA copolymers. (dw) ■

China Fines GSK Nearly $500 Million on Bribery Charges

GlaxoSmithKline (GSK), the UK's largest pharmaceutical producer, will pay the Chinese government nearly $500 million in fines after being found guilty of offering bribes to healthcare workers. Acknowledging that its local management had broken the law and also violated company rules, GSK has apologized to Chinese patients, doctors and hospitals and to the Chinese government. The company said it is working to end corruption, with planned measures to include changing the incentives offered to sales staff along with procedures for reviewing invoices and payments. GSK had been under investigation by Chinese authorities since last year after being accused of offering millions of dollars in bribes to officials in exchange for permission to raise prices. Mark Reilly, former head of the drugmaker's Chinese operation, has received a three-year suspended prison sentence and will be deported. (dw) ■

Evonik Expands Specialty Silica Capacities in Japan

As part of its majority-owned joint venture DSL Japan, German chemical producer Evonik is expanding production capacity for its Sipernat specialty silica at Ako, Japan. The new capacity is due on stream in 2015. The jv partners are Evonik (51%) and Japan's Shionogi (49%). The build-up in Japan will help strengthen the specialty character of Evonik's silica business, said chief operating officer Patrik Wohlhauser. Johannes Ohmer, head of the inorganic materials business unit, said the group projects higher than average growth for this market segment.

Beyond Asia, Evonik said it is making "good progress" on expanding its global silica capacities. For 2014 alone, it projects an increase of around 30% against 2010. An expansion of precipitated silicas capacity is expected to go on stream later this year in Chester, Pennsylvania, USA. Evonik's management recently approved construction of a new silica plant in Brazil, due to start up in 2016. The expansion in North and South America follows that of Europe and Asia. A larger production facility became operational in Thailand in March 2014. (dw) ■

BASF to Dissolve Paper Chemicals Division, Redistribute Assets

BASF will dissolve its paper chemicals division from Jan. 1, 2015 and spread its products and activities across other divisions of the Performance Products segment, where they fit well with other businesses.

Some 50 jobs will be eliminated in the move, which also foresees the division's headquarters at Basel, Switzerland, which also has responsibility for the paper coatings and additives operation, being closed at the end of 2014. Group sales with paper chemicals totaled €1.44 billion in 2013. BASF is a global supplier of paper chemicals, but profitability of a number of the businesses has lagged. (dw) ■

Discovering The Future

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We have seen entire industry sectors vanishing in the past because of fewer challenges. Do you think that the pharmaceutical industry is threatened as a whole?

M. Abou-Gharbia: The industry is indeed under threat, but it is highly unlikely that the industry will collapse on itself any time in the next several decades. There are many diseases and conditions, which remain poorly served or unserved, that can serve as profit centers for the industry once appropriate medications are developed. Novel treatments for Alzheimer's disease alone are a massive untapped market. At the same time, payer institutions such as insurance companies and governmental organizations are less willing to pay for "me too" drugs. Innovation is being rewarded, and companies that are unable to provide truly innovative therapies will almost certainly disappear.

Which new business models could turn out to be the most promising guarantors of success for pharma?

M. Abou-Gharbia: There are no guarantees of success in the pharmaceuticals business. Until we can accurately predict which drug candidates will work in a given clinical program, there will always be substantial risk in this industry. As to organizational structures, the best scenario is to establish an organization that bases program advancement on sound scientific data. In addition, companies that recognize that innovation can arise in many places outside of their own organization will flourish, while those that do not will flounder. Academic institutions and startup biotechnology companies are a thriving source of innovation that is available to the industry for those with the foresight to recognize opportunities in diverse locations.

Does the pharmaceutical industry have a social responsibility to discover new drugs, even if the R&D efforts and costs involved would not get remunerated by patients or the health-care systems?

M. Abou-Gharbia: No, they do not. They have an ethical obligation to their employees, investors and, most importantly, to the patient that they serve to remain solvent and able to provide medications to the patients in need. No company can stay solvent long term if it is forced to take on a program for which there is no hope of profit. Long term, no one is served on this path.

Commercial potential must dictate the direction of research, the selection of projects, and the final drug candidates that are commercialized. At the same time, however, the industry should take the initiative to create programs that provide commercially viable medications to patients who are unable to afford the medication. Many pharmaceutical companies have programs designed to substantially decrease the economic burden of therapeutic intervention for patients who cannot afford to pay for their medications.

> ***Blockbuster drugs are certainly important, but they are a rare find.***

Having worked in both industrial and academic research, do you believe that the task of discovering new drugs to treat unmet medical needs is best done by joint efforts of industry and academia, and with support from governmental research groups?

M. Abou-Gharbia: Multiple sources of support for research programs is almost always of benefit to scientific advancement and the discovery of novel therapeutics, but support from each of these entities may not always be warranted. Decisions should be made on a case-by-case basis with respect to the importance of the disease/condition and its impact on society as a whole. Support from all three of these entities to develop novel treatments for drug addiction, Alzheimer's disease and ALS, for example, could be rationalized by the clear need in each of these areas. The same is not necessarily true of less threatening conditions such as erectile dysfunction, male pattern baldness and restless leg syndrome. All of these conditions provide significant profit and may improve life for some patients, but it would be difficult to argue that government or academic resources should be directed towards these types of programs. The pharmaceutical industry focuses primarily on programs and research that are low-risk opportunities, while academic institution and governmental organizations have more freedom to take on riskier programs and orphan diseases where there is no guarantee of a return on the investment. To be clear, however, novel clinical candidates identified in academic or government research laboratories will not make it to market in the absence of a commercial partner.

Since the beginning of the 21st century, pharma M&A activity has exploded, reaching a total value of about $800 billion. Have these transactions had a positive effect on drug R&D?

M. Abou-Gharbia: The final determination on the overall impact of the industry consolidation that has occurred in the last two decades remains unclear. Short term, these transactions have bolstered the profitability of companies, allowing them to satisfy the investment community. Whether or not this will translate into a more viable industry, however, has yet to be determined. Many of the mergers and acquisitions were predicated upon increased efficiency in the identification of new marketable therapies, but the FDA – Food and Drug Administration – approval rate remains unchanged. The merging companies often claimed that they would take advantage of "synergy" that existed between the two companies to improve efficiency. Those of us who have direct experience with mergers and acquisition understand that the term "synergy" is a synonym for "severe job cuts" with a heavy focus on drastic cuts to R&D budgets. The industry as a whole has decreased scientific head count, which has in turn decreased its ability to conduct cutting-edge research, which will limit the industry's ability to develop novel therapies internally. This will likely create a greater dependence of the industry on academic and governmental laboratories for the identification of novel clinical candidates and increases in partnership agreement between pharmaceutical companies, academic organizations and biotech startup companies. Clinical trials, however, are likely to remain the purview of the pharmaceuticals industry.

> ***Pharma has shifted its focus from small molecules drugs to biopharmaceuticals.***

The patent cliff is one major challenge for Big Pharma. Some estimates say that over $290 billion in sales may be at risk for the period 2012-2018. Do pharmaceutical companies have to abandon the blockbuster mentality and consider other approaches to survive?

M. Abou-Gharbia: In short, yes. Blockbuster drugs are certainly important, but they are a rare find. When they are identified, they can change the course of a company, catapulting it into the major leagues of the industry. There are, however, many very profitable drugs that are not blockbuster in status that can provide the revenue required to maintain operations within an organization. Baseball players do not swing for the fences every time they come up to bat; they hit the pitches they are thrown in the best way that they can. The pharmaceuticals industry should adopt the same approach. At the same time, the blockbuster mentality is increasingly driven by payer demands. Payer organizations are only willing to pay top dollar for truly innovative therapies. The industry has responded to an extent by increasing its focus on biologics, which can command a high price and, at least for the moment, are not as vulnerable to generic competition from biosimilars. This will certainly change over time, at which point the industry will have to regroup and determine how best to face the new set of challenges that present themselves.

In mid-August of this year, Magid Abou-Gharbia (right) and his fellow scientists from Pfizer (formerly Wyeth) were honored with the 2014 Heroes of Chemistry Award of the American Chemical Society. With the award, the ACS honored the team's discovery of Venlafaxine, commercialized by Pfizer under the brand name Effexor.

The establishment of shared risk/shared reward partnerships has increased significantly. Can these partnerships accelerate drug discovery and fill up the innovation pipelines?

M. Abou-Gharbia: Drug discovery and development take time. The formation of a partnership does not change this fact. In vitro assay, animal studies and clinical trials time requirements are still the same, irrespective of whether they are done as part of a collaborative effort or within an individual organization. The value of the partnership is in shared access to resources, scientists and expertise, as well as distribution of risk across multiple organizations. It is likely that these partnerships will help refill the pipeline, but the speed at which this is accomplished will still be dictated by the time required for scientific exploration and navigation of the bureaucracies that are a part of the industry for better or worse. There is also a benefit to be derived from the shared risk aspect of partnerships. The cost of developing novel therapeutics is extremely high. The most recent estimate is on the order of $1.7 billion. Partnerships and collaborations diffuse the risk, and at the same time provide opportunities for companies to use their resources to explore other opportunities. The opportunity for a single company to take part in the development of new therapies is expanded, while the risk of failure is diminished. Of course, shared development also means sharing the profits, so individual companies will reap the same level of reward in partnered programs. That being said, there are numerous examples of these kinds of partnerships, especially in high-risk areas such as Alzheimer's disease and cancer, some of which have produced marketed drugs.

The market for biopharmaceuticals has a potential to reach $320 billion by 2020, up from $139 billion in 2011. Can the biopharmaceuticals sector become a safe haven for pharmaceutical companies?

M. Abou-Gharbia: Over the last decade, the pharmaceuticals industry has shifted its focus from small molecules drugs to biopharmaceuticals. An enormous amount of capital and resources have been dedicated to biopharmaceuticals and as a result the biopharmaceutical pipeline has over 5,000 new clinical candidates under development around the world. Certainly, the biopharmaceuticals market has the potential to offer new therapies for the industry but is no longer the safe haven it once was. The creation of pathways for generic versions to enter the market has changed the dynamic in this commercial space. In the early days of the biopharmaceuticals market, patent protection and the lack of a clear path forward for generic biopharmaceuticals served to protect many important products for the branded companies. Now that there are defined mechanisms for the approval of generic biopharmaceuticals, generic companies are beginning to enter these markets. Today, strong patent positions are the only barrier to generic competition in the biopharmaceuticals sector, which is the same as it is for small molecules.

> ***The CRO sector may prove to be a launch point for the next generation of pharmaceutical companies.***

More importantly, can biopharmaceuticals provide the new drugs needed to cure the world's most serious diseases?

M. Abou-Gharbia: It is possible that they can, but just like any other platform, methodology or tool, there are limits to what can be accomplished with a biopharmaceutical. Biologics and macromolecular therapies have certainly proved useful in diseases that have been difficult to treat with traditional small molecules, but there are limitations to their utility as a result of the required mode of administration. To my knowledge, there are no examples of orally delivered biologics, which leaves them vulnerable to replacement with orally delivered small molecules.

Drug approvals are increasingly becoming dependent on the value a drug provides for the patients. How can pharma respond to these heightened regulatory hurdles?

M. Abou-Gharbia: The value proposition has certainly become a major issue as the overall cost of health care has come into focus over the last few decades. In order for the industry to thrive, it must adapt to the new, cost-constrained paradigm that has been established. It is easy to say that the industry should focus on developing drugs that are significantly improved over previous generations of drugs, but this is by no means an easy feat. Tackling unmet medical needs that prevent significant downstream medical costs, such as developing treatments for ALS or increasing the cure rates for hepatitis C are clear examples of this. The industry as a whole could also make significant strides towards lowering drug prices long term if it focused its cost efforts on areas other than research and development. Eliminating these areas makes a high-profile statement by lowering R&D costs, but it also substantially decreases the industry's ability to innovate and develop novel therapies that are truly value propositions for patients and the healthcare system as a whole.

The industry also has a serious image issue that must be addressed. The pharmaceutical industry improves the lives of millions of people on a daily basis. It is responsible for modern medical miracles such as HIV treatments that turned HIV infection into a chronic issue instead of a death sentence and cancer therapies that dramatically lowered the number of cancer deaths. At the same time, however, the pharmaceuticals industry is routinely taken to task and vilified for its lack of productivity and the production of "bad drugs." The industry needs to take on the challenge of promoting the good that it accomplishes and educating the public on the immense challenges and costs associated with developing new drugs.

Of course the FDA has established policies and guidelines for new drug approval, but they are subject to change. Some changes have created stricter guidelines, while others are aimed to speed approval of new drugs. In 2000, for example, the FDA altered the approval guidelines for anti-infective drugs by requiring companies to demonstrate their new drug candidates truly possessed superior efficacy when compared to existing therapeutics. This dramatically increased the complexity and cost of clinical trial, leading the majority of major pharmaceutical companies to abandon the area altogether. Efforts to speed up the new drug application review process, on the other hand, have been a welcome, positive change. Accelerated reviews, priority reviews and fast-track programs will almost certainly have a positive impact on the industry and patient in need. The first "breakthrough therapies" were designated in the last few months and have provided an indication to patient advocacy groups that the FDA is willing to take greater risks to move desperately needed therapies through the clinical process as rapidly as possible. Most HIV drugs were pushed forward under an accelerated approval process. There

are, however, many people who are concerned that this designation will be overused and will increase the likelihood that flawed or dangerous medications will reach the market. Post market-approval surveillance of new therapies will be required in order to mitigate this very real risk.

It is a fact that despite a four-fold increase in R&D spending between 1992 and 2012, the number of drugs or NCEs – new chemical entities – has stagnated. However, a recent increase in FDA approvals in 2011 and 2012 could indicate that the drug drought might be coming to an end. How can the pharmaceutical industry improve its R&D success rate?

M. Abou-Gharbia: There is no doubt that increased R&D spending has not increased the number of new drugs reaching the marketplace. With the exception of 1996, a year that saw 56 new drug approvals, the number of new approved drugs has been declining despite the massive increase in R&D expenditures. The number of new drug approvals has dropped to 19 to 20 per year. In 2011, there was cause for hope when 30 new drugs were approved by the FDA, but these results are misleading. Two of these agents were actually imaging agents and not therapeutics, and six more were already approved in the EU or for other indications. Thus, in reality, only 22 new therapies were approved by the FDA in 2011. The fact remains that increased R&D expenditures have not led to an increase in new drug approvals.

Why this is the case and how to fix this issue is the proverbial "$64,000 Question" that no one has been able to answer. The best answer is to focus efforts and resources on high-quality science, testable hypotheses, and remove corporate politics from scientific decisions. High-quality science will lead to high-quality therapies, but good science takes careful planning and time. Careful planning is the easy part. Time is the hard part. Management, investors, and politicians are often not willing to be patient enough for scientific advancement. Many high-quality programs that were headed in the right direction have been discarded because they were not advancing rapidly enough in the eyes of management, investors and politicians. This is especially true when mergers and acquisitions occur. Allowing high-quality science to runs its course probably will not shorten the cycle time, but it would result in an increase in the positive results at the end of the cycle, thus improving overall productivity. In order to accomplish this, the industry will need to reverse course and re-establish its ability to execute research programs and identify other areas to decrease overall company costs. There will also need to be an increased focus on optimizing clinical candidates in the discovery stage of research by ensuring that clinical candidates have suitable pharmacokinetic profiles, oral bioavailability and druglike properties. Clinical trials are by far the most expensive portion of the drug discovery and development process, but at the same time the failure rate of clinical candidates is 90%. A 25% reduction in the failure rate would dramatically decrease overall R&D costs. This can only be accomplished, however, by increasing resources and staffing in discovery operations.

Academic drug discovery groups have appeared to support the transition of innovative academic discoveries and ideas into attractive drug discovery opportunities. Will academic drug discovery groups fill the innovation gap left behind by the downsizing of pharma R&D groups?

M. Abou-Gharbia: Academic drug discovery has provided innovation for the industry for several decades, and this is unlikely to change. The development of academic drug discovery centers will certainly improve the quality of the drug discovery science that is developed in the halls of academia, but like everything else in life, it is not without costs of its own. While the industry will gain access to novel science by partnering with these centers, it will also have to share the rewards with the academic institutions and scientists that produce the innovations that move forward. Milestone payments, royalties and other financial compensation that would have been profit for the industry will instead go outside of the industry. Expertise and knowledge that had been previously available inside the industrial organizations will also decrease over time as more of the drug discovery process is moved from industry to academia.

Another challenge faced by pharma is the failure rate for compounds in clinical trials. How could clinical dropout be reduced?

M. Abou-Gharbia: The pharmaceuticals industry has already made great strides in adopting early testing of safety and pharmacokinetics by implementing numerous in-vitro ADME screening techniques designed to ensure that lead compounds have druglike properties. This has helped alleviate some of the issues that can cause clinical failures such as safety, toxicity and pharmacokinetic issues, but there is still a great deal of work to do. One possible avenue to an improved success rate lies in the ability to identify subpopulations within disease categories that are more likely to benefit from a particular new form of therapy. This has been very effective in the treatment of breast cancer, especially with regard to the BRCA gene. Expansion of this type of clinical targeting of novel therapeutics could help the industry a great deal.

Which role do CROs/CMOs or CRAMS play in the drug discovery/development value chain today, and how will their role change in the future?

M. Abou-Gharbia: Pharmaceutical contract research and manufacturing services – short: CRAMS – is an $80+ billion market, and contract research constitutes approximately 50% of the outsourcing activities in discovery and clinical research. Contract research organizations – CROs – will almost certainly continue to play a role in drug discovery and development, but as their importance to the process grows, it is likely that they will want an increasing share of the downstream profits. Milestone payments and profit-sharing clauses are likely to become more common in CRO agreements. In addition, some CROs have decided to take advantage of the infrastructure, capacity and experience that they have developed to launch internal drug discovery programs of their own. Scynexis, a small company in Durham, North Carolina, for example, was founded as a CRO in 2000. Over time, they built on the expertise and infrastructure required for CRO activities and added an internal drug discovery program to their operation. As of 2014, Scynexis has nine programs in its pipeline. The CRO sector may prove to be a launch point for the next generation of pharmaceutical companies.

Dr. Michael Reubold
CHEManager International

▶ Contact:
Dr. Magid Abou-Gharbia
Tel.: +1 215 707-4949
aboumag@temple.edu
http://moulder.temple.edu

Sibur Confirms Timetable for $9.5-billion Tobolsk Complex

After completing the front-end engineering and design contracts, Russian petrochemical giant Sibur said it is pressing ahead with previously announced plans for a $9.5 billion olefins and polyolefins complex at Tobolsk. News about the project originally announced in 2012 had gone quiet, leading some observers to speculate that it might not be realized as initially planned. The complex operating under the name ZapSibNeftekhim will include a steam cracker built by German engineering group Linde with capacity to produce 1.5 million t/y of ethylene, in addition to several polyethylene plants with a total capacity of 1.5 million t/y, and a 500,000 t/y polypropylene facility. The PE plants, which earlier reports said would include two 350,000 t/y HDPE lines and two 400,000 t/y LLDPE/HDPE swing lines, will use Ineos technology. For the PP plants, the Russian group has secured a license from LyondellBasell.

Sibur said the entire complex will be completed in five to five-and-a-half years. To accommodate the mammoth project, the group's board of directors is increasing its capital spending budget. For 2014, some $1.9 billion is planned to be spent. CEO Dmitry Konov said: "Sibur has a strong financial position. Over recent years, the company has delivered on ambitious projects to expand its gas processing and fractionation capacity, improve transport infrastructure reliability and build its large polymer production capacities, providing the basis for a smooth transition into the next stage of the project." NIPIgazpererabotka, Russia's leading engineering provider for gas processing, will handle design of infrastructure and off-site facilities. (dw)

Stora Enso to Build Test Plant for Sugar Biomass

Following its acquisition of biotechnology company Virdia, Swedish paper and packaging specialist Stora Enso has announced plans to build a $43 million demonstration and market development plant at Raceland, Louisiana, USA. The facility, set to go on stream in 2017, will seek to demonstrate the viability of Virdia's extraction and separation technology, which enables cellulosic biomass such as wood or agricultural waste to be converted into highly refined sugars. The end product could be used the Swedish group's existing pulp mills. The demonstration unit will be located close to sugar cane plantations and will use the by-product bagasse as a sustainable, non-genetically-modified feedstock to produce high purity five-carbon sugars and in particular xylose. The sugars will be converted and upgraded for use in applications such as food and personal care. Juan Carlos Bueno, executive vice president of Stora Enso Biomaterials, said the investment "marks the next step in our strategy for new markets and applications." The goal, he said "is to develop and commercialize cost-effective renewable solutions to address well-identified market-driven needs and add value to our current cellulosic streams." (dw)

Al Sejeel Petchems Project in Qatar Put on Ice

Industries Qatar (IQ) has announced completion of a new CO_2 recovery plant at its fuel additives joint venture Qafac. At the same time it has revealed that the large Al Sejeel petrochemical complex at Ras Laffan, planned to be operated by an 80:20 joint venture of Qatar Petroleum and Qatar Petrochemical Company (Qapco), has been put on ice. IQ holds the majority stake in Qapco, with France's Total Petrochemicals as partner. Instead of the original plans, the Qatari firm said a new downstream petrochemical project, expected to yield better economic returns, is under study. Construction on the $5.5-6 billion Al Sejeel project, initially expected to start up in 2018, was due to begin in early 2015. The complex would have produced 1.4 million t/y of ethylene, 1.04 billion t/y year of HDPE (two lines with capacity of 520,000 t/y), 550,000 t/y of LDPE, 430,000 t/y of LLDPE, 760,000 t/y of polypropylene and 83,000 t/y of butadiene. (dw)

Accelerating the Benefits Achievable from Biocatalysis

Codexis and GSK Enter into Technology Collaboration for the Development of Novel Enzymes

Recently, Codexis has signed a platform technology license agreement with GlaxoSmithKline (GSK). Under the terms of the agreement, Codexis, a developer of biocatalysts for the pharmaceutical and fine chemical industries, granted GSK a license to use the company's proprietary CodeEvolver protein engineering platform technology in the field of human healthcare. The license allows GSK to use Codexis' platform technology to develop novel enzymes for use in the manufacture of GSK's pharmaceutical and health care products. Dr. Michael Reubold asked John Nicols, President and CEO of Codexis, and Doug Fuerst, Technology Development Lead, Synthetic Biology at GSK, to explain the details of this agreement.

CHEManager International: Mr. Nicols, what are the specific properties of the CodeEvolver protein engineering technology and what advantages does it offer to your licensing partners?

J. Nicols: CodeEvolver, which is Codexis' proprietary protein engineering technology platform, enables the rapid development of custom-designed biocatalysts that are highly optimized for efficient chemical transformations and manufacturing processes. CodeEvolver is among the most advanced achievements standing on the intersection of three great technologies – molecular biology, high throughput chemistry, and bioinformatics. CodeEvolver excels at all three – it is comprised of a) proprietary methods for the design and generation of diverse genetic libraries, b) automated screening techniques that rapidly validate chemistry in high throughput on thousands of the best candidate variants and c) computational algorithms for the interpretation of screening data thereby enabling us to eliminate the need to run tens of thousands of additional costly experiments. It is only through the merging of these leading edge scientific capabilities that we can achieve the goal of rapidly engineering the ideal biocatalyst.

The advantages of CodeEvolver stem from the technology's unique ability to design performing proteins more effectively than other engineering tools on the market, both in terms of its speed and the specificity of the results it delivers. Our technology enables the design of proteins that can perform multiple potential functions for use in the field of human healthcare. These functions could range from biocatalysts that will catalyze chemical reactions more cost-effectively than alternative chemistries, to the creation of various types of potential new therapeutics, diagnostic or prophylactic products. GSK surely considered other protein engineering tools, including those that they might have in-house, and they chose the acquisition of a license as their preferred path to step up their ability to engineer novel proteins.

John Nicols, President & CEO, Codexis.

Doug Fuerst, Technology Development Lead, Synthetic Biology, GSK.

> *This approach truly accelerates a large pharma company's ability to apply biocatalysis.*
> John Nicols

Besides milestone payments for the successful technology transfer, and for successful application of the technology to making biocatalysts for small molecule manufacturing, Codexis will be eligible to receive further milestone payments and additional royalties based on net sales of a limited set of products developed by GSK. Is this your preferred licensing model or are there alternative options to get rewarded by licensing partners?

J. Nicols: This is a very attractive approach for Codexis to work with a major drug company wanting to accelerate the benefits achievable from the application of biocatalysis. This approach truly accelerates a large pharma company's ability to apply biocatalysis. By lining up other biocatalysis development partners working in parallel with us via CodeEvolver licensing, over time more drugs can be converted to incorporate biocatalytic processes. We see this as an ideal and a preferred way to work with our customers, and believe that all major drug companies with wide pipelines of small molecule drugs could benefit from this type of deal. Given that the drug majors all have multiple APIs that they could work on, we believe, as GSK has shown, that they could justify having their own in-house CodeEvolver protein engineering technology versus working with Codexis on an arm's-length project-by-project basis.

Of course, as Codexis has been doing for more than a decade, we are still very happy to work on a project-by-project approach with customers who prefer to work in this way. These two different approaches are very complementary to one another. Depending on how much applicability the customer sees for biocatalysis, how much they want to liberate the value that biocatalysis can generate, and how quickly they want to generate that value, we are now set up to work in either of these two partnering modes.

What kind of technical support or assistance does Codexis offer to a licensing partner to ensure proper function and successful application of the technology?

J. Nicols: We will provide tech transfer services to each prospective licensee with the same end goal for each - to enable a licensing partner to independently run CodeEvolver protein engineering. Potential licensing partners have varying degrees of expertise in using protein engineering technology today, with some having more advanced in-house capabilities than others. We would therefore tailor the technology transfer support services needed to a prospective licensee given their starting expertise.

For example, with GSK we are providing significant and intensive support services, including help in design of their lab and specifying the equipment and bioinformatic software, and we have also agreed to collaborate with GSK on four specific API biocatalyst projects during the two-year technology transfer period. We expect to run the first two projects in Codexis' facilities at Redwood City, California, where we will house GSK's scientists to work in partnership alongside Codexis' teams. In that way, GSK's scientists will be able to learn firsthand the full process involved in designing a novel biocatalyst and how we run a project, at the same time as GSK is building the lab in its Pennsylvania facility. Once GSK's facility is up and commissioned, then Codexis scientists will visit GSK's site, providing advisory support while the GSK scientists, many of whom were previously trained at Redwood City, take over the lead roles in running our technology platform on the first two projects at GSK. We envision the whole technology transfer process with GSK will provide substantial customer intimacy learnings for Codexis, as well as substantial access to our technological expertise for GSK. The process has already kicked off very well in the first two months since signing the deal.

The agreement marks the first time that Codexis has licensed this technology to a healthcare company. What are your expectations for the future?

J. Nicols: We are excited about the deal with GSK and we believe our offering of a CodeEvolver license makes sense to all pharmaceutical companies who have yet to fully apply the value creating potential of biocatalysis across their drug portfolio. This licensing approach allows the customer to run CodeEvolver at their facilities, and drive more of their portfolio to utilize the cost saving and sustainability benefits of biocatalysis than Codexis could ever provide them on a project-by-project basis. The licensing approach also changes the cost structure for the customer to install biocatalysts, as well as enables them to have more control over those projects and minimize their need for disclosure of confidential information and materials. As has been demonstrated now with GSK, we see these as substantial benefits enabling others to also get significant returns on the licensing investment.

> *Biocatalysts typically offer more efficient and sustainable manufacturing processes.*
> Doug Fuerst

We expect to deliver a series of CodeEvolver licenses for the foreseeable future, in the range of one new license every year or two. We are already in discussion with other companies who may be interested in licensing CodeEvolver, some of whom had begun discussions prior to the announcement of the GSK deal. We are encouraged by the reception of other major drug companies to the possibility of a similar CodeEvolver licensing deal. We can additionally envision executing CodeEvolver licenses in other industries beyond pharmaceuticals. Any company who can derive value from using or marketing novel, performance enzymes or proteins would be a candidate for a CodeEvolver license as well.

Mr. Fuerst, what will GSK use Codexis' platform technology for and where will you install the protein engineering platform?

D. Fuerst: The Codexis platform will be used to evolve designer enzymes to be used in the manufacture of GSK small molecules. The platform is being installed in GSK labs at Upper Merion, Pennsylvania.

What are your foremost goals regarding the use of the technology and why did you decide for the Codexis platform?

D. Fuerst: We chose the Codexis platform after a thorough evaluation of the enzyme evolution landscape. Codexis has a significant track record of delivering evolved biocatalysts for pharmaceutical and fine chemical applications over an extended period of time. The Codexis CodeEvolver technology is enzyme class agnostic which allows it to be applied to a wide range of chemical transformations. This flexibility allows for application across a wide range of chemical manufacturing opportunities. Codexis is also constantly improving the CodeEvolver platform which has allowed them stay at the cutting-edge of enzyme evolution technology.

For which pharmaceuticals and health care products in GSK's portfolio will the Codexis technology be used?

D. Fuerst: We are evaluating opportunities and planning to use Codexis technology across the entire GSK development portfolio of small molecule assets. This includes all therapeutic classes. We are also exploring all existing commercial GSK molecules for lifecycle management opportunities.

Experts believe that biocatalysts will increase the efficiency of pharmaceutical manufacturing. Which potential do you see in the use of enzymes to manufacture pharmaceuticals?

D. Fuerst: For individual transformations biocatalysts typically offer more efficient and sustainable manufacturing processes with lower costs than traditional chemical reactions. At GSK we are also excited about the possibility to use enzymes to design shorter and simpler synthetic routes that are not accessible by classical chemical approaches. By decreasing the number of steps to make a molecule the cost savings and sustainability benefits are even greater. Having access to Codexis technology will enable us to develop enzymes for these types of novel synthetic routes.

▶ Contact:
www.codexis.com

Bayer to Add Second Line to Indian TPU Plant

Bayer MaterialScience (BMS) has announced plans to add a 3,500 t/y production train to its Desmopan thermoplastic elastomers (TPU) plant at Cuddalore in India'sTamil Nadu state. The new capacity will lift total output capability at the facility to 6,000 t/y when it goes on stream in the second quarter of 2015. The Cuddalore plant facility supplies the Indian market and also exports to Europe. Marius Wirtz, head of the TPU business at BMS, said the planned increase of local capacity is an "important milestone to continuously support our customer's growth with custom-made TPUs in high-quality and with short lead times." The company is the sole TPU producer in India. Ajay Durrani, BMS country representative for the Indian subcontinent, said, the company continues to see strong growth opportunities in India across all business units. (dw)

Editorial

Plastics for a Better Tomorrow

Plastics make our daily life easier, safer and more enjoyable: Let's take the food packaging easy to carry and handle, the bike helmet protecting a kid, or modern entertainment electronics like LCD or LED flat screens guaranteeing finest amusement. But when it comes to sustainability, plastics sometimes has a reputation disproportionate to its real qualities. The truth is: Plastics help us to do more with less in many ways, thereby conserving natural resources and protecting the environment for tomorrow.

Protect and Preserve

Thanks to their unique features, plastics packaging extends shelf life, preserves food taste and protects food from contamination for example by bacteria. Plastics packaging for fresh meat, for instance, extend shelf life by three to six days. Considering that producing one kilo of beef leads to greenhouse gas emissions equivalent to three hours of car driving, this is a substantial reduction of the environmental footprint. In many developing countries, a lot of resources like water, land, and energy are wasted on food that never reaches the consumer, this often due to the lack of efficient packaging. And further savings for the environment are provable: While over 50% of all European goods are packed in plastics these plastics account only for 17% of all packaging weight. Furthermore, the plastics packaging weight has been reduced by 28% over the past 10 years!

Plastics also play a major role in sustainable construction. Just think of window frames, insulating foams or water pipes. Across their whole life cycle, plastic insulation materials save 150 times the energy used for their manufacture. Moreover, the durability of plastics and their anti-corrosion properties provide them with an impressive life span which can reach over 50 years for plastic pipes. And these pipes are produced with less energy than alternative materials, also saving transport costs and emissions due to their lightweight design.

Plastics in Transportation

While motorization in developing countries is rising and a growing number of people have access to modern transport systems, the development of lighter vehicles consuming less fuel must keep path. Today, in a modern car there are some 15% of plastics, replacing more and more components made from other, often heavier materials. The positive environmental impact is impressive: Over the average lifespan of a car, every 100 kg of plastics reduce fuel consumption of the vehicle by around 750 litres. In aircraft, the increased use of plastics enables weight savings and reduces fuel consumption. The Airbus A380, the world's largest commercial aircraft, is built from 22% of carbon reinforced plastics, while Boeing's Dreamliner is constructed mostly from plastic composites, generating fuel savings of around 20%.

Trend: Upcycling

And innovation doesn't stop here: Newest "upcycling" processes are already in use producing recycled plastics in almost the same quality and composition as new polymers. Bio-polymers made from sugar cane and used as packaging material are reducing the ecological footprint. Wind turbine blades now span up to 150 meters thanks to new carbon fiber composites withstanding greater forces and stresses. A pilot plant in Germany is producing plastics from carbon dioxide (CO_2) as an alternative to the production of polymer materials from fossil fuels. All these projects are expected to boost sustainability by decreasing the impact of CO_2 on global warming. So in a world that is growing in population, with ever-increasing demands for water, food, shelter, sanitation, energy, health services and economic security, plastics is key to help deal with these issues.

Dr. Ruediger Baunemann, Director General, Plastics Europe Deutschland, Frankfurt am Main, Germany

▶ Contact:
Tel.: +49 69 2556 1300
info.de@plasticseurope.org
www.plasticseurope.de

Creating Moods with Light

Ambient Lighting in the Automobile Industry

Colors and light affect how we feel. That is why auto makers are placing greater focus on interior lighting elements. For this, the industry needs special light-guiding materials.

Dr. Wojciech Pisula
Senior Manager Business Development for Light Management Acrylic Polymers Business Line, Evonik Industries, Darmstadt.

In the XchangE concept car, it consists of a 1.2-meter-wide display strip made of Plexiglas LED in the steering wheel support. This strip is also transparent when unlit, and can change color when lit. In both cases, a clear view of the instrument panel is provided.

Reading lamps, floor light strips, a bright instrument panel — there are already a number of elements that light up car interiors. But the role of lighting inside vehicles is changing. Whereas lighting has so far been mainly functional, as in floor lighting strips that make it easier to get into the car, ambient lighting is now gaining growing attention from car manufacturers. Color and light not only give a vehicle its characteristic and recognizable look, they also create moods and contribute to well-being. Car manufacturers are therefore stepping up their efforts to develop complex light scenarios that change depending on the driving situation. For instance, the light may be brighter when the driver gets into the car, and be dimmed during the drive. At night, the interior lights are blue, since this color is believed to help keep drivers alert.

LEDs Drive Development

This development is being driven by LED technology, which has revolutionized the entire lighting industry. LEDs (light-emitting diodes) are slim, consume little energy over a long service life, and offer huge creative scope through their changing colors. In many applications, they are therefore increasingly replacing classic illuminants, for example in car taillights and front headlamps. But LEDs can only function to full advantage when they are combined with suitable materials. The strong light emitted by these point light sources needs to be distributed throughout the material to provide surface lighting.

Variants of Plexiglas LED, a thermoplastic material produced by Evonik Industries, allow both uniform backlighting without hot spots, and surface lighting, with light fed in via the edges. Special diffusor additives embedded in the material distribute the LED light across the surface. Another advantage is that Plexiglas LED is lightweight. This is an important aspect in automotive construction, where every gram of weight costs fuel. The material is also easy to fabricate and can be machined into any desirable shape. With a scratch-resistant coating, it also easily withstands heavy wear.

In car interiors, LEDs combined with suitable edge-lit light guides make it possible to install ultra-slim components. So far, delicate injection-molded light guides have been used for this purpose, and are concealed in the side doors for indirect lighting. But the manufacturers' new lighting scenarios open up other opportunities for large illuminated surfaces in car interiors. These include car headliners that divide the interior into zones of different brightness. The advantage of large illuminated surfaces is that they produce diffuse light from above, which does not dazzle the vehicle's occupants, unlike point lights.

Headliner Made of Light

One example is the XchangE concept car from Swiss think tank Rinspeed. In the design study, the headliner consists of a sheet of Plexiglas LED measuring roughly two square meters. Without lighting, it is crystal-clear and offers a clear view through the top. With lighting, it can be made to glow in different colors. The light from 358 LEDs is fed into the entire component via the edges. The material then distributes the light evenly across the surface. The car interior is thus homogenously illuminated, providing a light source when the car stops, or ambient lighting during the drive. Another possible use for large-scale applications in car interiors is the instrument panel (picture 2). In the XchangE concept car, it consists of a 1.2-meter-wide display strip made of Plexiglas LED in the steering wheel support. This strip is also transparent when unlit, and can change color when lit. In both cases, a clear view of the instrument panel is provided.

Autonomous Driving

The concept car shows impressively how LEDs can be combined for designing vehicle lighting scenarios. But cars like the XchangE won't be hitting the road any time soon. The vehicle represents a concept for autonomous driving. While experts believe the self-driving car has great potential, it will take some time yet to assert itself. When that time comes, though, interior lighting in vehicles will be sure to gain further importance. After all, if the car drives itself, there will be more time to relax during the drive. And that calls for suitable light, in the form of ambient lighting.

▶ Contact:
Doris Hirsch
PR Management Acrylic Polymers
Evonik Industries AG, Darmstadt/Germany
Tel.: +49 6151 18 4079
doris.hirsch@evonik.com

▶ www.plexiglas.net
www.evonik.com

Bio-based Acrylic Acid Milestone for BASF, Cargill and Novozymes

A joint research team of BASF, Cargill and Novozymes, at work since August 2012 to develop a process for the conversion of renewable raw materials into bio-based acrylic acid, said it has reached another milestone in the technology.

After demonstrating the production of 3-hydroxypropionic acid (3-HP), one possible precursor to acrylic acid, at pilot scale in July 2013, the companies said they have now successfully converted 3-HP to glacial acrylic acid and superabsorbent polymers. They have selected the process for further scale-up.

BASF, which claims to be world's largest producer of petrochemical-based acrylic acid, said it initially plans to use the bio-based product to make superabsorbent polymers. Teressa Szelest, senior vice president of the Global Hygiene Business at the German chemical giant, said it is "working full force" on the set-up of a small integrated pilot plant by the end of this year.

Together with the pilot plant for 3-HP operated by Cargill and supported by Novozymes, this will further support BASF's plans for fast market entry of superabsorbent polymers derived from bio-based acrylic acid, she said. Currently, acrylic acid is produced by the oxidation of propylene derived mainly from the refining of crude oil.

"Cargill came together with BASF and Novozymes to do what had not been done ever before," said Jack Staloch, Vice President of Research and Development at Cargill. "We have made great progress toward our common goal." (dw) ■

The Age of Substrate Change

Adhesives Take Center Stage in the Automotive Industry's Strive to Integrate Lightweight Materials

Vehicle manufacturers have set some ambitious targets to significantly reduce carbon emissions to 95g CO_2/km on the sale of all new cars by 2020. Laurent Pourcheron, Marketing Manager for Adhesives at Huntsman Advanced Materials looks at how structural adhesives can help the automotive industry to successfully integrate the latest lightweight materials and comply with future environmental legislation.

Laurent Pourcheron,
Marketing Manager Adhesives,
Huntsman Advanced Materials,
Basel, Switzerland

Carbon emissions limits are part of the EU's drive to switch Europe to a low-carbon economy and slow the impact of climate change. In Europe, legislation approved by the European Parliament stipulates that cars must abide by a carbon pollution limit of 130g/km by next year, and no more than 95g/km on all new vehicles sold by 2020.

Improving the components that generate power and reducing the rolling resistance of tires offer potential to boost energy efficiency and make progress on carbon emission reductions. But the most significant target by far is weight reduction.

A commonly accepted guideline states that for every 100kg in vehicle weight reduction, fuel consumption falls by 0.25l/km, delivering a reduction in carbon emissions of approximately 7g CO_2/km.

How Can Adhesives Help?

Manufacturers and suppliers now recognize that structural adhesives can help across the spectrum. In the assembly of parts for example, they can be used across a wide range of areas instead of rivets and other fastening elements to have a cumulative effect on weight reduction.

Adhesives can be seen as a potentially disruptive technology that will allow the sector to successfully embrace multi-material automotive lightweighting in the application of new weight-saving materials including aluminium, magnesium, composites and carbon fibre.

Lightweight, Heavy Impact

Without holes, rivets or fastening elements that can weaken structures, adhesives facilitate the strength of materials and provide improved aesthetics on finished parts. Adhesive bonds that have smooth joint surfaces also provide auto makers with greater design flexibility.

In providing a continuous bond which is less susceptible to fatigue cracks, a bonded structure is often described as a safer structure. This type of bond facilitates more uniform stress distribution within a leak proof solution that is less prone to corrosion and able to provide a longer service life under load. Adhesives can also join dissimilar materials together and compensate for variants in the coefficients of thermal expansion in different materials, which contract and expand at different rates. Whilst, producing a bond that is both strong and flexible, this key feature also assists in lowering ongoing maintenance costs. Adhesives also help manufacturers overcome traditional production challenges by adopting faster, cheaper processes and simplified assembly procedures.

Huntsman's Role

As a strategic partner, Huntsman has tailored its products and services to meet the evolving needs of the global automotive market for many years. The company's products help overcome a variety of challenges such as low emissions, fast curing cycles with high initial green strength, durability under strength, impact resistance and multi-substrate joining. Based on state-of-the-art epoxy, polyurethane, methacrylate and phenolic technologies, Huntsman's adhesives have specific characteristics that help improve manufacturing processes, secure long-term performance and the safety of assemblies, and all importantly, facilitate the use of the range of materials that enable car lightweighting.

Figure 1: Adhesives cover a wide range of automotive applications

High-performance Epoxies

For structural and semi-structural assemblies, such as transmission shafts or door modules, epoxy adhesives provide high strength, high stiffness, high temperature resistance, very high fatigue and thermal shock resistance on metal and thermoset composites.

Used by an Italian manufacturer to bond two parts of a carbon fibre spoiler together, Araldite 2015 is an example of an epoxy system selected for its tough and flexible properties.

These characteristics proved essential for helping the spoiler withstand mechanical stresses and vibrations when the car reached speeds up to 200mph. The material's high temperature resistance also acted as a key enabler for autoclave curing the finished part at 90°C for an hour. The same system has also proven its worth in bonding couplings onto the GRE transmission shaft of a French-made 4x4 vehicle, where it met important criteria with its high strength capabilities to successfully withstand torsion loadings.

Demonstrating the value that epoxy adhesives offer in combining high strength with easy processing, Araldite 2022 is another good example. This epoxy has been used by a German manufacturer to provide excellent adhesion on the steel and ABS components that make up the interior parts of a mini-van's tailgate. Helping to reduce the overall weight of the unit, this epoxy's short curing time at room temperature allowed the parts to be handled after just one hour, significantly enhancing and simplifying the assembly process.

Versatile Methacrylates

Methacrylate adhesives are suitable for similar and dissimilar materials and are most commonly selected for the time saving advantages created by their speed of cure characteristics.For a Polish vehicle maker, these fast curing properties proved particularly beneficial in allowing the PA6 and steel parts of a tailgate plug to be securely bonded and rapidly cured, making it the adhesive of choice for high speed production repeatability.

As well as offering a special balance of high tensile, shear and peel strengths with the maximum resistance to shock, stress and impact across a wide temperature range, methacrylates are extremely versatile in being tolerant to mix-ratio variations and remain strong and durable under severe environmental conditions.

Flexible Polyurethanes

Similar to epoxy and methacrylate adhesives, polyurethane adhesives are suitable for multi-material assemblies. By contrast, due to their flexible properties, polyurethanes also work well on tough-to-bond engineering thermoplastics, ridged plastics and composites. They are typically applied in the production of headlights, brake lights, reflector housings and often used to bond bumpers onto vehicles. Araldite 2029-1 for example, a cold curing polyurethane adhesive, has been successfully used on the dashboards of high-end sports cars and has primary applications where bonding of Carbon Fiber Reinforced Polymer to ABS is required.

Friction Resistant Phenolics

Phenolic adhesives are best used on metals and friction materials and are mostly used on brake shoes, brake pads, friction lining materials for clutches and dip-coating applications.

Araldite 64-1 is a phenolic adhesive that has been used by a Bulgarian car maker to bond antifriction composite liner onto the stainless steel plate of a brake pad. Fulfilling the manufacturer's objective to provide better resistance to brake fluid, use of this adhesive also resulted in the successful application of lighter weight materials alongside reduced costs.

Conclusion

Structural adhesives can be used to join a variety of similar and dissimilar substrates, helping to improve vehicle durability, reduce weight and manufacturing costs. By contrast to mechanical fixings, their use can help reduce fatigue and failure commonly found around spot welds and fasteners.

In an age of substrate change, where manufacturers are looking to use different materials that will have a significant impact on weight reduction, adhesives certainly have a big part to play. They are likely to be used in combination with mechanical fastening techniques for the foreseeable future, but it's true to say that the use of nuts and bolts will decrease as time goes on and targets for the low carbon-economy escalate.

▶ Contact:
Patricia Albisser
Huntsman Advanced Materials GmbH,
Basel, Switzerland
Tel.: +41-61-299 2664
patricia_albisser@huntsman.com
www.huntsman.com/advanced_materials

Bayer to Add Second Line to Indian TPU Plant

Bayer MaterialScience (BMS) has announced plans to add a 3,500 t/y production train to its Desmopan thermoplastic elastomers (TPU) plant at Cuddalore in India'sTamil Nadu state. The new capacity will lift total output capability at the facility to 6,000 t/y when it goes on stream in the second quarter of 2015. The Cuddalore plant facility supplies the Indian market and also exports to Europe.

The company is the sole TPU producer in India. Ajay Durrani, BMS country representative for the Indian subcontinent, said, the company continues to see strong growth opportunities in India across all business units. (dw) ■

SABIC Signs China R&D Collaboration

Saudi Arabian petrochemical giant SABIC has signed a five-year strategic R&D partnership agreement with the Chinese Academy of Sciences (CAS), the leading public research and education institution in the People's Republic. The Saudi company said the strategic collaboration agreement will help it further its research, intellectual exchange and talent development. China is SABIC's fastest-growing market. Under the plans, SABIC will make a multimillion dollar investment aimed at applying innovation and sustainability principles to expand the utility of feedstock, harness the potential of nanotechnology and explore advancements in composite materials.

Along with research collaborations, the two sides are jointly sponsoring an annual scientific forum of chemistry and chemical engineering. (dw) ■

A. Schulman Acquires Australian Plastics Producer Compco

US plastics compounder and distributor A. Schulman has paid $6.7 million to acquire Australian plastics producer Compco. The company based at Melbourne with sales of just under $A15 million in fiscal 2014 (30 June) manufactures plastics compounds and products such as masterbatches and custom performance colors for applications in packaging, wire & cable and pipe. Schulman CEO Joseph Gingo, said that although the acquisition – the company's tenth in four years – is relatively small, the benefits of Compco's industry-leading technology "will better position our business in the region and can be leveraged throughout our global footprint." (dw) ■

A Perfect Symbiosis of Material and Design

Saving Weight with Continuous-Fiber-Reinforced Thermoplastic Composites

Replacing sheet metal with Tepex dynalite continuous-fiber-reinforced thermoplastic composites delivers significant additional weight savings in numerous areas of plastic-metal composite technology (hybrid technology). As the latest series parts show, even thermoplastic compression molding processes benefit from the composite's potential in terms of lightweight materials and design.

Fig. 1: Despite its thin walls, the seat shell is very rigid and strong. In the event of a crash, it absorbs more energy than comparable designs such as those made of plastics reinforced with long glass fibers.

Fig. 2: The engine compartment guard plate shows that Tepex dynalite has great potential for use in underbody protection for cars – particularly for cars destined for countries where road conditions are generally poor.

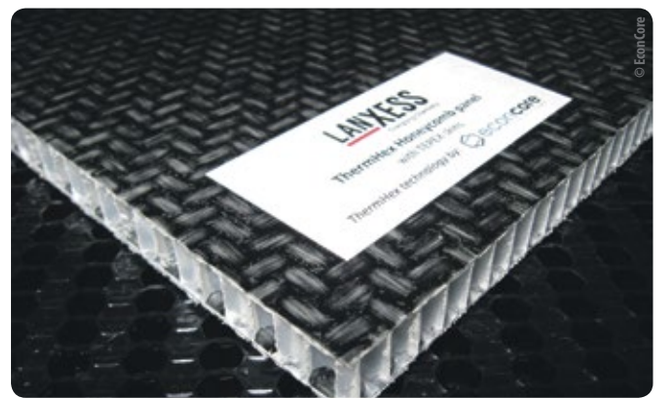


Fig. 3: Honeycomb cores and sandwich composites that combine the cores with Tepex outer skins have excellent potential for use in automotive, boat building, furniture making, transport and motorhome construction applications.

Tepex is a high-tech product from Lanxess subsidiary Bond-Laminates, which is based in Brilon, Germany. The composites are reinforced with balanced or strong-chain continuous-fiber fabrics made from high-strength glass, aramid or carbon fibers, are fully impregnated and consolidated and are produced in consistently high quality for large-scale series production. When it comes to structural components for automobiles, polyamide 6, polyamide 66 and polypropylene are mainly used for the matrix, while continuous glass fiber rovings are usually used for reinforcement. The continuous fibers are decisive for the mechanical properties of the composites and are as long as the part itself. A force applied along the orientation of the fibers will flow from one point of force transmission to another mainly via the continuous fibers. As a result, the component is very rigid and strong along the orientation of the fibers.

Prototype of an Infotainment Carrier

At a density of just 1.4 - 1.8 kg/dm³, Tepex dynalite is lighter than aluminum and sheet steel (2.7 and 7.8 kg/dm³ respectively), and has advantages in terms of weight-specific strength and formability. It significantly boosts the potential for lightweight design using hybrid technology, as evidenced by a prototype of an infotainment carrier for use in a car interior. The prototype was developed for series production by Audi, Lanxess, KraussMaffei Technologies and Christian Karl Siebenwurst Modell- und Formenbau. The component has to hold an amplifier and optionally a TV tuner. It weighs almost only half as much as a comparable steel component, is easier to install and can be produced in a process that is suitable for large-scale series manufacturing. Tepex is used to reinforce the connection points with the bodywork and add-on parts, these being subjected to very high mechanical loads. It is entirely feasible that other supporting structures in the automobile – such as carriers for electrical and electronic modules in hybrid technology – could be made with Tepex.

Seat Shell in Series Production

Another example of the weight-saving potential of composite hybrid technology is the seat shell {Fig. 1} of the Opel Astra OPC (manufactured by Reinert Kunststofftechnik). It is approximately 800g or 45% lighter than the previous component design. It is produced using an in-mold forming technique in a one-shot process that combines the characteristic lightweight capabilities and material qualities of Tepex with a cost-effective production technique. A heated composite insert is placed in an injection mold and shaped and ribs made of polyamide 6 reinforced with short glass fibers are injection molded onto it directly.

Reinforced Composite Overlays for Compression Molded Parts

Tepex has a growing range of potential applications in compression molding for fiber-reinforced thermoplastic matrices. This process can be used as a cost-effective means of manufacturing large components in a customized material mix with short cycle times. What's more, low mold costs also enable production in small to medium production volumes. The incentive to use Tepex is that, when used as an overlay, it significantly reinforces specific areas of components that are exposed to particularly high loads. Tepex grades based on polypropylene or polyamide are used, which can be combined with various compression molding or forming materials, for instance with direct long-glass-fiber-reinforced thermoplastics (DLFT), glass-mat-reinforced thermoplastic systems (GMT) and low-weight-reinforced thermoplastics (LWRT). The result is a sandwich component that is many times more rigid and stronger than an equivalent without a Tepex overlay and can also absorb more crash energy.

A recent example of such a sandwich design is the engine compartment guard plate in the Mini John Cooper Works GP {Fig. 2}. During production of this component, a polypropylene-based DLFT mass that has been compounded with continuous glass fiber rovings is compressed with two Tepex dynalite overlays. The overlays give the part three times the strength and energy absorption of a solely polypropylene-based DLFT component. Compared to guard plates made of sheet steel or aluminum, this construction method delivers a weight saving of up to 50 and 20% respectively.

Outlook

Thermoplastic sandwich composites with a honeycomb core are a new approach in lightweight design. They promise further improvements in terms of specific strength, rigidity and weight savings. That is why Lanxess and EconCore, based in Leuven, Belgium, are collaborating on the development of honeycomb cores {Fig. 3}. The goal is to manufacture these cores from Durethan polyamides using the automated, continuous ThermHex honeycomb technology patented by EconCore. The polyamide honeycomb cores would then be covered with Tepex outer skins.

▶ Contact
Udo Erbstoesser
Head of Trade & Technical Press
Corporate Communications, Lanxess Deutschland
Tel.: +49 221 8885-4529
udo.erbstoesser@lanxess.com
www.lanxess.com

Vision and Perspective

Polycarbonate Compounds in Automotive Glazing Applications - Growth Opportunities versus Potential Hurdles

Automotive original equipment manufacturers (OEMs) are evaluating every possible opportunity to reduce vehicle weight to achieve fuel savings and reduction in carbon dioxide (CO_2) emissions. As a result, automotive glazing has emerged as one of the major automotive applications that are expected to gain significant growth opportunities in the arena of lightweight materials.

Soundarya Shankar
Research Analyst, Chemicals,
Materials and Foods Business Practice
Frost & Sullivan, Chennai, India

Windscreens, side windows, rear windows and panoramic roofs are the key application areas for glazing in vehicles. Laminated glass and tempered glass are the most commonly used glazing materials while plastic penetration into these applications is also being witnessed. Polycarbonates (PC) and Polyvinyl Butyral (PVB) are the two main plastic compounds used in glazing applications. PVB dominates the plastics landscape for automotive glazing applications with approximately 98% share which can be attributed to its use as an interlayer in laminated glass, which holds a sizeable share in glazing applications. PC compounds, on the other hand, account for less than 2%. However, improved design freedom, superior mechanical properties along with its light-weighting capability has rendered PC as an ideal material in the glazing market. PC compounds have proven to offer up to 50% weight reduction as compared to glass.

The chart below depicts the existing and emerging applications for PC compounds in the automotive industry (fig. 1).

More Than just Light-Weighting

Apart from light-weighting, increased design freedom, part consolidation and improved functionality have gained importance among automotive OEMs while choosing materials. These aspects are becoming increasingly important as style, aesthetics and comfort have become paramount in automotive design. PC compounds have proven to offer significant advantages over conventional materials used in glazing applications. For instance, colored glazing, complex three dimensional shapes, innovative window design such as sharp edged corners, gaps in the windows have been made possible with PC compounds as compared to laminated and tempered glass. Wide varieties of design have been introduced where rear view mirrors, cameras and lighting modules are being integrated into the window assembly instead of attaching them to door panels. This has been possible through high level of parts integration and exceptional design freedom that PC compounds offer. These have rendered them more competitive than other glazing materials in the marketplace.

Superior thermal insulation properties of PC offer significant advantages that help optimize cabin environment, thereby reducing the overall load on air-conditioner. Another interesting area that is attracting the focus of market leaders is infrared (IR) and scratch resistance. PC compounds offer poor resistance to IR radiation and advancements in additive formulation are progressing to block or absorb radiations. Bayer MaterialScience has introduced colored PC glazing resin with IR absorbing additives for the Bugatti Grand Sport Targa Top. In addition to this, Sabic's Lexan resins, with an infrared formulation has proven to reduce heating, ventilation and air-conditioning (HVAC) load to 7.1% in winter and 6.3% in summer which in turn offers sizeable reduction of CO_2 emissions.

Regulatory Scenario

In spite of proving to be the most preferred material in other applications such as headlamps, tail lamp and other lighting applications, PC compounds have been facing significant hassles in penetrating into the glazing segment. Tempered glass is the most commonly used material for non-windshield glazing applications while stringent regulatory trends have resulted in the sole use of laminated glass for windscreen applications.

Regulation 43 in Europe governs the use of materials for windshield glazing applications while the standards specified pertains to glass and do not take plastics usage into consideration. The current situation therefore demands regulatory authorities to revise the standards and stipulate material preferences in the purview of using plastics. Test cycles and approval procedures are required to be correspondingly established. For instance, weatherability tests for glass and plastics will be significantly different from each other. Restricted penetration into windshield applications that account for a wholesome 20% of automotive glazing area curbs opportunities for PC compounds. However, compound manufacturers and component manufacturers are lobbying to permit the use of materials other than laminated glass for windscreen applications. Furthermore, polycarbonate windshields are used in German police cars and forestry machines in order to provide best in class protection against vandals that could potentially break into the vehicle. This suggests that PC compounds, due to high impact resistance, have immense scope to penetrate into the windshield applications.

It is also important to note the fact that PC compounds have not been able to easily penetrate into the non-windshield applications (that account for close to 80% of the glazing segment), that do not even fall under the regulatory purview. Poor scratch resistance properties of PC render them unsuitable for glazing applications that have movable windows, wiper systems and frequent washes. Sabic and Bayer MaterialScience, the market leaders in PC glazing applications are working towards developing PC grades that offer superior visibility, weatherability, impact and abrasion resistance. In order to develop PC glazing with superior optical and mechanical properties, specialized coatings have to be applied on the surface. Certain challenges exist in the existing coating technologies which considerably restrain the penetration of PC compounds even in non-windshield glazing applications.

Technological Advancement

State-of-the-art coating technologies that offer significant resistance for more than 10 years of outdoor exposure, which is the stipulated quality standard for PC in glazing applications, are being developed in the marketplace. PC glazing systems are further required to meet and exceed regulatory requirements for driver visibility such as FMVSS 205, R43 and JIS R 3211 that have been stipulated in US, Europe and Japan respectively. This will be made possible only with a well-established coating technology.

Coatings requirements vary with individual glazing application. For instance, abrasion and weatherability requirements vary amongst the front windows, rear windows and roofing applications, which in turn demand suitable coating formulation. Polysiloxane hard coating via plasma enhance vapour deposition method has proven to effectively meet regulatory requirements as well as OEM demands. However, coating facilities are yet to be well established to support mass production applications. Cost of coating these systems eventually boost total cost of product and it is therefore compelling that manufacturers establish a cost-effective coating technique to competitively position the product in the marketplace. PC manufacturers, coating companies and automotive OEMs are working closely to establish large-scale production facilities. Certain PC compound manufacturers are also evaluating options to add in-house coating capability to achieve cost efficiency.

What's the Future for PC Compounds?

PC compounds have a promising future in the automotive glazing landscape once the issues related to coating technologies and production capabilities are addressed. Revision of existing regulatory specifications and testing methodologies for plastic based glazing systems will further facilitate adoption of PC in windshield glazing applications. Over and above this, globalization of automotive OEMs and technology transfer across regions are compelling the need for standardization in material usage. Harmonization of regulatory standards at a global level therefore remains paramount to aid the replacement of glass by PC compounds. North American standards for plastic glazing materials are the most stringent as they specify high weatherability requirements. Harmonization of standards will consequently increase the requirements on material's chemical and mechanical properties paving way for R&D activities.

Mass production and application of PC in glazing applications are expected to commence by the end of the decade as they require considerable level of advancements in terms of technology, production capabilities and revision of regulatory standards. Market participants across the value chain, including raw material suppliers, compounders, component manufacturers, automotive OEMs are striving to address the existing challenges in the marketplace. Rapid adoption of PC glazing for sun roofs, fixed side and rear window applications are expected to progress during the next five years while penetration into movable side windows and windscreen applications are projected to go mainstream during the next decade.

Soundarya Shankar
Research Analyst, Chemicals,
Materials and Foods Business Practice
Frost & Sullivan, Chennai, India

► soundaryas@frost.com
► www.frost.com

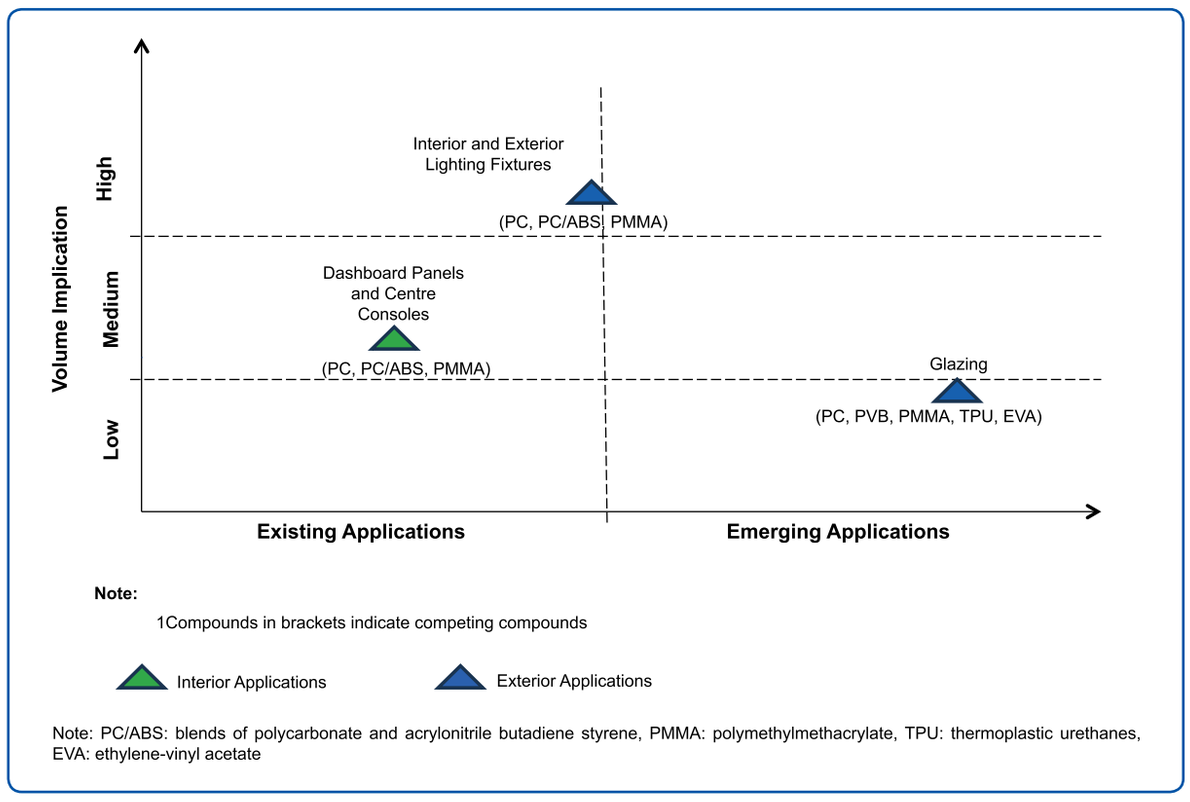


Fig. 1: Polycarbonate in Automotive Glazing Applications: Existing and Emerging Opportunities, Global, 2014

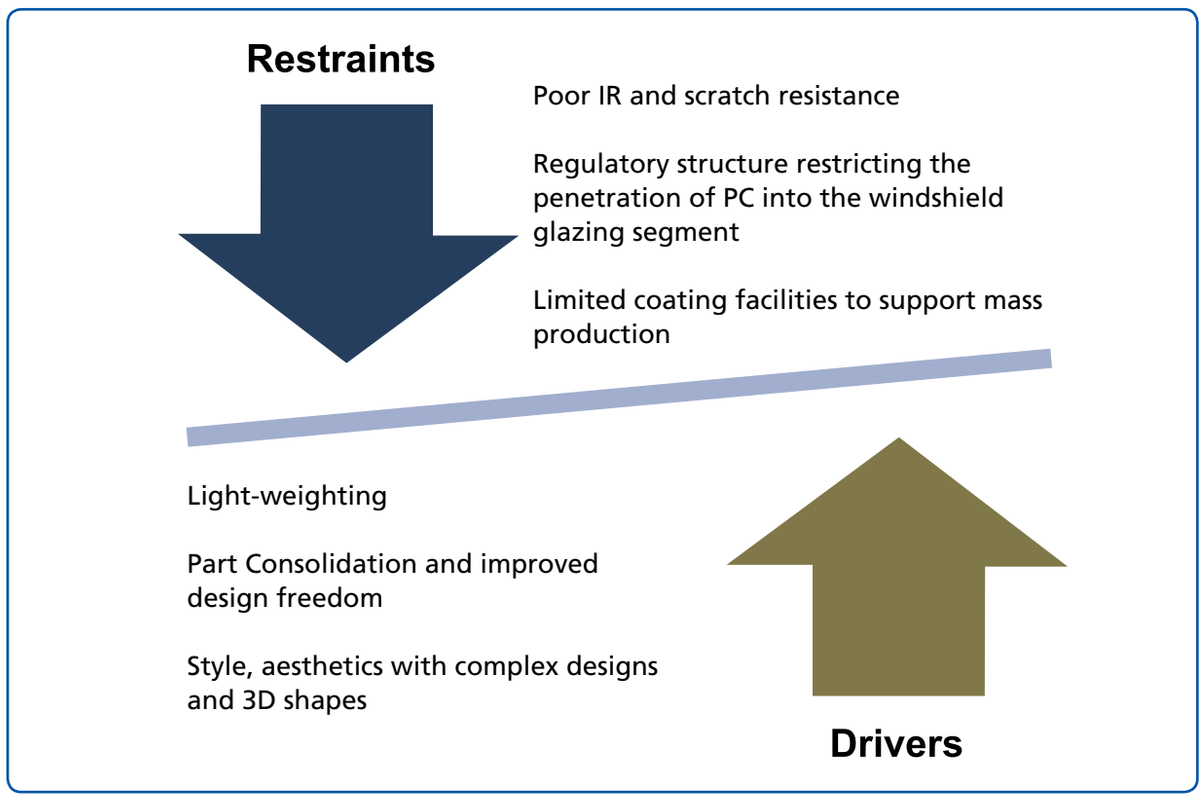
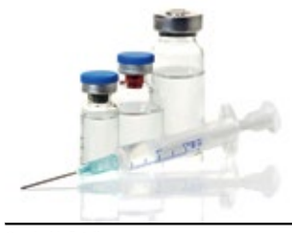


Fig. 2: Polycarbonate in Automotive Glazing Applications: Drivers and Restraints, Global, 2014



Pharmaceuticals

The different stages of pharmaceutical product development.

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Excipients

Pharmaceutical excipients suppliers and users face increasing regulatory demands.

Page 17

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Supply Chain

How Pharma can avoid serious implications caused by drug shortages.

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Today's Challenges, Tomorrow's Excellence

How the Pharmaceutical Ingredients and Custom Synthesis Industry Attunes to Rapidly Shifting Demands

As the pharmaceutical industry is faced with numerous challenges that it must address in order to thrive, it also demands from its service and technology partners to adapt to rapidly changing roles. CHEManager International asked experts from chemical manufacturers, CMOs and CROs to discuss the changes that are shaping the future relationship of their business with the pharmaceutical companies.
Read what they told us on the following pages.

Dr. Lukas Utiger,
President and CEO,
DSM Pharmaceutical Products

The CDMO players can help with their specialized know-how and deep experience.

Dr. Wilfried Eul,
Senior Vice President, Evonik

We see them — CROs and CMOs — as efficiency boosters now and in the future.

Dr. Markus Blocher,
CEO, Dottikon

Sharing the risks and rewards can yield good results if it is done wisely.

Ian Muir,
Managing Director,
Finished Dose, Aesica

Quality and reliability remain the cornerstones of the pharmaceutical supply chain.

Christian Jones,
Associate Director — Business Development, Dr. Reddy's

The best CMOs always seek to add value that will increase the chances of their client's success.

Dr. Michael Stohlmeier,
Senior Product Manager — Business Development, CU Chemie Uetikon

This is the big chance for any CMO to accelerate the drug development.

Dr. Max Braun,
Senior R&D and Business Development Manager, Solvay

Demand is changing for CROs and CMOs in the frame that the selected organization needs to contribute cutting-edge technology and unique skills.

Andreas Weiler,
Global Head of Strategic Marketing,
SAFC

There is no one-size-fits-all business model. A CMO's strategy must be adaptable.

Dr. Rudolf Hanko,
CEO, Siegfried

We don't see an increased fill of of the pipeline but a better management of pipeline failure and leakage.

Dr. Andrea Missio,
Business Development Director,
WeylChem

A successful CRO/CMO must expand the breadth of its competencies and offers.

Jörg Schneider,
Head of Marketing,
Saltigo

The task of identifying and selecting the right CMO is key.

High Performance

CPhI

CPhI (Convention on Pharmaceutical Ingredients) Worldwide – the International exhibition on Pharmaceutical Ingredients and Intermediates – is the leading networking event and exhibition dedicated to pharmaceutical developments, trends, products and services, including contract services, excipients, ingredients, APIs, machinery, finished dosage forms and packaging.

Hosting over 34,000 attendees from 140 countries and 2,200 exhibitors, CPhI Worldwide will take place on 7-9 October 2014 inParis, France. First held in 1990, 2014 marks the 25th edition of this prestigious and industry leading event.

The pharmaceutical sector has undergone rapid changes during the last few years and the event is going to underscore the latest developments in this sector. CPhI allows attendees to stay informed about the latest industry trends and remain one step ahead of a constantly changing pharmaceutical market. Industry professionals as well as enthusiasts are going to come together and get the opportunity to establish new business relations with each other.

CPhI has three co-located events: ICSE, P-MEC Europe and InnoPack. These events focus on specific sub-sectors of the Pharma ingredients industry and provide visitors and exhibitors with additional capability to network and do business in dedicated areas. Under one roof, the four exhibitions cover every step in the Pharma supply chain and create a unique environment where delegates can meet, learn, exchange ideas and form alliances that drive business throughout the year.

Ian Muir,
Managing Director, Finished Dose, Aesica

Kurt Hoeprich,
Business Manager, Custom Services, Albemarle

Elliott Berger,
VP Global Marketing & Strategy, Catalent

Dr. Michael Stohlmeier,
Senior Product Manager — Business Development, CU Chemie Uetikon

Dr. Markus Blocher,
CEO, Dottikon

Christian Jones,
Associate Director — Business Development, Dr. Reddy's

Today's Challenges, Tomorrow's Excellence

How the Pharmaceutical Ingredients and Custom Synthesis Industry Attunes to Rapidly Shifting Demands

Pharmaceutical companies have outsourced several critical steps in the discovery and development of new drugs and the scale-up of processes and the manufacturing of APIs. Pharma, therefore, depends and relies on numerous service and technology partners. CHEManager International asked experts from CROs, CMOs, manufacturers of APIs, excipients and catalysts, formulators and others to describe their changing role in the pharmaceutical value chain. Read their answers to our questions.

What roles do contract research organizations (CROs) and contract manufacturing organizations (CMOs) play in the drug discovery/development value chain today, and how will their role change in the future?

Dr. W. Eul (Evonik): As catalyst supplier to the pharmaceutical industry, we also work with CROs/CMOs as extended workbenches of our customers. We see them as efficiency boosters now and in the future. If they develop the chemistry for making the molecule, we work with them in the same way as we work with the pharma companies directly.

I. Muir (Aesica): CDMOs – contract development and manufacturing organizations – play an increasingly important role in the pharmaceutical supply chain, offering services from API – active pharmaceutical ingredient – synthesis through to packaging and shipping of finished dose products around the world. The drivers of growth within the CDMO sector remain the same as historically, with continued mergers within the pharma sector, reduced pipeline activity and the rise in generic prescribing all driving decisions around make versus buy.

K. Hoeprich (Albemarle): We believe one of the most significant roles leading cGMP-compliant CROs/CMOs play in the value chain today is enabling increased speed to market. This is achieved by efficiently conducting the extensive range of activities required for API development and manufacturing (e.g., analytical and process development, scale-up, CMC document preparation), while adhering to cGMPs – current good manufacturing practices. Ultimately, this saves drug developers' and marketers' time compared with conducting these activities in-house, as was historically done.

E. Berger (Catalent): The role of pharmaceutical service and technology partners is rapidly changing. Several factors are driving the change:

- An increasingly higher proportion of drug discovery and development is happening in smaller firms.
- Large pharma companies are increasingly slimming down to focus on specific areas and core expertise.
- Molecules in the pipeline are increasingly more challenging in their pharmacokinetics (e.g., bioavailability) and in delivery profile needs.
- Technology, development and manufacturing partners like Catalent provide advanced delivery technologies and often bring unique understanding and patient design factors associated with these molecules' routes of delivery. Specialized dose forms can help pharma enhance patient experience and clinical outcomes.
- Manufacturing requirements are becoming more and more challenging as well – due to more challenging molecules but also due to increasing regulations and globalization needs.

These factors drive the need for deeper partnerships between innovators and companies offering specialized technologies, drug development and supply expertise. Catalent, for example, has made significant investments in new technologies, capabilities and R&D expertise to help innovators meet these challenges, and is increasingly engaging in broader and deeper partnerships with both large pharma companies as well as smaller innovators.

These partnerships start early, sometimes in preclinical development, and as a partner in the development process, Catalent can help optimize the API and formulations of new drugs, span multiple dose forms and formulations for comparative studies, encompass deeper engagement, including analytical and clinical trial supply support, through late stage clinical and scale-up, and extend through global commercial manufacturing for the life of a molecule.

Dr. M. Stohlmeier (CU Chemie Uetikon): During the past years we have seen a trend by the innovators/drug-development companies to focus more and more on target molecule identification, drug design and computational chemistry. Consequently, the process development teams have been strongly reduced or even closed. Further, the innovative companies have decreased their capacity for the process validation phase, and first piloting campaigns, and will need to outsource those activities more and more to CRO/CMO service providers.

Dr. M. Blocher (Dottikon): In the area of drug discovery and development, the concept risks have increased because innovation pressure forces the companies to move into new modes of action and indication areas. At the same time, supply risks and regulatory requirements have intensified further due to squeezed timelines and stricter enforcement of quality-related regulations. In an effort to effectively manage the development process, pharma companies have to focus on managing their core processes such as research, clinical trials and the regulatory approval process. Other processes, such as route finding, process development, scale-up, optimization and production of the API itself, are equally important for approval, but do not represent core areas for pharma companies. Pharma has to join forces with reliable and strategic partners for development, scale-up and production to assure high quality for approval and supply for launch at reduced costs through efficient asset use and design to value.

C. Jones (Dr. Reddy's): CMOs play a vital role in the value chain today. Many Big Pharma and biotech companies are outsourcing far more than they used to, which means the role of CMOs is much more important than it was 10 years ago. We believe this role will become even more critical in the future as competition increases and the dependency of pharma companies on their suppliers grows further. We will see changes in risk-management profiles: Pharma and biotech will be taking on more risk as they outsource more work, so there will be a need for greater trust and closer relationships between CMOs and their clients. The level of relationships with suppliers will change accordingly, and the value that CMOs bring to the relationship should also increase as the role and outputs grow. Speed is also becoming an increasingly important part of the CMO's role in the value chain. Pharma companies' need for getting products to market and reaching developmental milestones will continue to increase in the future and, as a result, speed of delivery will become a more important factor than cost alone.

A. Weiler (SAFC): With 80% of innovation taking place outside of Big Pharma – here defined as the top 25 pharmaceutical companies – CMOs must be able to support the different requirements of small (and virtual) pharma and biotechnology companies. Regardless of the size of the customer, it is critical to build a true partnership with each customer that enables it to focus on core competencies while the CMO focuses on a proactive service and solution package. This works especially well when the right quality and project-management systems are in place to allow for fast and flexible action if/as requirements change during the project.

In the future, we will likely see a handful of giant CMOs offering everything from discovery to commercialization, with the more specialized CMOs (such as SAFC) remaining focused on specific technologies and markets. It will be interesting to see how these giant CMOs will maintain flexibility while staying on top of all new technologies.

Dr. M. Braun (Solvay): In the future, the role of the CRO/CMO will increase more and more. Pharma companies make the lead discovery and do patenting, registration and marketing. In between – after the lead, before marketing – there is a huge gap, which has to be filled by CROs/CMOs. Solvay is actively collaborating with all players of the pharma value chain, including projects with CROs and CMOs.

C. Le Ret (Umicore): We indeed see a higher involvement of the contract manufacturer not only in drug development but also all along the development chain first – and after launch all along the supply chain, ideally till the dosage form is ready.

This surely speeds up developments and reduces development costs – and may be a solution to pharma's problems of having too few drug-development projects and too high development costs? It also requires a closer cooperation with the pharma client, as well as to expand the fields of expertise of the CMO. Building a one-stop shop – with the potential drawback of building a generalist that misses expertise in one or more fields. I expect as a consequence a series of consolidations aiming to build drug-development and manufacturing experts out of CROs, CMOs, and formulation and packaging specialists.

Umicore follows the trend, willing to stay in its niche of expertise, though, and is developing closer and deeper relationships with its current clients, expanding according to their needs its expertise in highly potent API development and manufacturing, including all necessary logistics and regulatory support.

Dr. A. Missio (WeylChem): Modern CROs/CMOs have moved away from the simple offer/demand business model, which operated well in the last 20 years but no longer reflects the dynamics of the current pharmaceutical market. In these days, a successful CRO/CMO must expand the breadth of its competencies and offers. For example, manufacturing capacity abounds all around the globe, and in order to succeed a modern CMO shall offer additional service, e.g., storage of finished goods (in case there is a delay in market introduction), or it shall proactively seek to shorten the supply chain by developing partnerships with local suppliers. These activities offer the additional advantage to quickly react to a changing market environment, responding to either upsides (growing demand requires faster sourcing) or downsides (slow market acceptance may require storage capacity).

Dr. J.-L. Herbeaux (Evonik): Generally speaking, we observe a propensity on the part of pharma companies to increase their reliance on outsourcing as they seek to lower their fixed costs (e.g., in R&D and manufacturing), speed up drug development and launch, and focus on core elements of their value chain. This said, outsourcing behaviors vary greatly from one pharmaceutical company to the next depending on their respective tolerance for externalization of key value steps.

Besides these changes in the outsourcing models of pharma companies, other factors will drive up the importance of qualified CROs and CMOs, including the emergence of virtual companies as drug developers and the need for new technologies to re-energize product launch pipelines.

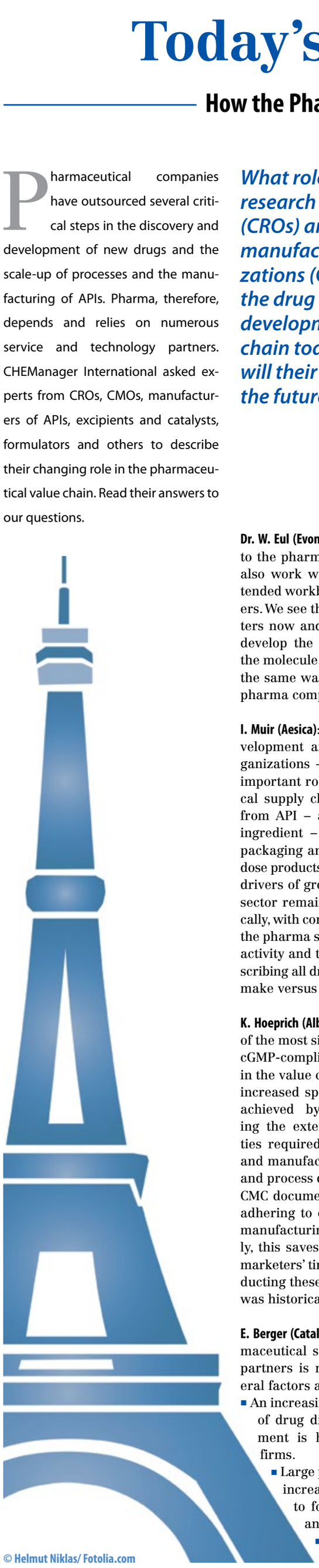
Dr. L. Utiger (DSM): CROs and CMOs deliver services in the area of $9 billion per year to the pharmaceutical industry. With more than 5,000 products still in clinical (CT1-CT3) phases in the hands of small or mid-size pharma companies, the role of CROs and CMOs has increased as there is a need for specialized service units to successfully deliver new APIs. This need includes API synthesis, stability tests, final dosage development and clinical trial production.

For launched products, CMOs' work in API or intermediates production and drug product production has increased as well. In addition, manufacturing services in generics are an important part of CMO work today, again in both areas of API/intermediates and drug products.

Dr. R. Hanko (Siegfried): There are numerous challenges to the industry that make investments for captive production capabilities increasingly unattractive: growing demands on clinical development, increased competition between innovators and generic companies, and a lower risk appetite among investors. This is a growing trend, which renders development offerings of the CMO industry increasingly attractive. The discovery process, however, will remain the home turf for captive activities of innovators.

Dr. G. Haering (Cerbios): I would start by saying that the classical and "old role" of supplier has gone. In order to be successful with a project, and due to project complexity, a CMO such as Cerbios (drug substance CMO) has to bring value to the customer with unique expertise and act as a consultant.

If, in addition, the CMO brings on board innovative technologies that can help in providing better bioavailability or lower dosages, chances are that drug development there will have a higher success rate. A real partnership approach is paramount to that.



Andreas Weiler,
Global Head of Strategic Marketing, SAFC

Dr. Max Braun,
Senior R&D and Business Development Manager, Solvay

Dr. Wilfried Eul,
Senior Vice President, Evonik

CPhI worldwide

How have the requirements by pharma companies changed over the years, and how can suppliers manage to live up to them?

Dr. W. Eul (Evonik): Pharma companies used to go to the market looking for products to fit with the production parameters they developed in-house. Increasingly, we have seen that a growing number of firms are going to the market looking for solutions to certain production steps instead of a standard product search. For Evonik, this means we can demonstrate our flexibility, creativity and reliability. In order to stand out from other suppliers, we develop and provide current solutions as well as proactively working on optimizing our customers' catalytic processes with the next generation of catalysts. Here, the early involvement of Evonik's catalyst experts pays off.

Another challenge for the pharma industry is to reduce complexity so it can concentrate on its core business of developing new chemical entities and bringing them to the market. For example, catalysts in pharmaceutical syntheses invariably contain expensive precious metals. Careful management of this key raw material is critical. To support the industry, Evonik offers a comprehensive precious metal management consisting of precious metal sales/leasing and refining once the catalyst has been used in production.

I. Muir (Aesica): A new future trend is that the CDMOs are changing themselves with merger activity driving scale, breadth of technology and geographic reach. Increasingly the CDMO sector, which was traditionally focused on development and manufacture, is overlapping with other sectors involved in electronic data transfer and management and supply-chain logistics, as they look for areas of expansion in nontraditional sectors.

K. Hoeprich (Albemarle): Many pharma companies have reduced or eliminated their API process development and manufacturing capabilities, so CROs/CMOs have had to expand capabilities to handle this demand. Concurrently with addressing this increased demand, CROs/CMOs must ensure they stay abreast of increasingly stringent cGMP requirements. One area Albemarle has focused on is utilization of Quality by Design (QbD) for all API process validations, including Design of Experiments (DoE) methodology, to fully understand the process design practice. We have found this approach is required by regulatory authorities and is critical for progressing an API through the regulatory approval process.

Dr. M. Stohlmeier (CU Chemie Uetikon): Basically, the existing capacity at the pharma companies for chemical processing has decreased over the years; this is also true for the production capacity. We have seen this trend with various companies in Europe and the USA, as well. As a consequence of this trend, those capacities must be provided by external companies. This is the chance for CROs/CMOs to step into the process of drug development. To support the innovators as a reputable CRO/CMO, you are strongly bound to the timeline of the customer. Therefore it is important to have sufficient capacity available and to be very flexible to follow the developmental stages very closely.

Dr. M. Blocher (Dottikon): We have observed an increased demand among pharma companies for quality and capacity under tight timelines with needs for innovative route finding, reliable and sustainable project management and short response times. Consequently, a CMO must meet these requirements by building best-practice project management and by providing flexible development and production capacities for various technologies in compliance with cGMP. Also, the CMO must have an impeccable regulatory track record.

C. Jones (Dr. Reddy's): In addition to the increased demand for outsourcing, there has been an increased requirement for quality and safety standards. All companies in this industry space have to meet these standards and see them as a basic requirement if they want to continue to do business with others; without them they will not succeed. Those suppliers who are serious about competing are willing to put the extra investment in, not only to meet today's standards but also to ensure they will be able to continue to do business with pharma companies in the future, as quality and safety requirements continue to increase. Speed and trust are also growing in importance, as are the needs for providing global delivery models and flexibility in the supply chain.

A. Weiler (SAFC): The requirements have become more stringent as regulations have tightened, but they have also changed based on the type of company. There is a difference in the way a small pharma company operates versus Big Pharma. Even with recent increases in outsourcing by Big Pharma, the vast majority has not embraced a strategic outsourcing philosophy for their APIs or registered key intermediates. On the flip side, many of the small pharma companies are more open to outsourcing partnerships because increased productivity is one of their key drivers over cost.

Despite declined in-house innovation, many Big Pharma companies use internal resources to manage their outsourcing activities. Cost becomes a big driver here, as the company may use different specialized CMOs during development, but choose to tap into internal manufacturing capacity for the final steps of their process(es) to reduce supply risk.

There tend to be three exceptions to this approach, where Big Pharma will outsource despite cost:

- Due to a lack of internal expertise or capability related to a technology area; these are often niche or very complex technologies.
- If a drug is in-licensed or acquired from a smaller company, many Big Pharma companies will maintain the existing supplier due to the risk and associated costs with technology transfer at such a critical phase of development. This practice especially increases in the case of biologics and drugs on an accelerated approval path.
- When critical raw materials or specialized services are not within Big Pharma's core competency.

Dr. M. Braun (Solvay): In the past (more than 10 years ago), pharma companies looked more for the generalists (especially in Asia and with focus on India). Today their demand is changing for CROs and CMOs in the frame that the selected organization needs to contribute cutting-edge technology and unique skills, which, due to complexity, the pharma companies don't have in their own portfolio. Solvay is globally based and best-positioned with its fluorine pilot plant as well as research and development expertise and team.

C. Le Ret (Umicore): We have also noticed the request for change from a catalyst and API supplier to a solution provider. As a catalyst supplier, we have improved our service, developing and customizing precious metal sourcing support, offering more efficiency and flexibility in precious metal recovery as well as more expertise in metal separation. We have also improved our development capabilities and can do accelerated catalyst development and scale-up, going from the idea to production in only a few weeks.

As a HPAPI – highly potent API – manufacturer, we have noticed that GMP and regulatory requirements are higher and higher, and that generic manufacturers need to start their developments earlier. And we cope with these requests with a better dedication and more focused resources, be it technology- or regulatory-wise.

We generally believe that bringing the best experts around the table leads to a better solution than trying to do everything alone. We have developed a network of complementary experts, and we encourage more and more of our clients to enter multiparty cooperation, in which we bring them on-demand and on-time world class expertise in drug development, process R&D, process optimization, catalyst or API development, scale-up and manufacturing, logistics, and regulatory affairs – a la carte.

Dr. J.-L. Herbeaux (Evonik): The increasing reliance of pharmaceutical companies on third parties calls for a rigorous selection of a limited number of reliable partner companies with tangible proof of expertise and sustainable operational and financial models. Opportunistic selection based on short-term criteria can lead to an explosion in the number of CRMOs to manage. Working with the wrong party can create a high burden for pharma companies in terms of deliverables and management attention. True partnerships are hard to come by, and experience suggests that they are facilitated by a shared set of values (e.g., safety and quality culture). Closely integrated communication and project management in combination with global operations are becoming more important for larger customers.

Jan Bebber (BASF): The predominant trends within the pharma industry, such as strong growth in generic products, rising R&D costs and increasing regulatory hurdles, are currently driving the need for reducing costs across the industry. This has driven change in the requirements of pharma companies in two major areas: a) intensified concentration of pharma companies toward core competencies lead to outsourcing requirements of other services and b) increased focus on market differentiation of products for survival in the generic environment leads to the need for fast solutions to formulation challenges as well as new formulation approaches. Pharma ingredients suppliers therefore need to be able to assist the pharma companies by providing

Nicolas Taillardat,
Global Marketing and Sales Manager, Organic Intermediates and Solkane Pharma, Solvay

Dr. Andrea Missio,
Business Development Director, WeylChem

John Nicols,
President and CEO, Codexis

Dr. Jean-Luc Herbeaux,
Head Business Line Health Care, Evonik

Jan Bebber,
Global Platform Marketing Manager, Pharma Ingredients, BASF

Dr. Lukas Utiger,
President and CEO, DSM Pharmaceutical Products

Today's Challenges, Tomorrow's Excellence

How the Pharmaceutical Ingredients and Custom Synthesis Industry Attunes to Rapidly Shifting Demands

more support in using their products as well as technologies to enable improved formulations, products or processes. A recent and very visible example for this evolved interaction is co-processed excipients, where existing and well-known materials are combined in a clever physical way using processing expertise to add significant performance advantage in the application. An example of this is BASF's Ludiflash for orally disintegrating tablets. In the long run, the product and industry know-how required is what makes the difference for the suppliers to be a sustainable partner for the industry.

Dr. L. Utiger (DSM): Heightened focus on quality and regulatory track record has definitely increased over the last few years. We've also seen increased FDA – Food and Drug Administration – and/or EMEA – European Medicines Agency – audits at CMOs in Asia, Europe and North America. In parallel, margin pressure is still ongoing, specifically in the API and intermediates area, since overcapacity still exists.

Dr. R. Hanko (Siegfried): Integration of the value chain, especially between drug substance and drug product, becomes increasingly important. That's why our unique selling proposition as a company with expertise in both primary and secondary production and our excellent compliance track record are key. The corporate strategy focuses on the continued development of these strengths. Our acquisition of Alliance Medical Products (AMP) in the USA gives us outstanding skills in the field of sterile fillings, and we've also invested in a high-potency suite in Zofingen – these steps broaden our technology base. At the same time, our new manufacturing facility for APIs and intermediates in Nantong (near Shanghai, China) is nearing completion and will begin operations this year – further enabling us to improve our offer to the market.

Dr. G. Haering (Cerbios): While once there were many Big Pharma companies doing everything, many pharma companies have now concentrated on specific stages of drug development.

- Startup on discovery
- Biotech companies on moving the candidates through clinical trials
- Pharma companies taking care of marketing and commercialization
- Generic pharma companies

There are, of course, companies active at multiple stages, but the global trend is in this direction. This means that the requirements are very different when outsourcing to a CMO. This also means that the CMO either has to have different departments specialized in accommodating the customer need at the given stage or has to also specialize. For a CMO, it is more likely to have three different levels.

- Discovery
- Supplier for clinical and commercial supply
- Specialist in the development of innovative processes, either for generic companies or providing life-cycle-management possibility to originator

Which new business models, like project-based or value-based outsourcing, could turn out to be the most promising guarantors for a successful cooperation with the pharmaceutical industry?

Dr. W. Eul (Evonik): Value-based collaborations are becoming more and more prevalent in the pharmaceutical industry. For the Business Line Catalysts of Evonik, our mutual success with the pharmaceutical industry depends mainly on a close partnership. When we become involved in development work, the earlier and more openly we are brought into the knowledge exchange, the more precisely we can adapt our products and services to our customers' requirements, and the faster and more smoothly the process flows.

I. Muir (Aesica): Quality and reliability remain the cornerstones of the pharmaceutical supply chain, and that has not changed. In fact, there are ever-increasing requirements from traditional regulators and agencies and also from newly emerging markets, which continue to drive the demands on the license holders and their supply-chain partners. CDMOs that can offer reliability and security of supply of product to international markets and work to reduce risk and help achieve inventory-management goals will continue to grow.

K. Hoeprich (Albemarle): At Albemarle, we utilize fee-for-service, project-based and value-based approaches with our customers. In the value-based area, we have found obtaining a royalty on net product sales from our customer's marketed product can be an attractive way to share risk in earlier stages of development.

E. Berger (Catalent): These partnerships may require new business model approaches versus traditional fee-for-service arrangements. At Catalent, we don't compete with our customers and don't currently market products. That has allowed us to maintain flexibility.

These arrangements have included a variety of elements, including collaborative development, success-based financial arrangements such as royalties or profit sharing, hybrid "development-sharing" models, faster collaborative approaches combining joint development contributions with licensing fees and even joint investment in new capability creation.

We have also collaborated with customers to externalize in-house developed technology to more broadly develop better treatments across the industry. Examples include our OptiForm API optimization technology originally developed by GlaxoSmithKline and OSDrC OptiDose advanced tableting technology for combination and controlled-released therapies developed by Sanwa in Japan.

Dr. M. Stohlmeier (CU Chemie Uetikon): From our perspective we have seen more project-based outsourcing requests. In these requests, the target molecule is well-defined and the existing basic process has to be developed. The target of this development is always a robust process that may be used on a commercial scale as well. For us, as a CMO service provider, our target would be to develop the process together with our customer to allow commercial production once the new drug may be launched. This always includes a very open communication, and we have experienced mostly positive results in talking to the customer openly from the very beginning.

Dr. M. Blocher (Dottikon): Outsourcing adds value if the supplier provides a more cost-effective service due to innovation, is faster thanks to its focus on development, and produces reliably at high quality levels. Close cooperation with the pharma company is essential as well, which requires strong project-management capabilities by the CMO. A well-defined technology platform, long-standing experience and reliability are the core prerequisites for a CMO to become a strategic and valuable development and manufacturing partner.

C. Jones (Dr. Reddy's): Most CMOs operate on a project-based outsourcing approach, but others do offer alternative models. Both approaches have their own merits and their own challenges, and it really depends very much on the project and the CMO as to which should be chosen. No single model will be applicable to all deals, and the CMO should have the flexibility to look at different models to suit its respective partner and ensure that it wins the business, but on the basis that the business won does not pose a risk greater than that which the CMO is prepared to take. The best CMOs always seek to add value that will increase the chances of their client's success independently of the model chosen, which translates to success for the supplier, so the most important question to ask is whether the CMO in the relationship is the right one.

A. Weiler (SAFC): There is no one-size-fits-all business model. A CMO's strategy must be adaptle to the different needs of big and small pharma companies; this is even more important as many projects start small but end within Big Pharma. In this case, value-based projects are often more successful. For example, if a CMO is specialized — in highly active, highly complex chemistry, or in a niche technology — it will add value even post-acquisition. In addition, many of these projects might get on a fast-track approval path, so it is unlikely to risk changing the CMO at such a critical phase.

N. Taillardat (Solvay): Pharma in-licenses needed technologies or skills project by project. Solvay believes more in a partnership relationship than the former toll-manufacturing situation/business model.

C. Le Ret (Umicore): We consider a project-based outsourcing as the clearest option: with transparency towards targets, timelines, costs, risk-sharing, allocated resources. We believe it is the most value-creating cooperation mode, which may be because it is for Umicore the best compromise between the level of flexibility we want to offer to our clients as a solution provider and the level of flexibility that our research, development and production resources can handle.

Dr. A. Missio (WeylChem): We strongly believe that the key to a successful cooperation with a pharmaceutical company is the added value that a CMO brings to the partner. By added value, one should understand the ability to quickly access existing assets, without the need to invest in-house. By leveraging those assets, the pharmaceutical partner gets access to the experienced staff that manages those assets. Another added value is the flexibility to accommodate changing delivery schedules. This is particularly advantageous in the early stages of development and in the initial launch phase. A talented pool of process chemists who are trained to work in a collaborative and transparent manner with their customers brings further value to the partnership. Life-cycle management plays an important role as the product matures on the market. To continuously improve the processes, while actively scouting for the leanest supply chain, rounds the offer in terms of added value that the pharmaceutical industry demands today. Quality is taken for granted since this parameter cannot be compromised at all. The WeylChem Group of Companies operates according to these principles and collaborates with its commercial partners to explore new avenues, which will add value to their business relationship.

J. Nicols (Codexis): In addition to project-based business models, Codexis offers a deeply collaborative licensing model to partners that enables not only faster delivery but also parallel capabilities for cooperation. These types of elite partnerships offer truly synergistic relationships that can teach both sides, empowering both partners to explore new boundaries and push the cooperation beyond that which each partner could achieve alone.

This is a new type of business model that effectively forms an alliance of the world's best protein engineers in collaboration, where Codexis and the licensee work together to develop better proteins for more and more applications. We have just entered into such an arrangement with GSK, licensing them our CodeEvolver protein engineering technology. This approach will generate findings that can also benefit other companies in the industry moving forward.

Dr. J.-L. Herbeaux (Evonik): We, at Evonik, believe that a seamless integration of our global competencies (e.g., in API and excipient development and manufacturing, drug product formulation development, scale-up, and industrialization) to create unique solutions is at the core of a successful offering. This integrating platform allows for constant addition and activation of new competencies whether developed internally or via external acquisitions. This model combined with flexible business models adapted to the customer's situation affords unique opportunities for long-term value creation for all parties involved.

Dr. L. Utiger (DSM): The pharma-CMO business model since the late 1980s is the same, mostly opportunistic outsourcing in case in-house capacity does not manage the production load. A slow shift to fully outsourced manufacturing is visible (e.g., Shire), mainly driven by mid-sized pharma houses. This trend may lead to a shift of the business model, where a CMO or DMO will take over the full supply chain (starting material to pharmaceutical product packaging). Such models are already used in electronics or nutrition industries. There is no reason the pharma industry could not move to such a model and keep the focus on its core activities, like research, sales and marketing, drug products, etc. Several industry leaders have already realized the capabilities to offer such an integrated offering, including DPx Holdings – the parent company of Patheon, DSM Fine Chemicals and Banner Life Sciences. It will be up to the industry leaders to catalyze the change. Besides simplified processes during the development timelines, such an integrated model will reduce drug cost due to lean management of the supply chain and fully optimized net working capital along the supply chain.

J. Schneider (Saltigo): Within the framework of project-based outsourcing, companies have the capability to offer different engagement models for their clients. The target is to gain maximum value in compliance with their overall strategic goals. All engagement models are based on the daily and weekly reports, which give a transparent overview of the entire progress. This is the basis of enabling the customer to make necessary adjustments throughout the entire process.

Entire-project outsourcing is the best solution for companies with clearly defined project scope and planning. Dedicated-team outsourcing is efficient in case the companies have a well-defined project idea and their own management teams but need some additional staff. Value-based outsourcing strives to deliver a business-focused solution to the client. To achieve these goals, value-based outsourcing includes the following key attributes: partnership-based and mature service-level agreements. Since cost management is a given in the current market environment, the aspect of value and differentiation prevails.

Dr. R. Hanko (Siegfried): Value-based outsourcing on the basis of long-term strategic partnerships is and will be an attractive trend.

Dr. G. Haering (Cerbios): Since the development of a new chemical entity or a future generic is related to risk (risk of failure of clinical trials or failure in the launch of a generic), production outsourcing to a CMO that brings certain values to the project is a good option for the pharma companies. At Cerbios, we have worked over the past five years on creating this value through innovation. Innovation in processes or technologies. We are one of the few companies offering HPAI (high-potency active ingredients) manufacturing of Safebridge category 4 compounds. But new players will join in the coming years. The addition of technologies around the containment such as

- Continuous flow chemistry
- Chromatography purification
- Particle size design, including nanoparticles
- Preformulation to lower the containment class
- Innovative drug delivery system for dermatology products

for HPAIs on one single site is unique, and this is what our partners are looking for: the possibility to increase their IP on their drug that will protect them longer.

Jörg Schneider,
Head of Marketing,
Saltigo

Dr. Rudolf Hanko,
CEO, Siegfried

Dr. Gabriel Haering,
CEO, Cerbios

The establishment of shared risk/shared reward partnerships has increased significantly. Can these partnerships accelerate drug discovery and fill up the innovation pipelines?

I. Muir (Aesica): A challenge which both the CDMO and traditional pharma industry face is how to meet these requirements cost-effectively, particularly as localization of manufacture and market-specific regulatory requirements, such as serialization, drive an increased fixed-cost base in markets with small demand and often low reimbursement rates.

K. Hoeprich (Albemarle): We believe shared risk/reward partnerships can play a role in enabling therapies to progress that might not have otherwise due to risk and/or cost.

E. Berger (Catalent): We believe all these approaches can help solve the major industry challenge right now: turning more compounds into successful treatments. By bringing together the best expertise in development, formulation and analytical sciences with the best of innovative applied drug-delivery technologies, we give more molecules a shot at successfully meeting clinical end points. By doing this together earlier in the process, we use development time and funds a lot more efficiently. By engaging in more flexible financial and business models, we give more products a chance of being advanced throughout the process. When you couple all that with the promise that these changes and innovations will result in better quality treatments for the patient, it's a win all around!

Dr. M. Stohlmeier (CU Chemie Uetikon): We can confirm that partnerships have increased significantly in our business over the past two to three years. Innovators do have substantially big scientific groups to identify new target molecules and lead structures, trying to find the best fit for the next blockbuster. Further, the departments dealing with medicinal chemistry are rather big, especially as many molecules have to be tested before one promising new entity has been identified. While the process development teams are decreasing in capacity, the need to outsource this activity is increasing. This is the big chance for any CMO to accelerate the drug development. However, it is important to recognize that this model is not free of any risk, and risk-sharing between the pharma company and the CMO must be well-defined from the very beginning of each new project. From our point of view, a milestone concept ideally fits the interest of both partners for their future cooperation.

Dr. M. Blocher (Dottikon): Sharing the risks and rewards can yield good results if it is done wisely. For this, it is important to identify the existing risks and to determine who in the value chain might be able to manage them best, at least partially. The risk for a drug-approval process in clinical trial Phases I-III, for instance, cannot be thoroughly estimated and managed by a CMO. However, an experienced CMO offers the know-how necessary to identify and manage the risk involved in finding a cost-effective alternative chemical route for API production. Wisely allocated risks and rewards as illustrated in this example create and add value along the value chain, allow for better risk management, and accelerate the drug discovery and development process. We are convinced by and committed to this approach.

C. Jones (Dr. Reddy's): The potential for success of shared-risk/shared-reward partnerships depends on both the client and the supplier's appetites for such business models. A partnership that successfully establishes projects on this basis can be an effective way to accelerate activity and fill up pipelines. It requires the right combination of client and supplier, where the supplier is willing to take on the additional risk; such suppliers need to be financially healthy and stable in order to support the arrangement. Suppliers with less appetite for risk are less likely to be able to speed up the process under a shared-risk/shared-reward arrangement, so project-by-project approaches are usually more effective in these cases.

A. Weiler (SAFC): Yes. In fact, I strongly believe that these risk-shared partnerships will accelerate innovation in drug discovery, especially if these partnerships are mutual and share a best-practice approach between partners – it allows for combined speed, flexibility and intellectual curiosity of the research organizations. It also takes advantage of the tremendous experience Big Pharma has managing complex supply chains and overcoming potential regulatory hurdles.

N. Taillardat (Solvay): From our point of view, Big Pharma still isn't open enough for a real partnership maybe due to IP reasons and educating potential competition as the partner/CMO might deal with other pharma companies as well.

Dr. J.-L. Herbeaux (Evonik): Flexibility in business and financial models is a prerequisite for many development programs to be born and to be value-optimized. Shared-risk/shared-reward models leverage the innovative and investment power that is needed in most stages of the value chain and, if well-designed and managed, can lead to meaningful value creation for both parties. We believe that the increasing trend to establish such partnerships contributes to reviving innovation pipelines particularly when the partner, like Evonik, can offer a strong combination of differentiated competencies and proprietary technologies.

Dr. L. Utiger (DSM): In my view, there is no correlation between shared risk and reward and the success of pipelines. The question should maybe be positioned differently. What is the most efficient and leanest way to get in clinical trials or progress in clinical trials? How should services be bundled (e.g., co-development of actives and fill/finish) and expensive corrections like reformulations of products prevented? Here, the CDMO players can help with their specialized know-how and deep experience, specifically if they can combine API synthesis and drug-product formulation.
How such developments are paid for is a different question. Some CDMO companies may be willing to bet on the success of an early-phase development by taking a share of future profits, while others may see their role as pure service provider and would like to get paid for services rendered. If the risk-sharing approach is used in the majority of early-phase collaborations, it will increase the risk profile of the CDMO companies substantially and may lead to a lot of failures in the industry, since the capital structure of a common CDMO company cannot deal with such clinical risks.

J. Schneider (Saltigo): In the past, relationships down the supply chains were based upon transactions relating to cost and efficiency. Outsourcing has a positive impact on flexibility and efficiency of processes. Costs are reduced, turning fixed costs into variable costs. Assets can be removed from the balance sheet. Therefore, strategic outsourcing will continue to receive much more importance than it has today. The growing outsourcing market provides services across the entire pharmaceutical value chain. Each industry player will have to concentrate on core competencies: For Saltigo, this would be scale-up and commercial manufacturing, process optimization and continuous improvements, technologies, high quality, low-risk environmental, HSE – health, safety and environment – and sourcing excellence.

Tightly aligned supply chains are forming at a rapid pace in the pharma market. Risk considerations and the risk aversion/sharing characteristics of players are also important. The search for reduced risk-sharing operational cost leads to the formation of supply chains among participants that are more willing to share risks, as well as rewards. More specifically, strategies to reduce internal/external transactions costs lead to the formation of supply chains among participants who are less risk-averse or have more ability to manage or mitigate risk. This will lead to more financial funds, which can be used in the discovery of drugs. But there is no real rule for this. It is subject to each individual project opportunity.

Dr. R. Hanko (Siegfried): Risk sharing, as stated above, will benefit both sides in development and launch as CMOs have an attractive offering to leverage such risk. On the discovery side, those risk-leverage sharing opportunities are much less pronounced. As a conclusion, we don't see an increased fill of the pipeline but a better management of pipeline failure and leakage.

Dr. G. Haering (Cerbios): The main question is, "Do we speak about risk-sharing or risk-shifting?" I have the impression that many companies are thinking of shifting their risk at the CMO level when talking about risk-sharing. The co-developments model with real risk-sharing resulting in profit-sharing later on is becoming more and more popular. For a company like Cerbios (small/medium CMO), it is possible to consider this model on a case-by-case basis. In fact, we have already applied it, and it is considered, of course, as an investment. But this is not sustainable if applied to all projects. It is more easily applicable for future generics with an originator or generic company. There is lower risk of failure and shorter time-to-market compared with NCEs. ■

Pharmaceutical Product Design

100 Years Ullmann's: From Drug Discovery to Formulation Development, from Pilot Plant to Scale-Up

The final design of a pharmaceutical product is very lengthy and involves several stages. The beginning stage is the drug discovery phase. During this phase, the active pharmaceutical ingredient (API) is determined. Once the API is known, the formulation of the pharmaceutical product must be determined. Other chemical compounds, called excipients, are added to the formulation to help stabilize the API and increase its efficacy. Successive phases involve design of the manufacturing process, from pilot plant to scale-up. The final delivery method of the pharmaceutical product is determined, with oral methods such as tableting or encapsulation the most common choices. Finally, the product can be approved and marketed.

Product design principles can be applied to many of the stages in the pharmaceutical development process. In practice, many new pharmaceutical products are discovered and developed using exhaustive trial-and-error approaches. Rational product design aims to limit trial-and-error expenses through optimization and property estimation of the target molecule. Property prediction can identify excipients which would most improve the API's stability and efficacy. The final delivery of the drug in vivo can also be improved by designing molecules that have properties allowing the drug to be delivered at the desired conditions.

Several concepts are vital to product design for pharmaceuticals. From a process systems engineering (PSE) standpoint, the most important are the target product profile (TPP), design specifications, critical quality parameters, and health, safety and environmental (HS&E) considerations. The target product profile sets the design space for the pharmaceutical product, while the other considerations place constraints on the design space. For the final design of the pharmaceutical product to be successful, the design should match the target product profile as closely as possible.

General Concepts in Pharmaceutical Product Design

The concepts of TPP, design specification, critical quality parameters, and HS&E considerations hold for all aspects of pharmaceutical product design. The TPP will determine which API and excipients are considered. The ultimate delivery method will also be influenced by the TPP. While designing any of the components of the pharmaceutical product, design specifications and quality parameters will constrain the possible targets considered. The specifications will also be used to identify the optimal molecule for the considered product component.

The TPP is established based upon a determined consumer health need. All key attributes of the product are listed in the TPP. The values for the key attributes are the ideal product properties. Some key attributes are the desired therapeutic effect, the efficacy, the dosage, and the safety or tolerability of the final pharmaceutical product. The key attributes are what defines the pharmaceutical product. The TPP should be met by the final design as close as possible.

The design specifications are a list of user-defined specifications that the final product must meet. Such specifications could include solubility, particle size, and pH (for liquid products). Quality parameters are added as well. Such parameters include cosmetic concerns such as the color and overall appearance of the pharmaceutical product. Taste is important in products that are delivered orally. Other quality parameters include desired shelf life and consistency of the product from batch to batch. Health assessment of the pharmaceutical product is very important. Toxicity must be evaluated during the product development process, for both the API and the final product. Often, established excipients are chosen for the formulation due to time constraints. Similarity to previously approved excipients is often cited as leading to similar toxicological effects, avoiding additional regulatory approval. Environmental concerns play a part, as use of environmentally benign excipients is encouraged. For example, much work has been done to determine alternates to the chlorofluorocarbons (CFCs) used in metered dose aerosols.

API Design and Development

The API is often designed with the goal of interacting with a certain biomolecule in the patient's cell. Usual target biological molecules are enzymes and receptors on the cell's surface. The API must also have minimal interactions with the biological molecules that are not being targeted. The stability and bioavailability of the drug molecule is also a concern when selecting a successful API. The constraints placed on the performance of a drug create a limited design space for the final selected molecule.

Drug candidates are identified by three primary routes:

- The most traditional route is discovery by serendipity. Scientific observation has led the discovery of many drug compounds, such as the discovery of the antibacterial properties of penicillin.
- Combinatorial chemistry can create hundreds of candidate molecules. High-throughput screening is used to scan molecular libraries and narrow down the candidates to several molecules that best match the desired properties.
- Computational screening is an increasingly popular choice for drug development.

Newer methods have led to direct design of the API. Molecular screening allows for the three-dimensional structure of biological molecules to be modeled. Structure-based drug design uses the structural information of the target molecule to design an API that will favorably interact with the target. Optimization of the API molecule can lead to a drug that will perform at a high level. Structure-based drug design offers a method of direct design of a compound rather than experimental screening of a large number of molecules.

Ligand Screening

Combinatorial chemistry and high-throughput screening focus on generation of a large number of candidate drug compounds. Testing reduces the number of compounds immensely to a small number of lead compounds that are then used for further testing. There are considerable time and cost investments involved with experimentally screening a large number of molecular species. The desire for a more rational drug design and development process is clear, where both time and cost requirements are reduced and success rate of the final pharmaceutical product is increased. The application of computational methods is increasingly being used to improve the drug development process.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Once a biological target is identified, a drug molecule can be designed which will bind with the target. Often the design is concerned with small molecules, but peptides and polymers are also design candidates. Ligand binding is a process used to model the interactions between a drug and its biological target, which is referred to as a receptor. The part of the drug molecule that binds to the receptor is defined as a ligand. The primary constraint for the drug candidate is the ligand–receptor interaction. Two fundamental approaches are used in drug design:

- Receptor-based approaches use knowledge of the three-dimensional structure of the biological target, usually a protein.
- Ligand-based approaches use information about compounds that are known to bind to proteins to search for new molecules possessing biological activity.

Receptor-Based Approaches.

Molecular simulation is used in receptor-based design to model the three-dimensional structure of a binding site on a target. Once identified, the binding site is categorized based upon hydrogen bonding, electrostatic, or hydrophobic interactions. The interaction sites can be used to limit the number of possible ligand structures that are considered. With the binding site finalized, a docking tool can then be used to computationally model ligand–receptor interactions. Two basic methods are employed in modeling ligand docking with the binding sites. (i) Lock and key approaches assume that the binding structure is rigid. Flexible ligand molecules are then docked with the fixed structure. (ii) Induced fit docking approaches allow for flexibility in both the ligand and the receptor structure and are therefore much more computationally intensive. To reduce computation costs, the protein backbone is often assumed to be rigid, while the side chains are allowed to be flexible. Docking algorithms use scoring functions, usually based on free-energy, to evaluate the interactions between drug candidates and identified docking sites. A docking that minimizes the scoring function being utilized identifies successful ligand candidates.

Ligand-Based Approaches.

When the three-dimensional structure is not precisely known, ligand-based approaches can be successfully employed. A ligand-based strategy is based on the known structure or topology of one or more ligands. From this known ligand, a pharmacophore can be established. The pharmacophore acts as a pseudo-receptor, which can be used to screen for binding sites that are structurally similar on a biological target. Then ligand docking models can be used as seen in structure-based design. To develop the pharmacophore model, the set of known ligands must be evaluated using one of two common approaches. The first approach is to develop a target quantitative structure–activity relationship (QSAR) that must exist between the ligands and a pharmacophore. Other molecules can then be screened to determine how well they match the QSAR specifications. The second approach computes molecular descriptors and similarity indices for the ligand set. Other molecules can then be screened for a match to the similarity index for a specific pharmacophore. All molecules that match on a similarity index are considered fits for the pharmacophore that the index was developed for.

Various computational approaches can be used for receptor-based and ligand-based drug design. The approaches vary in the fundamental building blocks, the basic algorithm employed, and the scoring function used. The computational approaches may only work for one approach or may apply to either design strategy. The fundamental building blocks are either atoms or commonly used fragments composed of several atoms. The main algorithms used in receptor-ligand approaches are: depth first search, breadth first search, random, Monte Carlo/simulated annealing, and evolutionary algorithms. The scoring functions are diverse. Some of the most common include force field, empirical scoring, and pharmacophore constraints. All scoring approaches are an attempt to approximate binding energies.

Structure-Based Drug Design

Once key binding fragments, or ligands, have been identified through computational screening, further lead optimization can be used to generate the final drug molecule. The ligand alone may not successfully match the specified TPP of the pharmaceutical product. Of specific concern is the absorption, distribution, metabolic and excretion properties (referred to as the ADME properties).

The ligand identified through receptor-ligand design serves as a scaffold to which functional groups can be added to improve the properties of the drug molecule that will become the active pharmaceutical ingredient. A growing procedure can be used to add fragments to the docked scaffold. Fragments can be selected from a database of molecular segments that are often found in drug-like molecules. When scanning molecular libraries, traditional QSAR methods are often used. New adaptive functional group reordering techniques use random sampling of the molecular fragments to measure targeted properties. Estimation over the entire library can then result in discovery of fragments or molecules with desirable property values. When multiple functional groups can be added to the ligand scaffold, the number of combinations can be very large. Using iterative rounds of adaptive functional group reordering, an optimal drug molecule can be more quickly found than when QSAR methods are used.

Pharmaceutical Formulation Design

Once a drug molecule has been selected, a formulation for the final pharmaceutical product must be selected. The physical and chemical characteristics affect the choices available during the formulation design. Pharmaceutical research and development has been primarily concerned with the design and development of the API, with formulation design as a secondary concern. Contemporarily, the pharmaceutical industry has experienced diminished productivity and fewer drug approvals. A possible reason for this trend is that the criteria for drug design are not sufficient.

API design often focuses on the potency and selectivity of the chosen drug molecule, as represented by ligand–receptor binding. However, other criteria are important for success of a pharmaceutical product. The final product must have an acceptable safety profile, as indicated by the TPP. The drug must have the correct pharmacokinetic profile as is often represented by the ADME properties. Finally, the drug must lend itself to successful scale-up and production. The correct formulation can improve the API's performance and ensure that the final pharmaceutical product meets all criteria. By considering formulation concerns throughout the drug discovery and development process, the final product will have more likely match the desired TPP and have an increased chance of regulatory and commercial success. Traditionally, the selections of excipient molecules for the formulation have been made from a preapproved list. The rationale is that using excipients that are generally regarded as safe (GRAS) or have been included in previous FDA approved submissions reduces regulatory concerns and therefore overall time to market. Similarity to previously approved excipients is often cited as leading to similar toxicological effects, avoiding additional regulatory approval. However, new progress made in biologics and the development of novel drug delivery systems has led to increased importance of innovation in formulation design.

By looking at new combinations of excipients or design of new excipients, formulation design can contribute significantly to the success of a pharmaceutical product. Computational molecular design is a possible strategy for the development of novel excipients. Optimization of molecular structure has been shown to create novel molecules with improved properties in many fields such as solvents and polymers.

Formulation Properties and Selection

The selection and design of an API focuses on optimizing the therapeutic or biological effect of the pharmaceutical product. However, for the product to be successful, the formulation must contain excipients that will lend the right physical properties to the final product. Such physical properties include solubility, density, viscosity, and particle size. The combination of known excipients can be optimized to best match the target physical properties.

The desired physical properties can be used to place restrictions on the types of excipients used and the amount used in the formulation. Experimental design can use the valid ranges of excipient amounts to rationally determine what excipient mixtures should be tested. The experiments on excipient mixtures then determine the properties of each mixture. The mixture that most closely matches the desired target properties can be identified and used in the final pharmaceutical product. Visualization techniques can be used to easily compare the experimental results. The excipient mixture that best matches the target can be identified visually very quickly and the pharmaceutical product development can proceed.

Rafiqul Gani, Technical University of Denmark, Lyngby,
Mario R. Eden, Charles C. Solvason and Nishanth G. Chemmangattuvalappil, Auburn University, USA;
Truls Gundersen, Norwegian University of Science and Technology, Trondheim, Norway;
Michael C. Georgiadis, Aristotle University of Thessaloniki, Greece;
John. M. Woodley, Technical University of Denmark, Søltofts Plads,
Teresa López-Arenas, Mauricio Sales-Cruz and Eduardo S. Perez-Cisneros, Universidad Autónoma Metropolitana, Mexico;
Philip Lutze, Technical University of Dortmund, Germany;
Brock C. Roughton and Kyle V. Camarda, University of Kansas, Lawrence, USA;
Elizabeth M. Topp, Purdue University, Lafayette, USA

Complete information of the team of authors and references are available.

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This article is an excerpt from the Ullmann's Encyclopedia of Industrial Chemistry (wileyonlinelibrary.com/ref/ullmanns) which celebrates its 100th anniversary in 2014. More about the topic can be found in the encyclopedia article on Process Systems Engineering, 4. Process and Product Synthesis, Design, and Analysis. More concept articles on general interest topics in industrial chemistry and chemical engineering can be found on the Ullmann's Academy homepage (http://bit.ly/YBEi8U).

Contact:
Frank Weinreich, Associate Publisher,
Wiley-VCH, Weinheim
Tel.: +49 6201 606 377
fweinrei@wiley.com
www.ullmanns.com

Safe From The Start

How Pharmaceutical Excipient Suppliers and Users Can Secure Their Supply Chain and Save Audit Costs

Excipients, together with an active pharmaceutical ingredient (API), are formulated into a final drug that is either prescribed to a patient by a doctor or bought over-the-counter without a prescription. Pharmaceutical excipient users now face increasing demands from regulators to ensure that they understand that the risks in their supply chain are not just API-related, but that excipients may also have an effect. Consequently, they need to secure their excipient supply chain to ensure their products are safe, of high quality and sourced from reputable and compliant suppliers.

Prompted by well documented cases whereby falsified medicines and substandard starting materials — both APIs and excipients — have entered the EU and US supply chains, regulators on both sides of the Atlantic have acted relatively quickly to minimize a repeat of such incidents. The new regulations affecting pharmaceutical excipients are the EU Falsified Medicines Directive (FMD or Directive 2011/62/EU), the Revision of Chapter 5 of the EU GMP Part 1 Guidelines, and the 2012 US Food and Drug Administration Safety and Innovation Act (FDASIA).

New Regulations

Both the EU and US regulations have been designed to improve product quality entering the supply chain by putting more and detailed requirements on the qualification and supervision of excipient manufacturers and distributors. This assumes there will be a risk-based approach to defining an appropriate level of excipient good manufacturing practices (GMP) and an increasing demand on distributors via good distribution practices (GDP).

The new regulations clarify the responsibilities of drug manufacturers regarding starting materials, with the expectation that physical audits of all excipient manufacturers and distributors are conducted. As this will inevitably increase the number of audits required, a cost-effective approach is needed to maintain the quality and safety of excipients. One such approach is to adopt the EXCiPACT Certification Scheme.

EXCiPACT Certification Scheme

EXCiPACT, a nonprofit organization based in Belgium, launched the EXCiPACT Certification Scheme in 2013 specifically to help pharmaceutical excipient manufacturers, distributors and users — the marketing authorization holders — to meet these new requirements.

This new, high quality certification scheme converted the well-known IPEC-PQG GMP and IPEC GDP guides for pharmaceutical excipients into EXCiPACT Auditable Standards as annexes to ISO 9001, making it simpler for them to be adopted and assessed by independent third-party certification bodies for all suppliers registered with the International Organization for Standardization (ISO). For suppliers without ISO 9001, the current GMP (cGMP) audit can be performed by the same certifying body to audit against the ANSI NSF 363 US national standard, which is equivalent to suppliers holding certification to ISO 9001 and the EXCiPACT GMP standard (figure).

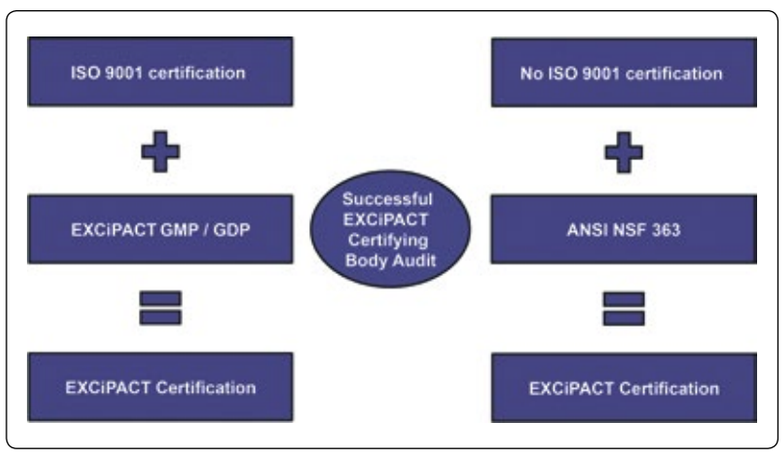
Use of the EXCiPACT Certification Scheme is already providing regulators, suppliers and users alike with full confidence in the audits and the use of the audit reports by the marketing authorization holders to help demonstrate regulatory compliance.

Three Key Elements

This confidence stems from the scheme's three key elements that must be covered: cGMP and cGDP standards, auditor competency, and independent third-party certifying bodies. Auditor competency is critical in maintaining the scheme's high quality and service provision. All auditors used by EXCiPACT-approved third-party certifying bodies must first complete a rigorous, two-day training program followed by a written examination before being witnessed on their first live audit to demonstrate their competence to meet the scheme's stringent requirements. All EXCiPACT-registered third-party certifying bodies are audited by EXCiPACT to confirm that their quality-management system meets the requirements set out in the ISO 17021 annex to the EXCiPACT standards. A key requirement is that the post-audit certification decision is made by an independent review board within the certifying body and not by the auditor.

Listings on the EXCiPACT website should be used to verify registered third-party certification bodies, registered auditors, and all certified excipient suppliers and their contact details.

Since the EXCiPACT Certification Scheme has been fully operational, five certification bodies have been registered, 10 excipient suppliers have been certified (mostly in Europe but one in Saudi Arabia and another in Canada) and at least 10 more audits are in progress (table).



EXCiPACT Certification Scheme

List of EXCiPACT Certificate Holders

Supplier	Country	Auditor	Scope	Certification date
A&C American Chemical Co.	Canada	SGS	GMP, GDP	February 2014
Aug. Hedinger	Germany	mdc	GMP, GDP	June 2013
BASF	Germany	mdc	GMP, GDP	January 2014
Biogrund	Germany	DQS	GMP	February 2014
Croda Europe Ltd.	UK	SGS	GMP, GDP	April 2014
Evonik Industries AG	Germany	mdc	GMP	March 2014
Merck KGaA	Germany	mdc	GMP, GDP	June 2013
Saudi Kayan Petrochemical	Saudi Arabia	SGS	GMP, GDP	February 2014
SEPIPROD	France	mdc	GMP	January 2014
Sonneborn Refined Products	Netherlands	SGS	GMP, GDP	February 2014

EXCiPACT plans to begin operations in the US early in 2015, and preliminary discussions have taken place to introduce the scheme in China and India.

Reducing The Audit Burden

The EXCiPACT Certification Scheme, while comprehensive with a scope, duration and quality greater than typical excipients supplier audits, may not replace all pharmaceutical company audits. EXCiPACT certificate holders will provide their customers with their certificates and audit reports, together with any corrective and preventive action plans. The scheme's annual audit frequency is higher than the industry average. This provides for a comprehensive profile of the supplier's compliance to EXCiPACT's high standards.

The scheme permits pharmaceutical companies to use EXCiPACT certification and audit reports to support the initial qualification of the excipient supplier, full qualification of suppliers of all but the highest risk excipients, and as an aid to auditing those aspects of a supplier that are critical to higher risk excipients.

Excipient users are already commenting that they are able to use EXCiPACT certificates and audit reports from their suppliers to determine the audit frequencies. The audit reports are well received, and with at least an annual surveillance audit report as well, a comprehensive profile of supplier compliance to cGMP or cGDP will rapidly build up — faster and more thoroughly than any audits the excipient user could manage. Although both excipient suppliers and users acknowledge EXCiPACT certification will not eliminate all audits, it will reduce the audit burden for both parties and allow the redirection of resources to the mitigation of higher risks.

▶ Contact:
Tony Scott
EXCiPACT asbl., Brussels, Belgium
info@excipact.org
www.excipact.org

Webinars & training

EXCiPACT runs webinars and training courses for potential auditors, excipients suppliers, users and other parties interested in the scheme.

Azelis to Distribute Myriant's Bio-succinic Acid

Belgian specialty chemicals distributor Azelis has begun distributing Myriant's bio-succinic acid in the Nordic countries, Benelux, France, Iberia, Italy, the UK and Ireland.

The companies are targeting customers in the industrial and base chemicals markets for the acid that is chemically equivalent to petroleum-based succin said to have a lower environmental footprint.

David LeBlanc, head of global sales and marketing at Qunicy, Massachusetts-based Myriant, said Azelis' extensive global distribution network will provide the renewables producer with the necessary support and connections at chemical companies seeking to integrate "green" chemicals into a wide range of applications.

Myriant currently supplies bio-succinic acid from its US flagship facility at Lake Providence, Louisiana, which has annual nameplate capacity of 30 million lbs (more than 13,500 t/y) per year.

Globally, the market for succinic acid is estimated at around $7.5 billion in existing and new applications, for the most part polymers, urethanes, plasticizers and coatings.

Azelis COO Laurent Nataf said the Myriant product further strengthens Azelis' offering in the renewable resources based chemistry for production of more sustainable polymers, for which it is experiencing "growing demand." (dw) ■

Merck Serono and Sutro to Collaborate on ADCs

Switzerland's Merck Serono, the biopharmaceuticals arm of Germany's Merck KGaA, and US biopharmaceuticals producer Sutro Biopharma have agreed a collaboration and license agreement to develop antibody drug conjugates (ADCs) for use in cancer drugs.

The joint research will leverage the Merck offshoot's knowledge about target biology in combination with San Franciso-based Sutro's technological and discovery capabilities.

In particular, the efforts will be directed at finding multiple ADCs, utilizing Sutro's cell-free protein synthesis platforms. The US partner will be responsible for delivering ADCs for Phase I clinical trials, while the Swiss company will have responsibility for clinical development and commercialization of any resulting products.

Merck Serono, which will be able to use Sutro's technology platforms in its oncology programs to develop ADCs for multiple targets, will make an up-front payment to the California firm. Sutro also will be eligible to receive payments on completion of certain R&D and regulatory milestones valued at around €230 million, as well as royalties on product sales.

The companies said they believe ADCs have the potential to directly target cancer cells while safeguarding healthy tissue. (dw) ■

Strem and Provivi Sign Enzyme Distribution Agreement

Strem Chemicals, a manufacturer of specialty chemicals for research and development and Provivi, a developer of biopesticides, have signed an agreement granting Strem distribution rights for research quantities of Provivi's carbene/nitrene transferase enzymes that will feature in the new C/N Transferase Screening Kit.

The kit contains 32 enzymes engineered in the laboratory of Professor Frances Arnold at the California Institute of Technology (Caltech) at Pasadena, for which Provivi has obtained a worldwide exclusive license. This allows researchers to quickly screen a small number of diverse biocatalysts to pick the best solution.

Using the technology, enzymes can efficiently activate diazo and azide compounds to generate iron-carbenoids and iron-nitrenoids through a mode of activation that the companies said has never been observed in nature. The activated intermediates can react with a variety of substrates such as olefins, N-H bonds, C-H bonds, and sulfides, offering great synthetic utility, as for example in the synthesis of chiral cyclopropanes and sulfimides.

Provivi CEO Pedro Coelho said Strem's established network of scientific customers will be able to use the enzymes to develop highly efficient strategies for the synthesis of drugs, pesticides, and other fine chemicals.

Ephraim Honig, COO of Strem, said the addition of the C/N Transferase Screening Kit will provide new pathways to the enantioselective synthesis of important functional groups extending the tools available to synthetic scientists. (dw) ■

Study Says Roche's Cheaper Eye Drug Without Serious Side Effects

Roche's cancer drug Avastin as a cheaper treatment for wet age-related macular degeneration (wAMD), a leading cause of blindness in the elderly, does not appear to increase deaths or serious side effects, an independent study has concluded.

An analysis of nine clinical trials, three of them unpublished, concluded that health insurance policies favoring the much more expensive Lucentis over Avastin were not supported by current evidence, the study published Sept. 15 by the nonprofit Cochrane Collaboration said.

Avastin is not licensed for wAMD but it works in a similar way to authorized treatments for the condition, including Lucentis, which is marketed by Novartis and Roche, and Eylea, from Bayer and Regeneron Pharmaceuticals.

A number of doctors in the US and Europe already use Avastin in wAMD on an unapproved basis.

French lawmakers voted in July to allow Avastin's use, while Roche and Novartis have faced recent regulatory scrutiny in France and Italy on suspicion of anti-competitive practices. The companies have denied any wrongdoing.

The Cochrane researchers now plan to conduct a larger review to assess additional sources of evidence. (dw) ■

Conquering A Global Problem

ISPE Develops a Plan to Help Industry Avoid Drug Shortages

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Drug shortages are a complex, global problem. While the primary impact of shortages will be felt most acutely by patients who have difficulty getting the medication they need when the supply chain suffers an interruption, shortages also have serious implications for the pharmaceutical industry in terms of costs and reputation.

Since 2012, the International Society for Pharmaceutical Engineering (ISPE) has been facilitating communication between the pharmaceutical industry and global health authorities to address this multi-faceted problem. ISPE recently announced that it will publish an actionable plan aimed at helping the pharmaceutical industry avoid drug shortages resulting from manufacturing and quality issues. An Introductory Summary to the plan has been released to highlight the Plan's key areas. The complete ISPE Drug Shortages Prevention Plan will be released during the 2014 ISPE Annual Meeting, which will be held 12 – 15 October, 2014 in Las Vegas, Nevada, USA.

ISPE's Plan – a first for the industry – was developed by ISPE's Drug Shortages Task Team of expert pharmaceutical and biopharmaceutical industry members, and describes how industry can best prevent drug shortages from occurring by discovering true root causes and by creating and sustaining organizational cultures supported by leadership, business processes and quality systems that will ensure a robust, resilient and reliable supply of medications – many lifesaving – to patients worldwide. By design, the Task Team limited the scope of its work to the manufacturing, quality and compliance issues associated with a company's supply chain and related to its ability to source, manufacture, and distribute products that have resulted in drug shortages.

The Plan is based in part on ISPE's groundbreaking 2013 study of the issues and root causes of drug shortages. While results of the ISPE survey pointed towards key areas such as quality systems and strong management controls as key levers to avoiding shortages, the ISPE Task Team augmented the survey findings through discussions with leaders of more than 30 major pharmaceutical companies and regulators from EMA, FDA, and MHRA, and for more than a year gathered stakeholder input from hundreds of industry professionals at ISPE conferences and workshops. Industry senior management, which has considerable influence on organizational culture and alignment, was highly engaged in the Plan's development. This analysis helped dispel common perceptions behind shortages (such as excessive number of recalls, non-availability of material, poor product quality), and identified strategies that can help address the underlying root causes behind shortages whether due to aging facilities and equipment, lack of product robustness, or poor cultural and behavioral aspects that can contribute to poor design and execution.

The ISPE Drug Shortages Prevention Plan is organized into a "six dimension" framework comprised of: Corporate Quality Culture, Robust Quality Systems, Metrics, Business Continuity Planning, Communication with Authorities, and Building Capability. The Plan provides recommendations and real-world case studies in each of the dimensions to answer the following questions:

- Corporate Quality Culture – How can organizations foster practices, values and a philosophy that require employees at all levels to subscribe to quality?
- Robust Quality Systems – What triggers can affect production and the integrity of the supply chain and potentially lead to a drug shortage? How can those triggers be identified and eliminated?
- Metrics – How can metrics be tailored to help identify risks and mitigate them?
- Business Continuity Planning – At a time when supply chains are more global and complex, how can quality and competence be assured in production, factories, materials, machines, equipment, and expertise?
- Communication with Authorities – How can rapid and comprehensive communication with health authorities help to prevent potential shortages before they occur, or mitigate with expedience shortages that do materialize?
- Building Capability – How can capability be built to identify the true root causes of drug shortages, train employees, improve knowledge and knowledge management, as well as strengthen employee commitment to quality?

The end "product" and strategic objective for these efforts is a "resilient end-to-end supply chain." ISPE recognizes that there are many other factors that may impact the supply of drugs, including regional economic factors, differing regulatory requirements, insurance programs, and government procurement procedures, which are outside the scope of its Drug Shortages Prevention Plan.

Because drug shortages are a critical public health issue, ISPE believes that efforts to address the multi-faceted problem require close technical collaboration and clear communication between the pharmaceutical industry and global health authorities. In the US, ISPE's report on its drug shortages survey was cited by the US Food and Drug Administration (FDA) in its Strategic Plan for Preventing and Mitigating Drug Shortages (October 2013), confirming the FDA's intention to engage with ISPE to analyze data on the technical, scientific, manufacturing, quality, and compliance issues that have resulted in drug shortages. In Europe, ISPE was invited to present an overview of its drug shortages survey findings to the European Medicines Agency (EMA) at a November 2013 workshop. Noting that an effective drug shortages prevention plan would require a broad representation of industry experts, the EMA charged the associations attending the workshop with working together to develop and deliver a single, collaborative action plan for the prevention of drug shortages. When published, ISPE's Drug Shortages Prevention Plan will form part of a multi-association collaborative plan which will be delivered to the EMA in November 2014. Other associations taking part are the Parenteral Drug Association (PDA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Generic medicines Association (EGA), and the Plasma Protein Therapeutics Association (PPTA).

Given the common goal of industry and regulating agencies to prevent drug shortages, consensus has been reached not only regarding the importance of communication with authorities, but also regarding the need for building capability by improving the scientific and technical knowledge of individuals and organizations. ISPE will continue to act as global facilitators and integrators in the effort to prevent drug shortages through facilitating forums with industry leaders and regulators, and through developing and holding training and education programs to help industry build capability in the areas critical to building resilient supply chains.

Contact:
Carol Winfield, Director of Regulatory Operations
International Society for Pharmaceutical Engineering (ISPE), Tampa, Florida, USA
Tel.: +1-813-960-2105 x215
cwinfield@ispe.org
www.ispe.org

Events

International SAP Conference for Chemicals, 7 – 8 October 2014, Amsterdam, The Netherlands
The chemical industry has become highly globalized, with emerging economies driving a continued need for efficiency in established markets. To ensure success in this demanding commercial environment, chemical companies must ensure they protect their brand, maintain profitable revenue streams, maximize the return on R&D investments, reduce energy consumption, optimize asset performance and utilization, synchronize supply chain management, and meet dynamic market demand. With globalization and market dynamics driving a continued push for innovation in the chemical industry, the two-day agenda has been built to demonstrate how solutions from SAP are helping chemical companies to stay ahead of the competition.

Keynote presentations will be complemented by breakout tracks covering themes such as supply chain, product safety and stewardship, laboratory information management systems, and other business-focused topics.

► http://uk.tacook.com

ISPE Annual Meeting, 12 – 15 October 2014, Las Vegas, Nevada, USA
The pharmaceutical landscape is constantly evolving. Now more than ever companies are being asked to do more with less, anticipate tomorrow's challenges today and solve issues that have not yet arisen. ISPE's annual event provides the latest technical, regulatory and organizational direction for pharma managers to keep their company on the leading edge of pharmaceutical innovation. Attendees can engage in learning, problem-solving and relationship building with colleagues from all sectors of the global pharmaceutical industry.

► www.ispe.org

OpEx 2014, 14-15 October 2014, Abu Dhabi, UAE
Operational Excellence in Oil, Gas & Petrochemicals (OpEx) focuses on the topic of Operational Excellence for the Oil, Gas and Petrochemicals sector. It will include a new emphasis on corporate strategy excellence, sustainability and safety, as well as the "People", "Assets" and "Technology" themes covered in last year's event. Companies are increasingly aware that to survive and thrive, operational excellence must become a way of life. The conference will provide a major platform for sharing best practices and staying up-to-date with current thinking from the leading industry players and will present practical ideas for implementing excellence strategies.

► http://www.europetro.com/en/opexmena14

Fakuma 2014, 14 – 18 October 2014, Friedrichshafen, Germany
Assuming that the world economy is persistently stable in 2014, insofar as no politically motivated disruptive action takes place, the manufacturers and distributors of plastic products are prepared to invest - especially against a backdrop of rising pressure to reduce the consumption of energy and resources in the broad ranging field of plastics processing. And thus outstanding prospects prevail for this year's industry meet on Lake Constance. Fakuma 2014 is comprehensively dedicated to all relevant issues covering all aspects of plastics processing and will present current offerings for technologies, processes, materials, machines, tooling, products and system solutions in a compact format.

► www.fakuma-messe.de

PolyTalk 2014, 4 – 5 November 2014, Brussels, Belgium
With the title "An Industrial Renaissance in Europe… Let's make it happen", PolyTalk 2014 will gather leading authorities from a broad range of expertise be it economy, finance, policy or industry. PolyTalk will also host an "Innovation Hub" where companies will be invited to showcase the latest technological developments happening in Europe.

► www.plasticseurope.org

ADIPEC 2014, 10 – 13 November 2014, Abu Dhabi, United Arab Emirates
The 30th Anniversary edition of the Abu Dhabi International Petroleum Exhibition and Conference (ADIPEC) is the perfect opportunity for attendees and exhibitors to get together to experience, discover, network, discuss and debate core industry issues. Under the theme 'Challenges and Opportunities for the Next 30 Years', the ADIPEC 2014 Conference presents two conferences in one, offering plenary and technical content. The multi-disciplinary conference is a platform for international and regional oil and gas professionals, who are involved in both the technical and non-technical functions within the industry.

► www.adipec.com

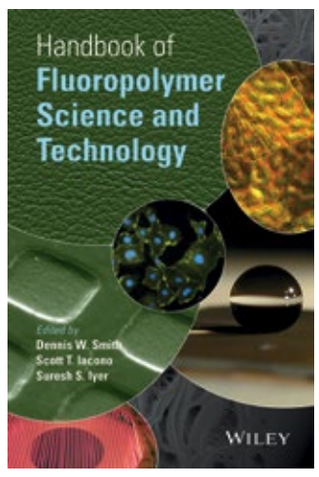
The European REACH Congress, 18 – 19 November 2014, Düsseldorf, Germany
It is mid-term for the REACH Regulation. With past experience and future uncertainty there are many issues to reflect upon and more to be managed in the coming years. Offering a combination of practical advice to the industry and direction from policy-makers, this Congress aims to bring together all stakeholders affected by the REACH Regulation. Topics range from registration to restriction and enforcement. The Congress will include an exhibition showcasing suppliers and service providers and will have a program designed to maximize networking opportunities.

► www.reachcongress.com

Biocides, 10-12 December 2014, Vienna, Austria
The conference focuses on key aspects of Regulation (EU) No. 528/2012 concerning the approval of active substances and authorization of biocidal products. Presentations will include the latest developments from the European Commission and EU authorities on the core procedures and features of this nascent legislation. Besides details of this complex law, speakers will address topics such as nanomaterials, the impact of the CLP Regulation, and fees. The program also includes views of the regulatory scene in the US and Turkey. Two optional half-day Workshops on topics of key interest will follow the conference. The first Workshop focuses on efficacy testing for disinfectants and preservatives. The second workshop looks at efficient use of R4BP. Both the two-day Conference and the Workshops will give stakeholders insight into the current state of play of the biocidal products regulation.

► http://www.europeanbiocides.net

Handbook of Fluoropolymer Science and Technology

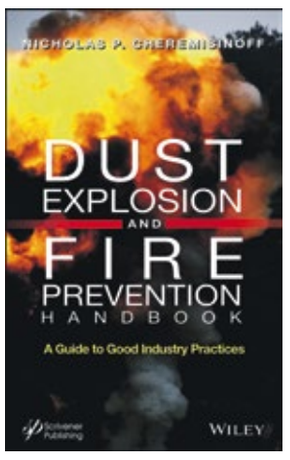


Fluoropolymers continue to enable new materials and technologies as a result of their remarkable properties. This book reviews fluoropolymer platforms of established commercial interest, as well as recently discovered methods for the preparation and processing of new fluorinated materials. The coverage emphasizes emerging technologies in optics, space exploration, fuel cells, microelectronics, gas separation membranes, biomedical instrumentation, and much more. In addition, the book covers the current environmental concerns associated with fluoropolymers, as well as relevant regulations and potential growth opportunities.

► Handbook of Fluoropolymer Science and Technology
Dennis W. Smith, Scott T. Iacono, Suresh S. Iyer
John Wiley & Sons
Price: € 159.--
ISBN 978-0-470-07993-5

Dust Explosion and Fire Prevention Handbook

Dust explosions can have devastating consequences, and, recently, there have been new industrial standards and guidelines that reflect safer, more reasonable methods for dealing with materials to prevent dust explosions and resultant fires.



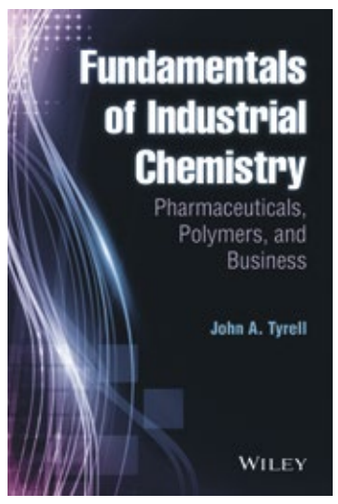
This book not only presents these new developments for engineers and managers, but it offers a thorough and deep coverage of the subject, starting with a complete overview of dust, how it forms, when it is in danger of exploding, and how this risk can be mitigated. There is also a general coverage of explosions and the environments that foster them.

This handy volume is a ready "go to" reference for the chemical engineer, plant manager, process engineer, or chemist working in industrial settings where dust explosions could be a concern.

► Dust Explosion and Fire Prevention Handbook
Nicholas P. Cheremisinoff
John Wiley & Sons
Price: € 169.-
2014. 392 Pages, Hardcover
ISBN: 978-1-118-77350-5

Fundamentals of Industrial Chemistry

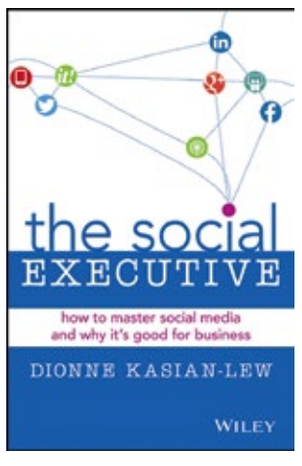
This book discusses the connectivity between major chemicals, showing how a chemical is made along with why and some of the business considerations. Not intended to give expert detail on all areas, the textbook puts chemical industry topics in context and ties together many of the principles chemistry majors learn across more specific courses. By exposing readers to these important industry topics, the book smooths a student's transition to industry and assists current professionals who need to understand the larger picture of industrial chemistry principles and practices.



► Fundamentals of Industrial Chemistry
John A. Tyrell
John Wiley & Sons
Price: € 77.90
ISBN: 978-1-118-61756-4

The Social Executive

Billions of conversations are taking place in social networks every day. But for busy executives and business owners, time constraints make it hard to dedicate time to demystifying these communication opportunities. In The Social Executive, readers are given evidence-based, data-driven strategies for mastering social media, and using it to enable business success. This book's easy, straightforward, practical style ensures that you will gain a solid working platform in the shortest amount of time possible. The focus is on the reasons why social media is important for executives, and how it aligns perfectly with business strategies.



► The Social Executive
Dionne Kasian-Lew
Wrightbooks
Price: $ 24.95
ISBN: 978-0-7303-1289-5

People

Dr. Marijn E. Dekkers

Dr. Marijn E. Dekkers has been elected as the VCI President by the general assembly of the German Chemical Industry Association (VCI). Dekkers is the Chairman of the Board of Management of Bayer and has been on the VCI's Presidential Council since 2011. The term in office of the new President started on 27 September 2014 and lasts for two years to the general assembly 2016. Following his election, Dekkers stated: "We need to become more innovative if the industry country Germany – and with it the chemical-pharmaceutical industry – wants to continue being successful on the global markets. The capability to innovate is key to strengthening the competitiveness of this location. As an export-oriented country with few raw materials, Germany needs companies which steadily develop new products and place them on the market rapidly and successfully. More scope for research and fewer obstacles to innovation help achieve this goal."

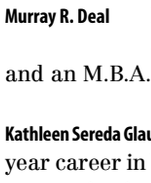
Frank H. Lutz

Frank H. Lutz (45) has been appointed CFO of Bayer MaterialScience effective October 1, 2014. He succeeds Dr. Axel Steiger-Bagel, who takes over on November 1 as Senior Bayer Representative for the Benelux countries, based in Diegem, near Brussels. Lutz – like his predecessor – will be a member of the Board of Management of Bayer MaterialScience and that subgroup's Executive Committee. He will be responsible for all finance-related matters of MaterialScience, which it is planned to float on the stock market as a separate company in 12 to 18 months' time. His responsibilities on the Executive Committee will also include administration and services along with the Europe, Africa and Middle East regions (EMEA / EEMEA).

Mark J. S. Tonkens

Mark J. S. Tonkens has been appointed as Chief Financial Officer (CFO) and member of the Executive Board of Borealis effective 1 November. He succeeds Daniel J. Shook who has decided to pursue career opportunities outside Borealis. Tonkens joined Borealis in 2009 and last held the position of Senior Vice President Group Controlling. Before joining Borealis he fulfilled a number of senior management roles in the Royal Philips group as CFO and Senior Vice President of various major global Business Units or Country Organizations located from the Netherlands and Greece in Europe to Taiwan and Hong Kong in Asia.

Murray R. Deal is the new Vice President and Managing Director, Europe, Middle East, and Africa (EMEA) Region for Eastman Chemical. He succeeds Jennifer Stewart, who has been appointed as Eastman's Vice President, Market Development and Innovation, recently. Deal joined Eastman in 1980 and has held many positions of increasing responsibility in financial, research, innovation, sales, marketing, and business organizations of the company. He has also led chemical and polymers businesses in Europe. Prior to his current position, he was Eastman's Vice President of Talent Development. Deal holds a B.S. degree in chemistry from the University of Tennessee and an M.B.A. from Emory University in Atlanta, Georgia.



Murray R. Deal

Kathleen Sereda Glaub has been appointed to Codexis' board of directors. Her 30-year career in leadership positions with drug development and technology companies is expected to bring strong company-building and business strategy experience to the Codexis board. Glaub has recently been appointed as CEO of Afferent Pharmaceuticals, a clinical-stage biotechnology company that is developing treatments for respiratory and urologic disorders and chronic pain, where she has been a member of its board of directors since 2013. Prior to Afferent, Glaub held positions at Plexxikon, Cell Genesys, Genentech, and Intel.

Adam Burgess has been appointed to the position of Product Release Manager at Aesica. Based at Queenborough, UK, Burgess has responsibility for pharmaceutical quality assurance across the Kent based site of the contract development and manufacturing organization (CDMO). A key function is to ensure on time release of products. Prior to joining Aesica, he held the position of Manager, Defective Medicines Report Centre and Import Notification at the MHRA and was an active Qualified Person at Martindale Pharma. Prior to that, he worked as a QA Manager in Preclinical Quality Assurance at GlaxoSmithKline.

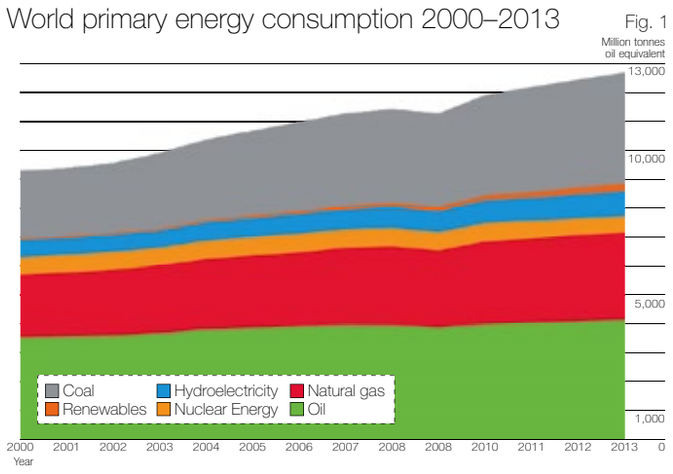
Shamsi Gravel has been appointed as vice president of the K-Flex line of non-phthalate, low-VOC plasticizers and coalescents of Emerald Kalama Chemical. Previously serving as the product line director for the Americas, she will now assume global leadership for the business platform. Prior to joining Emerald in 2009, Gravel served ChemQuest as a senior consultant. She also previously held business and technical roles at Bostik Findley and Henkel (formerly National Starch). She holds an M.B.A. in Finance, Marketing and Strategy from Boston University, an M.S. in Chemical Engineering from Rutgers University, a B.S. in Chemical Engineering from Villanova University and a graduate certificate in Polymer Engineering from the New Jersey Institute of Technology.

Dr. Thomas Colacot, Global R&D Manager of Homogeneous Catalysis for the Johnson Matthey Catalysis and Chiral Technologies (JMCCT) business unit, has been awarded the 2015 American Chemical Society (ACS) National Award for Industrial Chemistry. This award recognizes one person who has made outstanding contributions to the development and commercialization of ligands and pre-catalysts for metal-catalyzed organic synthesis, particularly palladium cross-couplings, for industrial and academic use and applications. Colacot was chosen for his strength in bringing academic concepts to life through practical commercial and industrial applications. At Johnson Matthey he is responsible for leading the research and development of homogeneous catalysts for industrial pharmaceutical and fine chemical applications. Colacot has been with the company since 1995, when he began as the US director of homogeneous catalysis research

Dr. Thomas Colacot

Energy in 2013: Global Markets Reflect Broader Themes

World primary energy consumption 2000–2013 Fig. 1

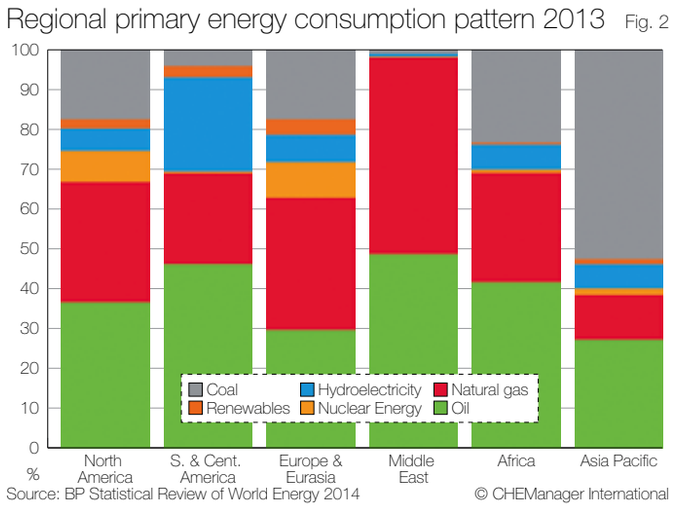


Source: BP Statistical Review of World Energy 2014 © CHEManager International

World consumption

The world of energy in 2013 echoed broader global themes – such as emerging differences in economic performance, geopolitical uncertainty and ongoing debates about the proper roles of government and markets. According to the BP Statistical Review of World Energy 2014, the world primary energy consumption accelerated in 2013 despite the stagnant global economic growth (fig. 1). Consumption increased for all fuels, reaching record levels for every fuel type except nuclear power. For each of the fossil fuels, global consumption rose more rapidly than production. Global primary energy consumption increased by 2.3% in 2013, an acceleration over 2012 (+1.8%). Oil remains the world's dominant fuel, with 32.9% of global energy consumption, but it also continued to lose market share for the fourteenth consecutive year.

Regional primary energy consumption pattern 2013 Fig. 2

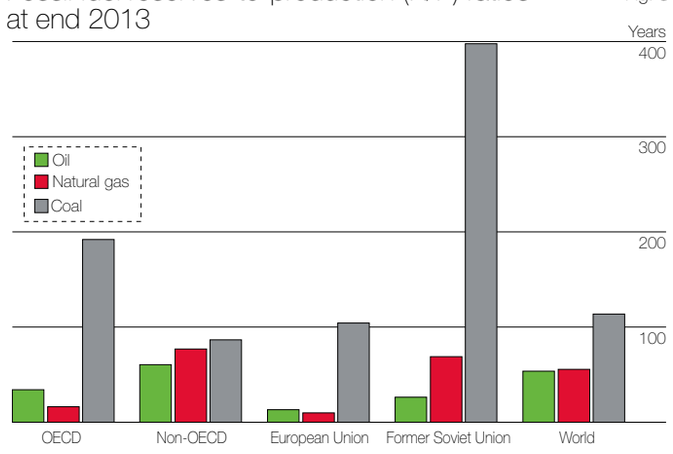


Source: BP Statistical Review of World Energy 2014 © CHEManager International

Regional consumption

Regionally, energy consumption growth was below average everywhere except North America. EU consumption continued to decline, hitting the lowest level since 1995 (despite economic growth of 35% over this period). The Asia Pacific region once again accounted for the largest increment to global primary energy consumption and continues to account for the largest share (40.5% of the global total). The region accounted for over 70% of global coal consumption for the first time in 2013, and coal remains the region's dominant fuel (fig. 2). Oil is the dominant fuel in all other regions except Europe & Eurasia and the Middle East where gas is dominant. In the Middle East, gas surpassed oil as the dominant fuel in 2013.

Fossil fuel reserves-to-production (R/P) ratios at end 2013 Fig. 3

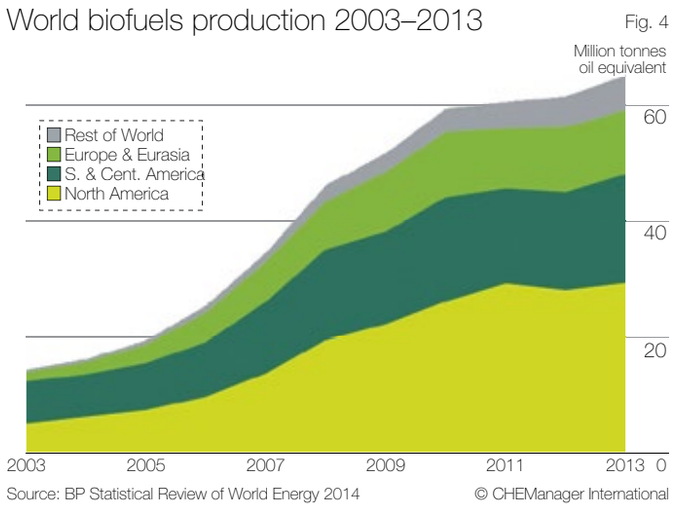


Source: BP Statistical Review of World Energy 2014 © CHEManager International

Fossil fuel reserves-to-production ratios

After global coal prices have fallen for two years in a row, coal is extending its competitive edge in power generation and was the fastest-growing fossil fuel, with China and India combined accounting for 88% of global growth. In contrast natural gas consumption growth decelerated and grew at a below-average rate. Coal remains – by far – the most abundant fossil fuel by reserves-to-production (R/P) ratio (fig. 3). Non-OECD countries hold the majority of proved reserves for all fossil fuels, and the highest R/P ratios for oil and natural gas. By region, the Middle East holds the largest reserves for oil and natural gas, and the highest R/P ratio for natural gas; South and Central America hold the highest R/P ratio for oil. Europe & Eurasia holds the largest coal reserves, and the highest R/P ratio.

World biofuels production 2003–2013 Fig. 4



Source: BP Statistical Review of World Energy 2014 © CHEManager International

Biofuels production

Biofuels have increased in popularity because of rising oil prices and the need for energy security. Global biofuels production grew by 6.1% (80,000 b/doe) in 2013 (fig. 4), driven by increases in the two largest producers: Brazil (+16.8%) and the US (+4.6%). The increased biofuels output in North America, South and Central America and Asia Pacific outweighed declines in Europe and Eurasia. Global ethanol production increased 6.1%, the first increase in two years. Biodiesel production increased 6.2%, despite declines in South and Central America and Europe and Eurasia. The International Energy Agency (IEA) has a goal for biofuels to meet more than a quarter of world demand for transportation fuels by 2050 to reduce dependence on petroleum and coal.

A Milestone on the Road to Boosting Plant Efficiency

Scientists have genetically engineered a tobacco plant to contain a cyanobacterial variant of a crucial photosynthetic enzyme, raising hopes that this strategy could someday be used to increase crop yields.

The ubiquitous enzyme Rubisco converts CO_2 into sugar during photosynthesis, but in plants, it's slow and inefficient. A faster Rubisco would mean faster photosynthesis, and potentially higher crop yields – something that might help feed the planet's growing population.

In contrast to plants, photosynthetic cyanobacteria not only contain more efficient variants of Rubisco, they also speed up photosynthesis with a collection of CO_2 pumps and other cellular machinery, together known as the CO_2-concentrating mechanism (CCM). CCM works by increasing the levels of CO_2 surrounding the Rubisco enzyme. Thus, researchers have considered cyanobacteria a possible focus for the genetic modification of plants.

Rubisco is a complex enzyme, and so far, scientists have failed to substitute cyanobacterial versions for the natural versions in plants. But now, a team at Cornell University, has created tobacco plants with the gene for Rubisco found in the cyanobacterium Synechococcus elongatus. Work by collaborators at Rothamsted Research, in England, showed that the engineered plants had higher rates of CO_2 conversion compared with a control group.

Nevertheless, further engineering will be required to assemble the complete cyanobacterial CCM in plants. To that end, the scientists have also engineered precursors to a CCM subcellular container, known as a carboxysome, into tobacco plants.

This could be a major step forward in the challenge of redesigning plants' photosynthetic machinery to harness the full potential of cyanobacterial Rubisco. ■

For leather that lasts - Seasons change, fashions change, leather remains. Chemical products are necessary for the manufacture of leather and help to preserve it. Among the chemicals used are tanning agents, preservatives and fat-liquoring agents, dyestuffs and pigments as well as finishing auxiliaries. German specialty chemical producer Lanxess is an innovator when it comes to technologies for a future-oriented leather production. For instance, the patent-pending Levotan X-Biomer range is an alternative to synthetic retanning agents. It is based on biodegradable polymers, which are produced from renewable raw materials and specifically functionalized for retanning applications in a biologically engineered process, thus making leather manufacture more sustainable and environmentally friendly.

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Geschäftsführer
Dr. Jon Walmsley,
Prof. Dr. Peter Gregory

Director
Roy Opie

Product Management
Dr. Michael Reubold (mr)
Tel.: +49 6201 606 745
michael.reubold@wiley.com

Editor in Chief
Dr. Ralf Kempf (rk)
Tel.: +49 6201 606 755
ralf.kempf@wiley.com

Editor
Dr. Roy Fox (rf)
Tel.: +49 6201 606 714
roy.fox@wiley.com

Media Consultants
Corinna Matz-Grund
Tel.: +49 6201 606 735
corinna.matz-grund@wiley.com

Thorsten Kritzer
Tel.: +49 6201 606 730
thorsten.kritzer@wiley.com

Jan Kaeppler
Tel.: +49 6201 606 522
jan.kaeppler@wiley.com

Roland Thomé
Tel.: +49 6201 606 757
roland.thome@wiley.com

Marion Schulz
Tel.: +49 6201 606 565
marion.schulz@wiley.com

Team Assistants
Bettina Wagenhals
Tel.: +49 6201 606 764
bettina.wagenhals@wiley.com

Jörg Stenger
Tel.: +49 6201 606 742
joerg.stenger@wiley.com

Freelancers
Dr. Sonja Andres
Dede Williams (dw)
Miranda Kennedy
Dr. Volker Oestreich
Sean Milmo (sm)

Production Managers
Christiane Potthast
Claudia Vogel (Advertising)
Ramona Kreimes (Litho)
Oliver Haja (Layout)

Reprints
Dr. Katja Habermüller
Tel.: +49 6201 606 719
katja-carola.habermueller@wiley.com

Subscription/Reader Service:
Silvia Amend
Fax: +49 6201 606 100
silvia.amend@wiley.com

Bank Account
Commerzbank AG Mannheim, Germany
Account No. 07 511 188 00,
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