CHEManager EUROPE

9/2010 September

THE NEWSPAPER FOR THE CHEMICAL AND LIFE SCIENCE MARKETS

Markets and Companies

C3X Chemical Customer Connectivity Index

The results of our latest management survey are in!

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Reach

Santa is not the only thing coming in December

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Newsflow

Glaxosmithkline has hired Goldman Sachs investment banker Simon Dingemans to succeed Chief Financial Officer Julian Heslop, 59, who will retire next March. Chief Executive Andrew Witty said the appointment reflected the need for Glaxosmithkline to operate with both creativity and continued financial discipline. "Simon will bring valuable experience and capability to support us in our strategy to grow and diversify GSK's business through organic means and bolt-on acquisitions."

Airgas announced it has signed a three-year extension to its industrial gases and welding products supply agreement with Kiewit, a construction company. The contract extension includes estimated annual revenues of $6 million.

Belgian drugs, chemicals and plastics maker Solvay said it had decided to build a new hydrogen fluoride installation for a Chinese joint venture. Solvay and its partner Sinochem Lantian have decided to build the installation for the venture Lansol Fluorchem. Commercial electronic grade hydrogen fluoride of the new installation will be available by the end of this year, Solvay said in a statement. The product is used in the electronics industry, particularly for the production of photovoltaic cells.

Novo Nordisk, the world's biggest maker of insulin, said it would double the size of its research and development centre in Beijing to 200 employees by 2015. "The expansion will mainly be dedicated to a new diabetes research unit," Novo Nordisk said in a statement.

Potash has held discussions with China's Sinochem, a source close to the matter said, as the Canadian fertilizer producer looks for options to BHP Billiton's $38.6 billion hostile bid. "One wants to explore all the options and you can't do that by telekinesis," said the source, who asked not to be named. Separately, a second source confirmed that Potash was considering joint ventures with third parties as one possible option. Sinochem, as well as Brazil's Vale, have made inquiries with the board of Potash about the possibility of talks.

Eastman said it is in the process of expanding CHDM capacity by 25% at its Kingsport, TN., site. The company expects to complete the expansion in two phases, with the first phase to be completed in mid-2011, and the second in 2012. CHDM is a monomer used to manufacture various specialty plastics products.

Inside Pharma

Suppliers to the Pharmaceutical Industry: high expectations in a challenging market

At this years CPhI Worldwide event in Paris, the leading exhibition on pharmaceutical ingredients, pharma professionals from over 125 countries will gather to intensify or build new business relationships. Prior to the show, CHEManager Europe interviewed industry leaders about trends, current developments, business challenges and perspectives. Read more in our special starting on page 15. Learn from the market leading fine chemical companies, their opinions and strategies.

Dr. Andreas Meier
Head of the Regional Business Unit Europe and Managing Director of Solvay Fluor

Fine Chemicals

The highroad through an economic crisis is reducing spending to an absolute minimum.

Dr. Christian Dowdeswell
Sales Director
Dishman Group

Custom Manufacturing

The CMO sector suffers from a lack of differentiation among suppliers, with a common standard for production facilities and the use of similar technologies and chemical processes.

Dermot Pearson
Marketing Director
Novozymes

Excipients

Excipient choice can influence development timelines and acceptance of final drug products, thus influencing costs along the entire product lifecycle.

Dr. Andreas Stolle
Head of Business Line Pharma
Saltigo

Custom Manufacturing

After years with of high growth rates, custom manufactuers now need to adapt their traditional way of doing business to the new directions dictated by the market.

Burghard Freiberg
Senior Vice President
Life Science Solution
Merck KGaA

Excipients

… two requirements are particularly strong right now: functional excipients and risk mitigation.

Mark Cassidy
Director of Global Sales & Marketing
SAFC

Custom Manufacturing

Many of our customers have exited from non-core activities and as part of this process, and they have carefully identified the best strategic partners to fulfill their manufacturing needs.

Bodo Fritzsching
Head of Sales & Technical Services Pharma
Beneo-Palatinit

Excipients

"Although being essential, such a variety of procedures causes extra cost as well as hurdles for market growth. "

Dr. Heinz Sieger
CEO
CU Chemie Uetikon

API

The worldwide market for APIs and intermediates will be very much influenced by the changes within the pharma industry that are resulting from strong cost pressure…

Dr. Andreas Dietrich
Head of Pharma Chemicals and Business Operations
Boehringer Ingelheim Pharma

API

In order to compete in today's marketplace, we have to offer superior manufacturing reliability, a better product quality and a fast time to market.

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CONTENT

Air Products Raises Offer for Airgas to $5.5 billion

Air Products and Chemicals raised its bid for Airgas to $5.5 billion, the latest salvo in its hostile bid for the rival company. The new Air Products cash offer of $65.50 a share represents a 3 % increase from its previous bid of $63.50.

The company said the price would mark a premium of more than 50 % to the Airgas closing price on Feb. 4, the day before the takeover drive began. Air Products had made a $60 a share bid for the company in February.

Airgas said its board will review the offer and advised stockholders to take no action at this time. If successful, Air Products would become the biggest industrial gas company in North America, and it could gain substantial benefits from the economy's resurgence as the recession abates.

Air Products, which supplies gases such as argon, helium and nitrogen to customers in the metals, chemical and pharmaceuticals sectors, wants Airgas for its large sales and distribution network and 1,500 sales representatives. ■

Novartis to Push Ahead With Disputed Alcon Buyout

Swiss drugmaker Novartis is pushing ahead with its contentious buyout of Alcon minority shareholders after completing its acquisition of stock from Nestle to get control of the U.S. eyecare group. Novartis, which now holds a 77 % stake in Alcon and has a majority on the board, has been seeking to snap up the remaining 23 % since exercising its option to buy Nestle's stake in January.

Alcon's independent director committee has, however, dismissed Novartis's offer for the minority stake as too low and repeated it could take legal action in a bid to secure a better price. Novartis is seeking to diversify and insulate itself against losing patent protection on big selling medicines, such as blood pressure drug Diovan, by buying Alcon.

Alcon is the dominant player in the multi-billion-dollar intraocular lens market and is also No. 1 in cataracts – an area that is set to benefit from ageing populations. ■

Genzyme Begins Layoffs to Cut Costs

U.S. biotech company Genzyme has begun laying off an unspecified number of employees, a move it said was unrelated to Sanofi-Aventis' takeover bid. The company did not reveal the number of employees it is letting go, but The Boston Globe said Genzyme plans to cut 1,000 employees worldwide over 15 months. It cited a memo sent by Genzyme Chief Executive Henri Termeer to employees on Friday. Genzyme spokesman Bo Piela declined to confirm the figure cited in the Boston Globe.

"We feel the right thing to do is to take a couple of days to speak to employees before making a public announcement," spokesman Piela said on Friday.

Piela said the Cambridge, Massachusetts-based company will cut throughout the organization as a part of restructuring announced in May to reduce costs. "Since May we have been working to evaluate the company and identify ways to bring down our costs," he said. "We've completed the first phase, which included streamlining the organization." Genzyme has 12,800 employees worldwide. ■

China to Probe BHP's Bid for Potash

China may launch an antimonopoly probe into BHP Billiton's $38.6 billion bid for Canada's Potash, the China Business News reported, citing a source familiar with the matter.

China will also review the merger case of two Russian potash firms – Uralkali and Silvinit – given the major impact the two deals would have on China. Government departments and state-owned Sinochem have held meetings recently to review the possible impact the two high profile acquisitions could have on China, which is a major purchaser of fertilizer, and about possible countermeasures. BHP, last month launched a hostile takeover bid for Potash, the world's largest fertilizer company. Industry analysts have noted that China, as a big importer of potash, would not like to see further concentration in the market that could affect the price of the key fertilizer. Some have mentioned Chinese companies or the government's sovereign wealth fund as possible counter-bidders.

China's largest fertilizer distributor, Sinofert, said last week it was worried about the impact that a BHP deal would have but would not say if its parent, Sinochem, was planning a rival offer. ■

Sanofi Sticks to $69 per Share Genzyme Offer

French drugmaker Sanofi-Aventis poured cold water on a report it had raised its offer for U.S. biotechnology company Genzyme, saying it was sticking to its bid of $18.5 billion or $69 a share. "There is one offer, at $69 a share," spokesman Jean-Marc Podvin said on Thursday. "No other offer has been made to or discussed with the Genzyme board, its management or shareholders." He reiterated Sanofi wanted to enter into constructive dialogue with Genzyme to best serve its interests. A financial news service said on Wednesday Sanofi had pitched a new offer, at $71 a share, to buy Genzyme in return for the opportunity to conduct "partial due diligence.

Questions remain about what price would be high enough for Genzyme to open its books for Sanofi to clearly assess where the maker of rare disease drugs stands in solving its manufacturing problems following plant contamination. In response to Genzyme Chief Executive Henri Termeer's refusal to get around the table to discuss the offer, Sanofi CEO Chris Viehbacher flew to New York to sound out Genzyme shareholders.

Buying Genzyme would help see Sanofi through the years when patent issues will slice about one third from sales and give Sanofi some breathing space in its hunt for growth which so far has consisted of bolt-on takeovers and drug partnership deals. Rare diseases would add a new growth platform to Sanofi's business, expand Sanofi's overhauled drug portfolio with mid and final stage products, and expand its foothold in the world's biggest drugmarket. ■

Glaxosmithkline Head Says No Plan to Bid for Genzyme

Glaxosmithkline will not step in as a rival bidder for U.S. biotech Genzyme and take on Sanofi-Aventis, the British drugmaker's head of research and development told a French newspaper. "An offer by GSK for Genzyme does not make sense. It is too expensive," Moncef Slaoui told Les Echos on the sidelines of the inauguration of a GSK research centre in France. Analysts have said it looked unlikely a white knight would emerge and start a bidding war that could force French drugmaker Sanofi to significantly raise its $18.5 billion non-binding offer to buy Genzyme. ■

DOW CORNING

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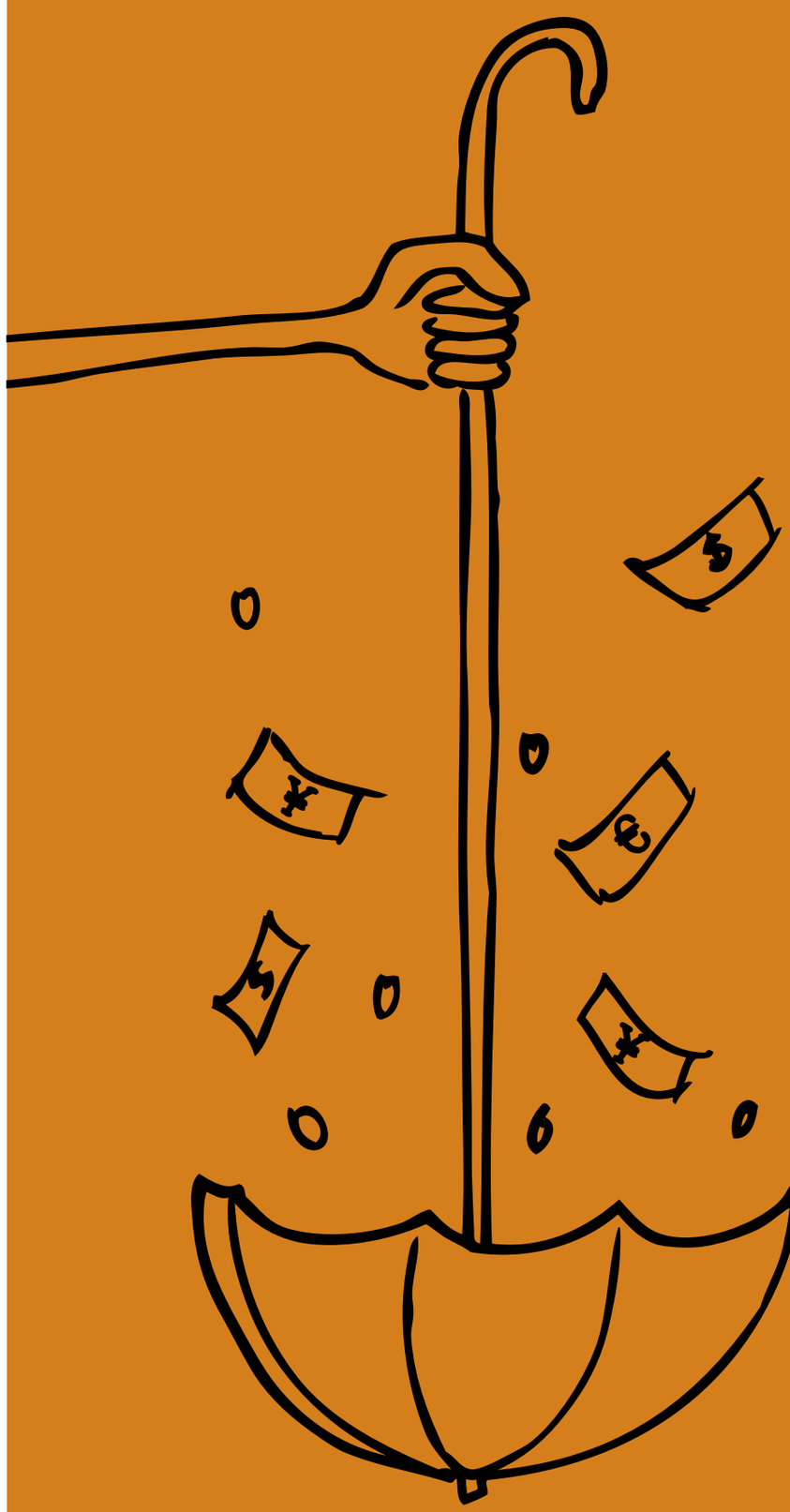

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Chemical Customer Connectivity Index (C3X)

Sustainable Complexity – Or How to Win in a Volatile Market Environment

Marked Improvement – Economic times are changing for the better, markets have returned to life: Chemical demand is outperforming recovery of the global economy following last year's drop in demand and destocking of supply chains. The recently conducted top management panel "Chemical Customer Connectivity Index" (C3X) of the management consultancy A. T. Kearney, CHEManager Europe and the Westfälische Wilhelms-Universität Münster confirms these latest market observations.

Dr. Tobias Lewe
Partner in A. T. Kearney's Chemicals and Oil Practice

Dr. Marc Vathauer
Senior Manager in A. T. Kearney's Chemicals and Oil Practice

The survey showed that 85 % of all participating chemical suppliers said demand for their products grew significantly within the last 12 months – for more than every fourth supplier by more than 30 %. Prices for chemicals as well have exhibited a clear increase. In addition, 80 % of the chemical suppliers reported an increase in production capacity utilization of up to 30 % to cope with the demand increase.

Hopes for a brighter future are backed by demand prospects: The vast majority of both chemical suppliers and their customers expect demand for their products to further grow over the next 12 months – and reinforce the cautiously positive trend that began to show last autumn when the crisis was abating. Finally, also raw material prices are expected to benefit from the upward trend.

Lessons From The Crisis

Inventory level analyses show that chemical suppliers have learned from the crisis: After they had already been reduced during the downturn, they are expected to further decline. This clearly shows that chemical suppliers are trying to reduce their exposure to material price volatility.

This, however, is not the only learning: Chemical suppliers have also reinvigorated their attention to the customer interface in order to better address their requirements – and thereby gain market share. It appears that the improving business climate has recently led suppliers to re-adjust their priorities and turn from their own operations towards the market again.

"In spite of this good news, there is no doubt that the economic crisis has taught chemical suppliers and their customers lasting lessons: Being able to adapt swiftly to any changes in the competitive reality is not only key for a sustainable performance and for growth – when the going gets tough, it can make the decisive difference," said Dr. Tobias Lewe, a partner in A.T. Kearney's chemicals and oil practice. "As market conditions will most likely remain volatile, a continuous and tireless focus on improving agility will become increasingly important."

Manifold Agility Levers

For the majority of chemical companies (82 %) and their customers (65 %), agility mainly translates into an active management of business complexity. This implies both the external complexity e.g. in the form of a broad product assortment, and the internal one, which is basically invisible for the customers and whose added value is not apparent. The importance of an improved complexity management differs by business model in chemicals and becomes all the more important the higher the specialty chemicals character is.

The second important lever consists in faster reaction capabilities (about 60 % of respondents of both groups), which are mainly linked to the ambition to standardize internal processes, as well as to find ways to improve standards and practices across a supplier's entire business system.

As a third priority, chemical companies focus on cooperative network models (45 %) while their customers work on the variabilization of costs (50 %).

Increased Relevance of Agility Confirmed

As a consequence of the economic crisis, all levers to improve business agility have gained in importance. With regard to their implementation, about half of suppliers and customers report that they have conceptually completed actions to improve business system agility and that operational adaptation is now in progress. Roughly one fourth of both groups have, in turn, not yet started at all with the operational implementation.

However, the levers have not become equally important for suppliers and customers. The biggest gap exists for variabilization of costs: Three quarters of all chemical customers attest more variable cost structures an increasing importance since the crisis, while not even half of the chemical suppliers are of this opinion.

"This reveals that obviously an increasing number of customers are considering ceding parts of their value chain to e.g. their suppliers. This in turn raises the question for chemical companies, whether there are possibly parts in the customer value chain that are suited for further integrating downstream and thereby increasing customer proximity," Lewe said.

The ability to react faster to customer needs and market/supply chain requirements has also considerably gained in importance.

"This is attributable to the significant challenges chemical suppliers faced during the crisis when they had to quickly align production to demand cut backs while keeping inventory levels and cash flow under control," said Dr. Marc Vathauer, a senior manager in A.T. Kearney's chemicals and oil practice.

Get a Grip On Complexity

What has most gained in importance for chemical suppliers in light of the crisis, though, is a better management of their business complexity (59 %).

In the past years, chemical companies and particularly specialties manufacturers have increasingly tried to differentiate themselves from their competitors by offering their customers ever more tailor-made products and solutions. This inevitably led to increased costs for manufacturing, supply chain, raw materials and logistics.

Vathauer explained: "What we do observe, particularly in the aftermath of the crisis, is an increasing attention to better understanding what is the core value offering to the customer and what can be cut back. Consequently, many companies have already started to approach the issue in a more holistic way, setting up internal processes and responsibilities so that products are steered from the market down to the production line."

The key challenge for chemical companies is now to standardize and tighten those activities whose value-add is not truly perceived (and paid for) by chemical customers – without losing proximity to them. This implies questioning the entire business system. Given an increasing trend towards commoditization this suggests that specialties suppliers are becoming increasingly open-minded about sourcing services. As a consequence, the make-or-buy question will be often raised in the future.

Greener – But Not Yet Green Enough

The current survey also confirms: Sustainability is on the advance and plays an increasingly important role for chemical companies and their customers alike.

While social sustainability and corporate governance are rated nearly equally important by both groups, a gap persists with regard to the relevance of a company's environmental track record: This is clearly considered more important by chemical customers.

"Chemical companies are recommended to catch up – as being committed to getting greener is undoubtedly worth the effort," Lewe said. A recent A.T. Kearney study has shown that companies committed to corporate sustainability practices achieved above-average performance in the financial markets during the last slowdown: Between January 2008 and June 2009, sustainability-focused chemical firms exhibited a stock performance that was on average 7 % higher than the performance of their peers. Among others this is attributable to the fact that investors seem to reward companies that focus on long-term health and not only short-term profits.

Questioned about how they help their customers to become more sustainable, 60 % of chemical manufacturers stated by securing sustainability in their supply chain. Some suppliers, for example, closely cooperate with their customers regarding required delivery times and segment their supply chain accordingly. Others, in turn, are setting high standards so as to guarantee highest possible safety for the transportation of their products.

About 60 % of suppliers are furthermore providing their customers with technical services which help them improve their operational sustainability. One third of all suppliers offers its customers the possibility of product return and re-use and provides them with alternative, renewable raw materials.

Although customers perceive their suppliers very positively in providing them support to become more sustainable, the suppliers themselves feel that there is still more need for action from their end. Unlocking these reserves will become an interesting challenge for chemical companies in the near and mid-term future.

Lewe concluded: "Though the economy has clearly lifted the future needs to be prepared for. Today, we see two main differentiators for chemical companies to improve their competitive edge. First, optimizing the complexity of internal structures and processes without weakening the offering portfolio will be key. Second, a continuous focus on sustainability is awarded by customers and the capital market alike and therefore represents an important milestone to success."

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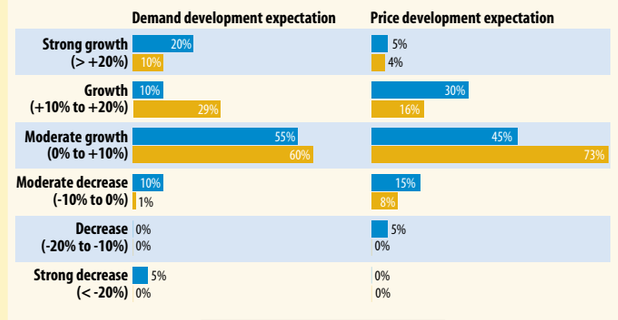
chemanager-online.com/en/tags/c3x

About C3X

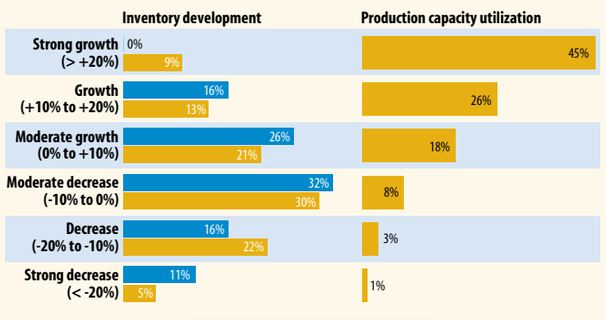
C3X's objective is to analyze the chemical industry from the vantage points of chemical companies and their customers. The panel comprises the senior executives' view of leading European chemical companies and decision-makers in customer industries working at the interface to their suppliers. Participants in the fourth C3X survey, which was conducted during June/July 2010, included executives from 15 European countries, representing chemical firms and client companies, which translates into a total of roughly 110 executives. The customer industries cover 12 different sectors, ranging from the automotive and food industry to the cosmetics sector.

How will the overall market and the (product) prices develop within the next twelve months? Figure 1



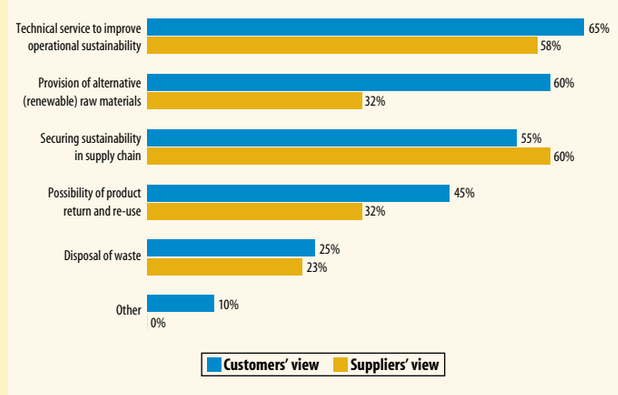
Source: A.T. Kearney © GIT VERLAG

How did your overall inventory level and your production utilization develop in the last twelve months? Figure 2



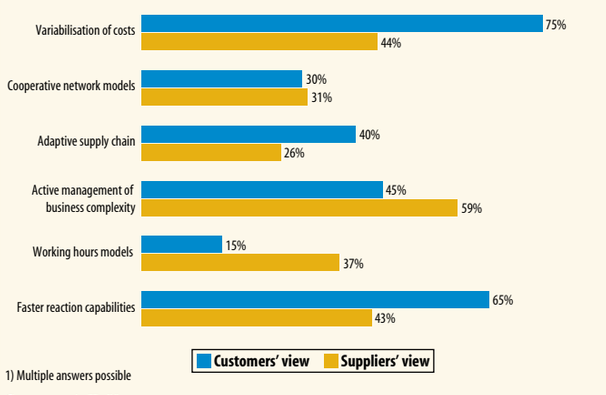
Source: A.T. Kearney © GIT VERLAG

How do you help your customers to become more sustainable? Figure 3



Source: A.T. Kearney © GIT VERLAG

Importance of levers of business agility due to the economic crisis (4th panel)[1)] Figure 4



1) Multiple answers possible

Source: A.T. Kearney © GIT VERLAG

Praxair Sets Middle East Gas Joint Venture

Industrial gases maker Praxair is expanding its business in the Middle East by buying a 49 % stake in the ROC Group's businesses in three countries from the Al Khaled family of Kuwait.

Financial details of the transaction for the operations in Kuwait, United Arab Emirates and Qatar were not released. The ROC Group's sales in those countries totaled about $80 million in 2009.

Praxair currently has only modest operations in the Middle East based out of offices in Abu Dhabi, and the new joint venture represents "a major move" to expand in the region, according to company spokesman Nigel Muir.

Praxair expects demand in the region to grow as Middle Eastern governments spend heavily on new infrastructure projects and to increase energy production through technologies such as enhanced oil recovery, a process that uses gas to boost output from wells. ■

Clayton, Dubilier and Rice Buy Stake in Univar

Clayton, Dubilier & Rice and CVC Capital Partners announced an agreement for CD&R to acquire a 42.5 % ownership in Univar, a leading global distributor of commodity and specialty chemicals to a broad array of end markets. The transaction values the company at approximately $4.2 billion. Funds advised by CVC will retain a 42.5 % stake in the business. The remaining equity will be held by Univar management and other existing investors.

With revenues of $7.2 billion, Univar is a market-leading distribution platform serving highly fragmented and diverse markets and customers. The company operates a network of 179 distribution facilities and distributes more than 11,000 products and 110,000 SKUs to over 80,000 customers in more than 100 countries. "Univar's business profile fits our investment focus perfectly, and we look forward to working with CVC and the Univar management team to continue to build the business," David H. Wasserman, a CD&R partner said. John Zillmer will remain Univar's president and chief executive officer. CD&R operating partner, William S. Stavropoulos, former chairman and chief executive officer of The Dow Chemical Company, will become the non-executive chairman of Univar. ■

Abbott Ends Auction of Vaccines Business-Company

Drugmaker Abbott Laboratories has decided against the sale of its European flu-vaccine business after initial bids came in below its expectations, a company spokeswoman confirmed. The auction had drawn interest from four or five bidders, but the offers came in at less than €500 million and proved too low for the company's liking, a person familiar with the matter told the newspaper.

"We explored the option of potentially selling the vaccine business … We have (now) decided to retain it," Abbott spokeswoman Melissa Brotz confirmed by phone. She said the company will now integrate the unit into its other businesses. ■

Air Liquide Signs Major Contract with 3Sun

Air Liquide has signed a major long-term contract with 3Sun to become the sole supplier of gases and services to the new company. 3Sun, a manufacturing joint venture using Sharp advanced triple-junction technology to produce solar panels in Sicily, Italy has recently been established by Enel Green Power, Sharp and STMicroelectronics. The Catania-based factory will start operations in 2011, with an initial capacity of 160 MWp per year. Yearly output is expected to reach 480 MWp in the next few years. The 3Sun factory will be the second largest Si thin film solar factory in the world after Sharp facility in Japan, and its output will be used by Enel Green Power and Sharp to serve a large market that extends to Europe, Middle East and Africa. This agreement covers the supply of very large volumes of specialty gases, the pipeline supply of carrier gases and the provision of all related services. Air Liquide will build the entire gas distribution and gas abatement networks on a turnkey basis. In order to meet these needs, Air Liquide will invest in additional hydrogen production capabilities in Sicily and also in the specialty gases supply chain. ■

Driven By Innovation

Merck Millipore Merger Prime Example for a Strategic Acquisition, New Division Performance Materials

Smart Move – There are various reasons for companies to make acquisitions: expansion, investment, synergies, elimination of a competitor and strategy. The acquisition of Millipore by German pharmaceutical and chemical company Merck KGaA is all about strategy. Millipore has joined the business sector Merck Chemicals, which now comprises two new divisions: Merck Millipore and Performance Materials. Dr. Michael Reubold talked to Dr. Bernd Reckmann, member of the executive board of Merck and head of the Merck Millipore division, about the strategic approach behind the acquisition and the challenges that lie ahead in the chemical, pharmaceutical and materials industry.

Dr. Bernd Reckmann
Merck KGaA

CHEManager: Dr. Reckmann, Millipore complements Merck's existing portfolio. Were there any conditions imposed by the authorities to clear the transaction?

B. Reckmann: No, as you said, the product offering is highly complementary – Merck Millipore is a perfect fit. There are only very small areas where we have an overlap in products. At the end of the day, we will be one of the leading global players in the life science supply market with highly specialized products in highly growing markets. This whole business is driven by innovation. This is a deal that puts together complementary businesses instead of justifying itself out of cost savings. And, fortunately, there was absolutely no problem with the authorities neither in the U.S. nor in Europe. That was exactly what we had expected.

To really benefit from a merger it needs a good integration. What is your strategy to ensure a swift integration process of the Millipore part into Merck Millipore?

Dr. B. Reckmann: The keyword to describe this process is "best of both." We applied this approach in the integration of Serono, which was extremely successful. Merck is open to learning from and also to adopting processes where we think that the Millipore legacy works better to serve the future needs of the markets and the other way around. I think this is one of the key issues. The second key issue is speed in the integration decisions, because we have to recognize that an acquisition creates a lot of uncertainty and anxiety in the organizations. You get it resolved only if you make the decisions in a speedy, transparent and honest manner. Finally, the third important thing is to retain the key talents. I am glad to say that we kept the top talents in level one and level two of the Millipore management team, and with this strong team we can continue to deliver great results.

> *"The pharmaceutical and the biotech industry will have to reinvent how they do their business."*

When do you expect the integration to be completed?

Dr. B. Reckmann: I think the major integration effort will take until the end of the year, but even then there will be a lot of things that need to be done, for example the harmonization of IT systems. For me the integration is completed when the people working for Merck Millipore do feel like Merck Millipore, and according to my experience this will take at least three years.

How will Millipore be integrated into the Merck organizational structure?

B. Reckmann: Millipore will be truly transformational for Merck Chemicals, and we will end up with having two high-growth innovative businesses. One is the life science tools business, which as a division we have named Merck Millipore, with pro forma revenues of €2.1 billion. The other is the high-tech business, which we have named Performance Materials, with pro forma sales of more than 1 billion.

What businesses will Merck Millipore include?

B. Reckmann: Merck Millipore will consist of three business units – Bioscience, Lab Solutions and Process Solutions – and each unit will itself comprise a number of key focus areas, such as protein research assays and reagents, cell culture solutions and drug discovery services for biopharmaceutical companies as well as laboratory chemicals for research, analytical and hospital laboratories. With this setup, I think we can really create something completely unique in the industry. Merck Millipore is committed to fully live up to what we have already agreed on as a vision: "unleash the potential of science for life."

And Performance Materials?

B. Reckmann: Performance Materials will comprise Merck's specialty chemicals materials activities, i.e. the Liquid Crystals, Pigments and Cosmetics and other material-driven businesses. The division will combine our successful range of materials-based products, technologies and innovative solutions, our strong application know-how and our distinctive customer focus to open up additional growth opportunities. Examples are liquid crystals for displays used in TVs, PCs and consumer electronics, LED and OLED materials for displays, lighting and photovoltaics, pigments for the cosmetics, paints and coatings industries, as well as active ingredients.

What does the acquisition mean for Merck's presence in North America?

B. Reckmann: We finally have reached critical mass in North America. In the chemical business we always have been underrepresented. Now, out of this combined business Merck Millipore we will do 35 % of sales in North America.

Do you see opportunities to leverage synergies between Pharmaceuticals and Chemicals?

Dr. B. Reckmann: Basically not, synergies are not key. In fact, we are active in different businesses – Pharmaceuticals and Chemicals – for risk balancing aspects, not for synergy aspects.

On the market side, how do both parts of Merck Millipore compare?

Dr. B. Reckmann: Millipore has a very strong relationship with the biotech industry. We have very strong relationship more with the chemical pharmaceutical manufacturing industry. These things work together nicely. We will also use some of the "go-to-market" processes of Millipore and merge it into something more agile and more powerful than what we had before.

More agile and powerful suppliers – is that what your customers demand?

Dr. B. Reckmann: Yes, because one thing is clear: if you want to develop new drugs – and that is what our customers do – you need more than one discipline. Everything has become more complex today and you have to interact with networks. Otherwise you fail anyway. And both the pharmaceutical and the biotech industry will face tremendous challenges and, therefore, they have to reinvent how they do their business: how to do research more efficiently, how to take costs out of the manufacturing processes. There will be an enormous pressure for this industry to change. And I think that by combining the strengths of both organizations and by understanding exactly what our customers are doing we are able to add value on each level of the process chain and are in a very attractive position to help them to manage this transformation.

You said that this business is driven by innovation. Can you give us an idea of how much money you want to spend on R&D?

B. Reckmann: For Merck Millipore, we will have a very attractive R&D budget in the range of 6–7 % of sales, or more than €120 million. This is number 3 in the industry and gives us critical mass to transform our knowledge and the needs of our customers into the solutions that really drive this innovation.

> *"In the high-tech area we want to generate new growth engines."*

Merck uses parallel synthesis to investigate new liquid crystals.

Can you also give a number for your R&D budget in the Performance Materials business?

B. Reckmann: In the Performance Materials business we invest even more on R&D – about 10 % or even more of sales. For a chemical company, this number is outstandingly high, but Merck has a reputation of being very innovative. In the high-tech area we definitely want to generate new growth engines like liquid crystals, and we are addressing areas like organic electronics, flexible displays, photovoltaics, energy materials, lighting, and performance additives. Through our R&D focused on future demand drivers and a broad portfolio of innovative solutions the division will be able to more effectively address current and future megatrends.

What is essential for specialty or performance materials businesses to generate value or growth?

B. Reckmann: I think the key driver in these high-tech areas is understanding application technology. In these businesses just offering a molecule does not help, because you really have to educate your customer what additional value it could generate by implementing this chemical substance in a specific product or process. Therefore, you need a strong application technology. It is very often a project-driven business and at the end of the day you get a customized product, more or less.

Are you also open to grow that business by acquisitions?

B. Reckmann: Today, we don't see a big acquisition in this high-tech area because every chemical company would be more than happy if they had something like this and, thus, would definitely not be in a mood to divest it.

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Welcome To Pharma 3.0

Part 3: Strengthening Support Functions to Enable Business Model Transformation

Evolution in Pharma – Pharmaceutical business models continue their rapid evolution. The industry's legacy business 1.0 model, based on marketing blockbuster drugs, is morphing into a more innovative, collaborative, diversified and global 2.0 model. Now we are seeing inroads into a 3.0 model, one that is focused on health outcomes. As business environments and business models evolve, excellence in support functions will be essential for delivering this transformation. Improved supply chain, finance, information technology (IT), and human resources (HR), as well as the ability of these functions to move beyond support – and actually partner with the business for enhanced performance and strategic decision-making - will be critical for success.

Frank Kumli
Ernst & Young

Patrick Flochel
Ernst & Young

Managing costs and cash flow have been key areas of progress in the evolution to Pharma 2.0. For years, many companies relied on "instant-gratification" cost-cutting measures that paid little attention to, and sometimes even jeopardized, their future growth plans. Today's CFOs are taking a more strategic approach by looking to create a long-term, sustainable cost advantage. Companies with an end-to-end perspective of their entire value chain have a better understanding of how they source, manufacture, price and distribute products. They can also make better decisions on business improvements. While most admit they have a long way to go in the quest to grow lean, this new emphasis on efficiencies that contribute to long-term profit growth represents a marked shift in mindset. Now the focus is on increasing organizational flexibility for a nimble response to emerging growth opportunities.

In the evolution to Pharma 3.0, support functions will play a central role in creating this nimble response. They are already becoming more efficient taking measures to reduce costs, delivering better insights, thinking and acting strategically, and learning how to become true partners to the business. In Pharma 3.0, this ability to partner will be critical to the success of support functions and to the business itself.

Supply Chain 2.0

Over the past few years, the industry has taken initiatives to reduce supply chain costs. From redesigning distribution networks, and looking at synergies between business units in warehousing, operations, and sales, to increased teaming between supply chain operations and finance, delivering for example increased accuracy of supply forecasting.

For most pharmaceutical companies, optimizing the manufacturing footprint is an ongoing effort, with the goal of achieving a more focused, streamlined and competitive manufacturing operation. Streamlining global manufacturing networks involves revising make-or-buy decisions, resulting in plant divestment as needed and a move to outsource non-core operations. Procurement is becoming more strategic, integrated in the business, globalized and leaner – with fewer suppliers and more support from efficient information technology platforms.

As the industry's footprint expands, and entering new markets becomes more complex, harmonizing processes is an essential yet challenging goal. Harmonization is further complicated by multiple import regulations, local country legislation and customs processes, and the need to ensure global compliance to avoid the dangers of bribery and corruption.

Finance Transformation 2.0

Pharmaceutical companies are at different stages of the finance transformation journey. However, overarching goals are to reduce costs and improve effectiveness in partnering with the business. In an industry that has grown rapidly through mergers and acquisitions, legacy finance functions are often fragmented across business units and countries. The focus now is on harmonizing processes and systems, streamlining transactional accounting operations, and reinvesting in business partnering to drive corporate performance and support business strategy, while managing risks through effective controls.

The goal of reducing transaction costs can be significantly accelerated by unifying technology platforms and creating shared service centers or improving efficiencies through harmonizing business practices.

Information Technology 2.0

In IT 2.0, cost savings can be achieved through process automation, streamlining application providers and data centers. Pharmaceutical companies have started to virtualize their computing through online servers, or "cloud computing." These flexible solutions enable companies to increase the quantity of applications, servers and storage platforms, while reducing costs. Although cloud computing provides many benefits, it also brings new challenges in data security, integrity, privacy and compliance.

Human Resources 2.0

Yesterday's HR professionals spent much of their time on transactional, reactive work – from writing recruitment letters to documenting performance reviews. Little time was left to add strategic value to their companies. Recently, efforts have been made to centralize processes to free up HR from transactional work and enable the function to become more involved in strategic decision-making. For example, headcounts have been reduced; HR transactional activities have been outsourced to more economical external providers or to internal shared service centers; and IT has been used to automate some processes to save time and cost. And while all recognize that innovation comes from innovative people, not products, companies have only started to execute on the potential to transform themselves by changing the way they recruit, train and develop the diverse workforce of the 21st century.

Risk Convergence 2.0

Improving the performance of risk management functions has also become a priority for pharmaceutical companies. Many companies are faced with legacy internal risk functions that are often siloed, disparate and uncoordinated and as a result inefficient and ineffective. By adopting a more holistic approach to risk companies can not only to save costs but also be better positioned to prevent problems. The concept of risk convergence is simple: rather than managing risks locally, risk convergence aligns all risk management functions across the enterprise. As companies achieve convergence in their approach to risk, they can improve risk management, ensuring that critical risks are appropriately addressed and costs contained.

Performance Management 2.0

Today's performance management cycle is often inconsistent. Decoupled from strategy, it may be held together by manual spreadsheets and weighed down by excessive detail. To link business drivers to planned performance companies need to use leading indicators instead of simply relying on outputs and financial results (e.g., customer demand, production volume, capacity utilization). This is particularly important as organizations look to drive greater efficiencies through the value chain or to assess the effects of alternative restructuring and cost reduction strategies.

Progressive companies are breaking free from this manual, overly detailed cycle to deliver more effective decision support. This requires integrated planning across such key measures as market share, income statement, balance sheet, cash flow, and shareholder value.

Successful companies today are integrating their strategic decision making with their performance management processes, such as long-range planning, annual budgeting, forecasting and management reporting, through a common set of drivers. This includes rolling forecasts and rolling trend analysis to improve visibility and eliminate the bias that outcome-only incentives may encourage.

Transformation From Pharma 2.0 to 3.0

The transformation from Pharma 2.0 to 3.0 will have a tremendous impact on the role of support functions in their ability to support the business and navigate the rapidly changing business environment.

Supply Chain 3.0

As the pharmaceutical industry develops new business models, with increased partnering with non-traditional players and a more customer-centric approach, it will need to shift its view to supply chain and manufacturing. Managing a supply chain in the "extraprize" of alliance partners and transferring assets into this collaborative environment will be challenging. Customer centricity will also imply moving from a "push" approach to a highly customized "pull", with smaller batch sizes, new packaging requirements, and flexible assets to support different product technologies as well as an increasing complexity of product mix from encompassing chemicals, biotech and diagnostics. Maintaining the integrity of the supply chain in this complex and rapidly evolving environment will require managing the extraprize in an integrated and systemic way.

Information Technology 3.0

With much of the Pharma 3.0 world centered on customer data, information management will become a key driver of value for the industry. Information technology will play a central role in delivering a competitive advantage in this new business environment. From social media to new digital marketing platforms to patient data analytics, the IT function must ready itself to support a host of new business initiatives. Data privacy and security risks will grow exponentially as patient data becomes increasingly central and as non-traditional players become involved.

Human Resources 3.0

Non-traditional alliances in Pharma 3.0 will create the need to engage new talent. – For example, subject matter experts who understand the new business drivers and non-traditional partners. HR will need to support a change in the collective skill set by helping to attract and retain people who have broad perspectives, high social agility and the ability to work across programs. Diversity is becoming a key success factor for innovative companies and companies that can find and retain the most innovative people will position themselves ahead of their peers in product and business model innovation.

Risk Convergence 3.0

New data and customer-centric business models will bring a host of compliance risks as the industry becomes more closely engaged with key stakeholders, such as patients, physicians and customers. Risks are also inherent as pharmaceutical companies align with industries unaccustomed to the regulatory scrutiny on their sector – and unfamiliar with the ubiquitous presence of government in the life sciences industry.

Performance Management 3.0

The "Measures that matter" will evolve as business models evolve. In the health-outcomes-driven ecosystem of Pharma 3.0, the focus is shifting toward value co-creation with customers, governments, patients and other stakeholders. In this rapidly shifting business environment, pharmaceutical companies will be faced with high levels of uncertainty that may impair their decision-making.

As such, pharmaceutical companies must review and improve the way they make strategic decisions. This will require integrated planning across multiple 1.0, 2.0 and 3.0 outcomes, and ecosystem-related measures, such as health outcomes, comparative effectiveness, quality of life, value of prevention, marginal value of expanding access, and societal value of outcomes.

Thinking Ahead of the Business

Support functions are usually fully focused on ensuring their operations run efficiently and also reactively support transformation initiatives led by the business. Looking forward, support functions must think ahead of the business, and act proactively to partner with the business to drive new growth.

To position themselves as business partners, support functions will need to think ahead of the business. To achieve this, support functions must:

Understand the business and the developments in the extended health care ecosystem

Understand the transformation happening across industries segments (for example in the fields of social media, or of innovative customer centric approaches)

Be innovative and visionary, supporting ideation

Work closely with the business, creating insights from information

Strive to working more closely with the business in decision-making and supporting business transformation and growth.

Frank Kumli and Patrick Flochel

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Reach Is Everywhere

How to Fulfil Your Commitments to Your Customers under Reach and CLP

It's A Small World – Chemical legislation is becoming something of a hot topic around the world; in addition to Europe, many other countries, such as the U.S., Canada, China, Japan, South Korea, Malaysia, Taiwan, Turkey and Switzerland are currently either developing new or amending their current chemicals legislation. There are similarities between the different legislative instruments but essentially each country or region is developing their legislation to meet local requirements. Grasping the nettle of harmonization now would have benefited everyone in the supply chain but as it stands companies will have to ensure that they monitor developments in each country closely to ensure compliance.

Reach and CLP (Classification, Labelling and Packaging of Chemicals) are being phased-in in a series of discrete steps until 2018, when the main requirements defined in the process will essentially be complete. The CLP regulation is the European implementation of the Globally Harmonized System (GHS) for the Classification and Labelling of Chemicals developed under the guidance of the United Nations but, in the European version, some parts have been left out and others added to achieve the original objective of harmonizing without lowering the current level of protection of human health and the environment. The regulations are not only being introduced in the 27 EU Member States but, because of the legal framework in Europe, also in the three additional states that signed up to the European Economic Area Agreement – Iceland, Liechtenstein and Norway. In addition, membership of the EU is not static and a number of other countries, such as Croatia, Macedonia and Turkey, have recently applied to join, so they may also apply in these countries at some stage in the future.

Why New Regulations?

The regulatory authorities believed that the new legislation was necessary because the previous EU legislative framework for handling chemicals was inadequate. It was 40 years old and a complex mixture of different directives and regulations. In spite of being continuously updated, there were many anomalies. These include the lack of information about the effects of the majority of existing chemicals on human health and the environment; and different rules for "existing" and "new" chemicals, which the authorities believed hampered research and innovation, causing the EU chemicals industry to lag behind its counterparts in the rest of the world.

In addressing these concerns, especially those related to exposure to the chemical substances used, the authorities decided to broaden the scope of the legislation to not only cover chemical substances and mixtures but also include articles. This decision placed a number of many new responsibilities on chemical manufacturers and importers into Europe. While some of the responsibilities were not particularly onerous, some were new; some weren't actually new but involved changes to the information supplied because the legislation had changed; and some were new to companies simply because they had not been impacted by the legislation associated with chemicals before.

Supplier responsibilities often vary with the industry concerned. Some are voluntary, like the completion of customer questionnaires confirming the compliance status of products; others are obligatory, like describing the use of the chemical substance, supplying the safety data sheet and label for hazardous products, and informing customers when the products they receive contain more than a threshold amount of certain specific hazardous substances. This is in addition to the need to supply certain specific information to the European Chemicals Agency (ECHA) and ensuring that your suppliers have also fulfilled all their responsibilities.

Fulfilling Multiple Roles

Deciding what information has to be supplied is well defined in the legislation but varies with the role assumed by the company. What is often forgotten is that a company may fulfil multiple roles. Sometimes they will be supplying the chemical substance or mixture and the information but other times they will be purchasing the chemicals from another company which means they will mostly receive information. It is critical that the different roles, as defined in the legislation, are assigned accurately and the information, received and distributed, is stored for reference purposes. Another key factor to consider is where the companies are based, because this could also impact on both the role and the responsibilities under the Reach and CLP Regulations. Typically, if the supplier and the customer are both based inside the EU, then the responsibilities will remain with the supplier. However, where the supplier is based outside the EU, the customer must be cautious; otherwise they could inherit the responsibilities from their supplier.

Classification Of Articles

In practical terms, customers seldom want to have all the details but are looking for reassurance that their suppliers have everything under control and that the products they are currently using will continue to be available in the future. The information required involves understanding the type of product supplied, i.e., is it a chemical substance or a chemical mixture and, if it is an article, the supplier needs to identify which type of article it is. The four different types of articles are all defined in the legislation, and companies must determine the product type to identify current and future requirements. The classification of articles is less intuitive because, in the search for clarity, the number of different types has increased.

"What is often forgotten is that a company may fulfil multiple roles."

Example 1 – Chemical Company A, based in the EU, supplies a hazardous chemical substance to Chemical Company B, also based in the EU, for use in their process.

- The supplier may have to reassure the customer that the chemical substance has been pre-registered, and, where necessary, will be registered at the appropriate time under the Reach regulation and also, where necessary, be notified at the appropriate time under the CLP Regulation with ECHA.
- The supplier will have to label the product correctly and supply a safety data sheet to the customer in the correct format. It is worth noting that the format of the safety data sheet will soon change, and the information on the label and in the safety data sheet may also change.
- The supplier may have to complete a chemical safety assessment (CSA) and ensure that the information in the safety data sheet supplied to the customer is consistent with that contained in the CSA.
- The customer may have to inform the supplier of the use made of the chemical substance in his process and implement the risk management measures given in the safety data sheet.

Example 2 – Chemical Company A, based in the EU, supplies a non-hazardous chemical mixture to Chemical Company B, also based in the EU for use in their process.

- The supplier may have to reassure the customer that all the chemical substances present in the mixture have been pre-registered, and, where necessary, may have to be registered at the appropriate time under the Reach regulation, and may also, where necessary, have to be notified to ECHA at the appropriate time under the CLP regulation.
- The supplier will have to label the product correctly and, where necessary, supply a safety data sheet (SDS) to the customer and the conditions, when this is applicable, are listed in Article 31 of the Reach regulation. Should a SDS not be required, then certain information must still be supplied and the requirements are all listed in Article 32 of the Reach regulation.
- The supplier may have to complete a chemical safety assessment (CSA) and ensure that the information in the SDS supplied to the customer is consistent with that contained in the CSA.
- The customer may choose to inform the supplier of the use made of the chemical mixture in the process and consider implementing any risk management measures recommended in the safety data sheet.

Example 3 – Chemical Company A, based in the EU, supplies a non-hazardous chemical mixture to Company C, also based in the EU, for use in the manufacture of an article.

- The supplier may have to reassure the customer that all the chemical substances present in the mixture have been pre-registered, and, where necessary, may have to be registered at the appropriate time under the Reach regulation, and may also have to be notified to ECHA at the appropriate time under the CLP regulation.
- The supplier will have to label the product correctly and, where necessary, supply a SDS to the customer and the conditions, when this is applicable, are listed in Article 31 of the Reach regulation. Should a SDS not be required, certain information must still be supplied and the requirements are all listed in Article 32 of the Reach regulation.
- The supplier may have to complete a CSA and ensure that the information in the safety data sheet supplied to the customer is consistent with that contained in the CSA.
- The supplier must inform the customer of the presence of any Substances of Very High Concern (SVHCs) present in the mixture.
- The customer may choose to inform the supplier of the use made of the chemical mixture in his process and consider implementing any risk management measures recommended in the safety data sheet.

By choosing to base all the companies in the EU the above examples are rather simple and may not be either representative or typical. Supply chains and markets are, in the most part, far more complicated because most companies either source raw materials or manufacture products globally. In practice, it is rare for a company to source all the raw materials inside the EU as well as selling the finished product locally. This adds a level of complexity when determining compliance and requires an in-depth understanding of how a company operates in order to determine what information has to be distributed within the supply chain.

Summary

The implementation of the Reach and CLP regulations in Europe has placed new responsibilities on the manufacturers and importers of chemical substances, mixtures and articles. While these new responsibilities may not be particularly onerous, many are new and have to be complied with if companies wish to continue placing their products on the European market. The search for clarity by the regulatory authorities, especially with articles, has caused confusion because the process is now less intuitive, but companies are working diligently to ensure that the data required is collected and communicated along the supply chain.

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Solvay Invests in Minority Stake in Polyera

Solvay announced it is investing $4 million in a minority stake in Polyera, a leading materials developer for the printed electronics market, based in Skokie, Illinois. Polyera develops and commercializes organic semiconductors and dielectrics for organic thin-film transistors (OTFT) and organic photovoltaics (OPV), enabling applications such as flexible display backplanes, printed RFID tags and printed solar panels. This investment is being made under Polyera's series b financing, in which its prior investors are participating. Printed electronics is an emerging industry that relies on printing technologies to manufacture electronic devices with a wider variety of form factors, and supports including thin, lightweight, and flexible substrates. These new electronic devices can be produced very efficiently in high volume and at low cost, and enable totally new applications which can not be addressed today by traditional silicon-based electronics. "Polyera enjoys a worldwide recognition in the development of cutting-edge organic semiconductor material, and in just its few years of existence has built substantial know-how in printed transistor and photovoltaic fabrication," comments Leopold Demiddeleer, senior executive vice president future businesses at Solvay. ■

An Appeal For Calm

Everyone is on the Learning Curve in Reach

Legal Soup – Too short timelines, confusing information, unclear tasks – Reach is as much of a legal jungle as it ever was. With the first deadline approaching in December, many companies are beginning to feel hot under the collar, and some are not even aware of their responsibilities under Reach. Chemical distributors have also not been spared from the expansive legislation. Peter Brandhofer, who leads the Reach activities at Hamburg-based chemical distributor Helm, told Brandi Schuster about the role his industry plays within Reach and why it is better to see Reach as a learning experience instead of panicking.

Peter Brandhofer
head of Reach Department/ Quality Management, Helm

CHEManager Europe: Mr. Brandhofer, what role do chemical distributors play in communication in the supply chain, particularly concerning the flow of information?

P. Brandhofer: A very important one. The cooperation between chemical distribution and chemical production in Europe is very close; hence the role of chemical distributors in the supply chain communication under Reach is essential for the workability of Reach.

What do distributors have to do within Reach?

P. Brandhofer: The major task for the chemical distributors will be the fast and secure forwarding of information up and down the supply chain. This process is not just done by using the forwarding button of the e-mail program; the chemical distributor has to create an administrative link between the supplier/producer of chemicals and the customer. In situations where there are confidential business interests to protect, the chemical distributor cannot use direct forwarding; rather, the communication has to be edited without changing the basic information.

According to article 36 of the Reach regulation, the chemicals distributor has to document any communication concerning the health and safety information and about the uses notified by the customers. Due to the huge number of customers, the chemical distributors have to carry an additional administrative burden.

If the chemical distributor is acting as an importer, the company has the same obligation like any other chemical producer in Europe.

In your presentation at the Handelsblatt Chemie 2010 conference, you mentioned several problems: missing guidelines; IT tools; and lack of experience with guidelines and IT tools. Which of these problems are the most acute?

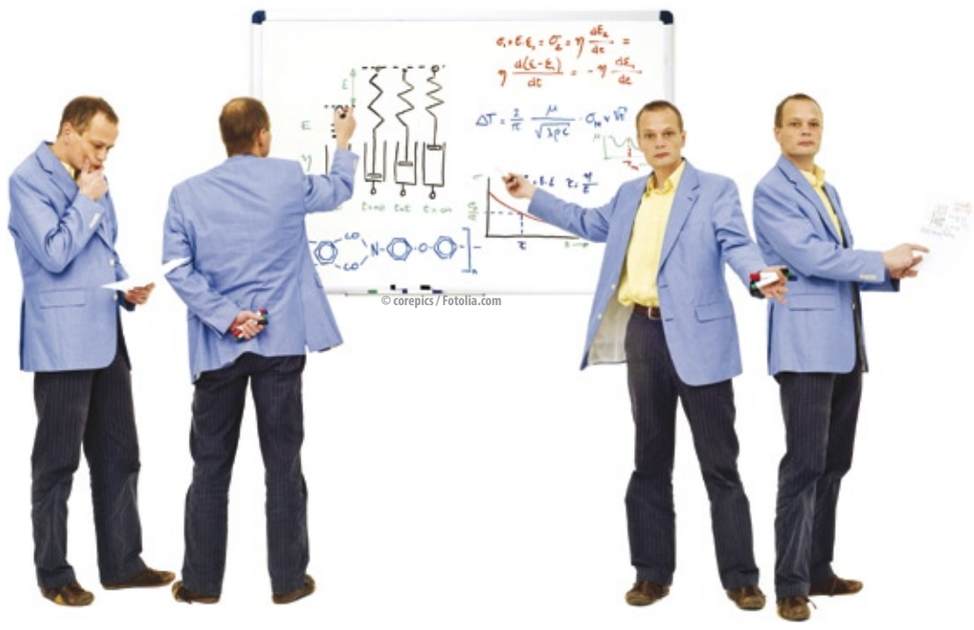
P. Brandhofer: Reach is creating a totally new approach in guaranteeing the safe handling of chemicals. On one hand, you have the change in the burden of proof, which means that now manufacturers and importers are responsible for the data as well as for the communication of the information on how the customer has to create working conditions to avoid harm humans and the environment.

Over the last three years, it has become apparent that the given timeline to reach this goal is too short. We had massive delays in creating guidance on how to get the data, how to interpret the data and how to communicate the results.

The European Chemicals Agency – ECHA – itself has dramatically shown that the process of creating software tools, combining legislator interests with scientific information, is not easy. I was disturbed when I read that ECHA was perplexed about the smaller-than-expected numbers of registrations from May to July. Registration delays are understandable when you consider how late the publication of the final format for the IUCLID software was, along with the tools to create the chemical safety report and then especially the final format for the exposure scenarios.

One gets the impression that ECHA is thinking that the companies should be able to act immediately on receipt of such information without first reading, understanding and testing the guidelines and tools and this is simply not the case. ECHA is expecting responsible implementation of Reach by the registrants and the different members in the supply chain, but not giving enough time for implementation by the ECHA is irresponsible.

I think this is all a part of the general problem with the lack of time to create guidance, tools and lastly, experience within both industry and at the authorities as well. From the political objective and legal situation, it's a pipe dream to ask to postpone the deadlines for one or two years.



What would make more sense?

P. Brandhofer: It is more realistic to appeal for calm in the supply chain. This means not sending out serial letters on subjects that cannot be replied to or resolved within the obligatory legal dates.

If one has been receiving timely, well-presented, good quality safety data sheets from a well-known supplier for years, then there is no need to bother the supplier with letters and questionnaires. One can be satisfied with receiving these documents bit by bit.

This will create the time to learn how to handle these documents.

Are there other challenges that Reach has brought to the industry?

P. Brandhofer: Yes. Beside the normal questions which influence a buyer's decision for chemicals, like price, quality and availability, supply chain communication on health and safety aspects will become more and more important.

My impression is that especially downstream users do not realize what is expected of them under Reach. In fact, I would assume that the majority of downstream users are not familiar with their obligations. Help and guidance is needed, and the instinctive defensive reaction will be to request help from the supplier.

This will not happen immediately on Dec. 1, but the demand for good services on this subject will grow after this first registration deadline has passed. As a service-orientated chemical distributor, Helm is looking optimistically into the future; we have the set-up and we are prepared to offer the required service to our business partners.

How is the situation in the industry now compared to when Reach went into effect in June 2007?

P. Brandhofer: I am witnessing a dramatic exhaustion on side of the registrants. The experts are doing really an awesome job, but the willingness to deal with new formats and definitions from ECHA is next to nothing.

At the moment, registrants are only interested in getting the dossier ready and in receiving the registration number. In the supply chain, the least progress in awareness on the Reach obligations can be seen at the downstream users. I personally expect a rude awakening in 2011, when the first extended safety data sheets with exposure scenarios arrive in the companies and no one really knows how to handle them.

Pressure is mounting as the first registration deadline approaches on Dec. 1, and many companies and Substance Information Exchange Forums (SIEFs) are uncertain they will be able to meet the deadline. What are the consequences for SIEFs who don't manage to make the deadline? How realistic will enforcement of Reach be?

P. Brandhofer: I am not in possession of a crystal ball but I expect that some SIEF will fail in delivering their registration dossier in time. Reach is clear on that – article 5 is called "No data – no market."

The question really is who will solve the resulting problems without losing the reputation? I am confident that the industry will be able to provide a pragmatic approach to continue industrial processes. But how will the authorities handle pragmatic solutions? The authorities will have the task of sorting really problematic tasks from intentional violation of Reach.

I believe that Europe is well advised to accept that some violations will be undetected in the first run, but a pragmatic solution will be found to continue production or import of substances that fail the registration because of problems in the SIEF or the registration process.

ECHA itself is showing a pragmatic approach with the creation of the Directors Contact Group. My impression is that there is a problem because of the fact that the competent authorities are not invited to participate in this group. It looks like the competent authorities are a little bit offended by this, but I hope all participants will come together to solve the upcoming problems in a pragmatic way.

Do you see Reach achieving its intended goals in the long run?

P. Brandhofer: I think that Reach will change the common approach of working with chemicals in the long run. We are just at the beginning of a long process and all participants must persevere. I am sure that Reach regulation itself will change over the years. The legislative body has to implement the legislation within the practical experiences of the supply chain.

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A Few More Months

The Reach Deadline is Approaching Fast

Preparation – The next milestone in Reach is coming up: the 2010 deadline. So what are the hurdles in completing registration, and what happens if it doesn't go to plan?

Annette Elizabeth Ewence
The WRc Group

2010 Deadline

All phase-in substances manufactured or imported into the EU taking advantage of delayed registration via pre-registration at more than 1,000 tons per year must be registered by Dec. 1. Substances deemed to be of great hazard (e.g. carcinogens, mutagens or reproductive toxicants, also known as CMRs) that are manufactured or imported into the EU at more than 1 ton per year; or substances deemed to be very toxic to aquatic organisms (R50/53) that are manufactured or imported into the EU at more than 100 tons per year are also to be registered by this date.

Dossier Preparation

So, you've read the guidance, completed pre-registration, Substance Information Exchange Forum (SIEF) registration strategies, data sharing and entered all the data into the much improved IUCLID 5 dossier system (the electronic platform within which data on the manufacture and use, mammalian toxicity, eco-toxicity and environmental fate of chemicals can be added and assessed), and completed the chemical safety report (CSR). The deadline is finally here, so what's next for a successful registration?

Registration dossiers submitted to European Chemicals Agency (ECHA) go through a virus and XML format check and a business rules validation; if they pass, they are forwarded for technical and financial completeness checks. If the dossier fails at these points, it is returned to the submitter for completion before the deadline. Dossiers are then randomly selected for a dossier check. Those dossiers submitted closer to the deadline that fail may not be verified until well into 2011, so it is a good idea to submit your dossier as early as you can!

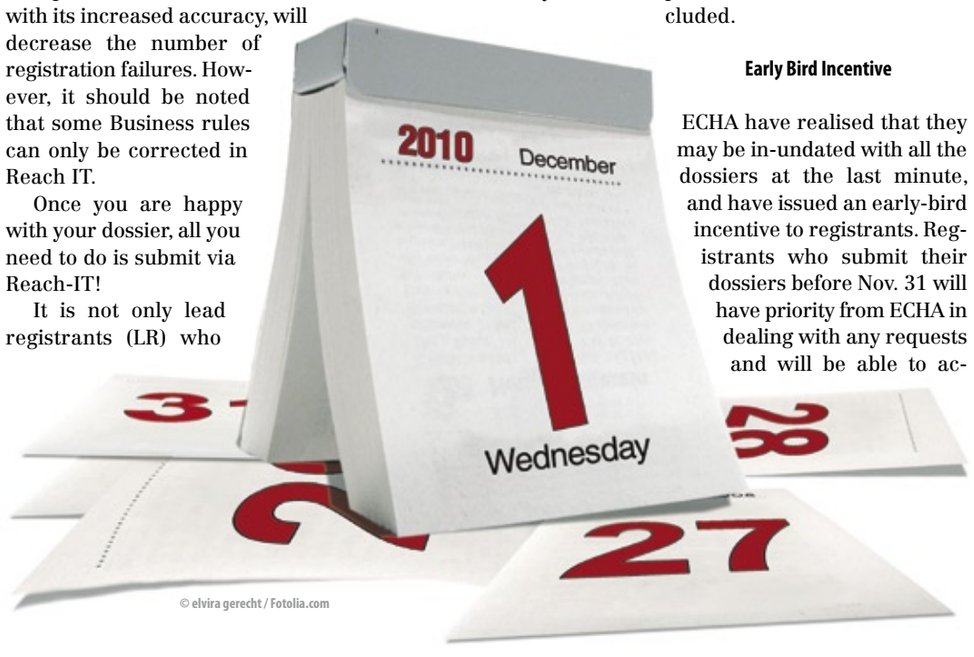
To see if your documentation is acceptable from a technical viewpoint a plug-in tool is available that will run a technical completeness check (TCC) on your IUCLID dossier. This tool highlights any gaps in the dossier that will need completing before submission, to avoid it being rejected by ECHA. The process is very much one of iteration, as the tool may reveal more gaps on subsequent runs. Although not a concrete failsafe for ensuring that the dossier will be accepted, the TCC tool will ensure that the dossier is robust. The most recent version of the TCC was released in July and now includes a check for compliance with business rules, inquiry and Classification, Labelling and Packaging of Substances and Mixture (CLP) notifications. It is hoped that this new version, with its increased accuracy, will decrease the number of registration failures. However, it should be noted that some Business rules can only be corrected in Reach IT.

Once you are happy with your dossier, all you need to do is submit via Reach-IT!

It is not only lead registrants (LR) who need to plan carefully for these next steps. Joint registrants (who are encouraged in Reach) with a 2010 deadline may only submit their necessary information when the lead dossier has been successfully submitted. Also, how a particular substance may be used is included in the registration and is it is important that downstream users of chemicals have made their uses known to their supplier so that these can be included.

WRc and NCET

The National Centre for Environmental Toxicology (NCET) within WRc can assist with Reach obligations at all stages of the process. The NCET team consists of experienced mammalian and eco-toxicologists, risk assessment analysts, chemists and experts on Reach legislation. NCET is able to provide advice, conduct chemical safety assessments, and prepare registration documentation to aid in the meeting of submission requirements.



Early Bird Incentive

ECHA have realised that they may be in-undated with all the dossiers at the last minute, and have issued an early-bird incentive to registrants. Registrants who submit their dossiers before Nov. 31 will have priority from ECHA in dealing with any requests and will be able to access assistance over the phone, which may be vitally important when ensuring that everything is submitted correctly. To have access to this service, LRs have to notify their appointment in this role via the web form on ECHA's website and create the "joint submission object" in Reach-IT.

ECHA has assured stakeholders that they are ready and are able to cope with the massive influx of registration expected.

CLP Coming Up Quickly

Also, don't forget that CLP notification is required by the quickly following deadline of the Jan. 3, 2011, when notification of the classification of substances on the CLP inventory is required by ECHA. Registrants submitting by December 2010 can notify as part of their registration.

Consequences

Only substances that have been registered can be used legally (taking into account the registration dates) within the European Union. Therefore, any of the substances to be registered by 2010, that have not been registered – or have been rejected for failing the completeness check – will be deemed to be in breach of the regulation.

Reach is enforced at the state level, with an overall Forum for the Exchange of Information on Enforcement operating at EU level. Each member state has put into place varying levels of enforcement, from encouraging better tactics, all the way to fines, which can range from €50,000–€100,000 for the first infringement.

Summary

The first deadline for Reach registration is only a couple of months away, and approaching fast so there is little time to waste. Unless data are submitted to ECHA before the deadline, companies will not be permitted to market their products within the EU.

Are you ready?

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Reaching Out, Working Together

Communication Vital within SIEFs

Exchanging Information – The first deadline for Reach registration is approaching fast. This process requires that future registrants work together in Substance Information Exchange Forums (SIEF) in order to submit one joint registration dossier for one substance. In its efforts to make this registration process a success, Mercedes Viñas, manager of chemical regulation at Cefic, along with the Cefic SIEF working group have developed recommendations and tips in order to allow SIEFs to deliver.

Following the pre-registration phase, companies who have the intention to register the same substance are put in contact via Reach-IT system. Once the sameness of the substance is confirmed, companies can form a SIEF for that substance.

SIEF members need to nominate a lead registrant (LR) to submit the joint registration dossier on behalf of the SIEF members. The joint submission contains the main part of the technical dossier including the classification and labeling of the substance, study summaries and the proposal for further testing, if applicable. The rest of the SIEF members must still do a separate registration after signing up to the joint submission created by the LR in Reach-IT.

Recommendations For LR

Most of the recommendations for LR to kick off the activities in the SIEF should have taken place by now. Those include sending out a survey on the registration intentions of the SIEF members, establishing a system to support communication and keeping all the members of the SIEF informed. LR should have also coordinated the agreement on substance identity: indeed, the name and identity of the substance to be used for registration purposes should be agreed by all SIEF members.

Cefic recommends members of a SIEF to agree on operating rules, for example using the available Cefic model agreements.

It is extremely important to keep the SIEF regularly informed on the progress towards the joint submission, keeping communication channels open. For that, it is also advised to establish a single contact point for the SIEF and make this contact point known to all members. LRs are also advised to keep the SIEF distribution list up-to-date, taking late comers into account. Also, the use of old versions of software for SIEF communication is preferred in order to avoid problems when opening communications.

Communicate decision on the scope of Joint submission: Article 11 of the Reach Regulation defines the information that must be submitted jointly and the information that must be submitted individually by each registrant. There is also some information for which the registrants can decide whether it is submitted jointly or separately.

The scope of the joint submission, and particularly whether the Chemical Safety Report (CSR) is done and submitted jointly, must be communicated to all SIEF members as soon as possible.

If it is not decided to do a joint CSR, this very demanding task has to be carried out by the individual registrants (for all volume bands greater than 10 tons/year).

It should be noted that the CSR may need to be updated once the outcome of the newly generated tests is available, if any. Some SIEFs may decide to prepare the CSR jointly but submit it separately. This option may facilitate subsequent updates, which can then be handled by individual registrants.

Please consult Cefic guidance on ES development and Supply chain communication for more information and start early!

The other points that the LR should pay attention to are to set up an efficient system for invoicing and payment, find out availability of data, and create a joint submission in Reach-IT.

Besides the discussions regarding data sharing and the preparation of the registration dossier, it is highly recommended that all SIEF members (even with no intention to register) are informed of the agreed classification. This will facilitate having a harmonised classification in case SIEF members have to notify the substance classification to the European Chemicals Agency (ECHA).

Once the information is available and ready, attention has to be brought to the actual submission procedure. The submission process entails a number of checks, and many submissions may not be successful in the first attempt. Therefore, it is important to make sure your dossier passes the corresponding checks (in order of appearance):

- Business rules
- Technical Completeness
- Financial check (to check that registration fee has been paid).

We insist that SIEF members don't forget to activate the confidentiality claims if they wish to prevent some data from being published! ECHA has published a manual that explains which fields of the registration dossier will be published unless claimed confidential.

Please check Cefic tips on how to overcome the business rules and available information at the ECHA website.

All SIEF members need to take into consideration future updates of the registration dossier (joint submission) that may occur beyond the registration deadline, for example:

- The follow-up of test proposals for which ECHA gives a green light. The tests related to such proposals will need to be carried out, their results evaluated and submitted jointly.
- ECHA may also request additional information following the evaluation of the registration dossier. SIEF members need to decide beforehand the way such requests will be handled.
- Moreover, newcomers may come into the picture, for example companies who start to manufacture/import the substance for the first time may want to join the SIEF and the Joint submission in the future.
- Updates of the CSR may be needed following the outcome of tests.

Therefore, companies should bear in mind that SIEFs will be maintained at least until 2022 and beyond!

Cefic Recommendations for All Co-Registrants

The LR is not the only one who has work to do. All other members of the SIEF have to do their part and prepare and submit their individual registration dossiers. Although they are smaller dossiers, this task should not be underestimated.

First of all, be aware of deadlines! Cefic has prepared a chart that shows the main tasks that need to be carried out in the SIEF and the recommended timing for these tasks. This chart may give companies a useful overview in order to monitor the progress of the various SIEFs they are involved in and react if necessary. The chart follows the Gantt chart structure and can be found at the Cefic website, section "Reach/Reach for industries."

Find out the scope of joint submission and in particular whether the CSR will be jointly submitted:

If the CSR is not submitted as part of the joint submission, each individual registrant needs to prepare and submit their own individual CSR. This task may be quite burdensome; therefore it is central to find out whether you have to do it as soon as possible.

Before you submit your dossier as a member of a Joint submission, the following steps must be followed:

- Sign up to the joint submission: Once the joint submission object (JSO) is created by the lead registrant in Reach-IT, it is always associated with a name and a specific unique token generated by Reach-IT. The lead has to communicate this combination (joint submission name and token) to those SIEF members that have fulfilled the corresponding conditions agreed in the SIEF operating rules. Cefic encourages SIEF members to sign-up to this JSO in Reach-IT as soon as they receive the token.
- SIEF members need to wait for the LR to submit his registration before submitting the individual registrations as JS member.
- Each member of the SIEF should make sure that the dossier passes business rules and completeness check before submission. As explained above, there are a number of checks that the dossiers undergo in the ECHA systems. It is very important that individual registrants become familiar with these checks, in particular the business rules. Please see below links for more information.
- Set-up an efficient system for payment of registration fee: The companies' accounting departments should be informed about the upcoming Reach costs and invoices. Cefic recommends to considering the set up a different legal entity and separate bank account for SIEFs transactions. Outsourcing is also a possibility.
- Don't forget Classification and Labeling (CLP) notification! If the individual registration is not submitted by December 2010, a separate notification of the substance classification may be needed.
- It is highly recommended that all SIEF members (even with no intention to register) are informed of the agreed classification and on the possibility to join the joint notification if there is one.

Companies should bear in mind that SIEFs will be maintained at least until 2022 and beyond! As explained above, SIEFs may need to continue working together in case of newcomers, or requests for more information from ECHA.

Cefic recommends establishing clear and transparent SIEF communication, using available guidance and tools as much as possible and becoming familiar with the submission process in order to have a smooth registration well in advance of the Dec. 1 registration deadline.

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More Links

ECHA Guidance on SIEF:
http://echa.europa.eu/sief_en.asp
ECHA Guidance on data sharing:
http://reach.jrc.it/docs/guidance_document/data_sharing_en.pdf
ECHA manual on business rules:
http://echa.europa.eu/doc/reachit/how_pass_business_verification.pdf

Surviving Purple Fever

Navigating the Minefield of Labeling Under the CLP

Labeling is Mission Critical – Within the last several years, the industry has seen an unprecedented change in the legislation that impacts the chemical industry and users of chemicals. Reach and the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) have been the main drivers.

Fraser Goodey
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The GHS addresses classification of chemicals by classes of hazard and proposes harmonized hazard communication elements, including labels and safety data sheets (SDS). It aims to ensure that information on physical hazards and toxicity from chemicals is available in order to enhance the protection of human health and the environment during the handling, transport and use of chemicals. GHS also provides a basis for harmonization of rules and regulations on chemicals at national, regional and worldwide level, an important factor also for trade facilitation. The EU has implemented the United Nations' GHS model regulation into EU law as the Classification, Labeling and Packaging (CLP) of chemical substances. CLP is currently based on the second revision of UN GHS.

CLP includes its own nuances, additional hazard classes, etc. and inherits some of the basic features and procedures from the Dangerous Substance Directive/Dangerous Preparation Directive (DSD and DPD). CLP will eventually supersede DSD and DPD. These catalyst legislations have changed the rules of the game when shipping products within the EU and external markets.

The European chemical industry is fortunate that CLP, like its predecessor, associates symbols based on the product/substance classification. When Occupational Health and Safety Association (OSHA) in the U.S. finally implements GHS, they will be introducing for the first time labeling based on prescribed symbols. The education and re-development of labeling will be a massive undertaking.

That said, in Europe we still have large hurdles to overcome. The starting point of how you manage and label your goods today plays a large part in how easy or difficult it will be to implement CLP labeling into your business. Labeling is mission critical. If a product can't be labeled to meet industry legislation, then it can't be shipped.

Labelling is Complex

So how should labeling be approached today? There are many different starting points and levels of sophistication and complexity.

There is no standard methodology that companies use to implement labeling. It can be a standalone process handled at a business unit, country level or centralized within the corporation. Labelling may be outsourced to a third party. Regardless of the methodology used, there are numerous stakeholders including sales, marketing, EH&S and IT that are typically spread across the organization.

Because labeling is mission critical, companies need to be able to label products 24 X 7, in multiple formats and in multiple languages. Hazard information needs to be made available in the native language of each country where the product will be transported/sold.

Data for labels comes from multiple sources including the ERP system, EH&S, SDS systems and logistics.

The actual physical printing of labels adds another dimension of complexity. There are different types of printer technologies such as laser and thermal and many different label substrates and inks (black and color). Labels may be pre-printed or images can be lithographed onto tins or consumer packaging.

A company's supply chain, production and logistics play a large part in how they approach labeling and manage the associated costs.

Additional GHS/CLP Challenges

With CLP, some classification criteria is different to the DSD/DPD, or uses different cut-offs. In general the consensus within the industry is that more substances under GHS/CLP will be classified as hazardous. For example, under the new legislation, the flashpoint cut off for combustible/flammable liquids was increased from 55 °C to 60 °C (category 3 for flammability); current hazard symbols defined in DSD/DPD have been in place for years in Europe and are being replaced with CLP hazard pictograms; DSD/DPD has seven symbols whereas CLP has nine; the CLP pictograms are black symbols outlined by a red diamonds on a white background. An extra level of complexity will be added as the size of pictograms is not harmonized worldwide; currently, EU pictograms are specified at a different size than pictograms in Korea and Australia, etc.

	DSD / DPD Symbols	CLP (GHS) Symbols
Health Hazards		
Physical Hazards		
Environmental Hazards		

Example Of Impact

Here is an example of the impact of the CLP for one marine paint company, who recently conducted an impact analysis on their product portfolio. Under the DSD/DPD, 47 % of their labels required one hazard symbol and 46 % required two hazard symbols. With CLP, the analysis showed that 16 % of their products will require two pictograms, 63 % will require three pictograms, and 10 % will require four. With additional pictograms come additional signal words and hazard statements. Under CLP, 110 precautionary statements will replace 50 safety phrases needed under DSD/DPD. The regulation states, "Not more than six precautionary statements shall appear on the label, unless necessary to reflect the nature and the severity of the hazards."

Selection of these precautionary statements may be a complex process for some products, because there is currently no guidance on the use of each individual statement, as there was for the safety phrases. This is an issue that is currently under discussion at the level of the UN Economic Committee for Europe (UNECE) subcommittee of experts on the GHS.

So Much Information, So Little Space

The result of the additional pictograms and text means that greater pressure is applied to the space on the label; and the only way to reduce this is to reduce the number of languages printed. Many companies predict they will be able to print a third less languages on their labels which may force them to print additional labels.

To satisfy the need for more label space, firms have been exploring the use of different types of labels such as fan folded booklet labels. There is nothing in the legislation that prohibits fan fold labels, however some national authorities are discouraging the use of them.

Pre-printed label stock is very expensive and companies will have to review their label requirements due to the increase in pictograms. One favored option is to have one label with the maximum amount of pre-printed red diamond borders. This has initiated a lively discussion on what to do with the empty borders when all pictograms are not in use. Should they be left blank? Should they be blacked out? How will the end user interpret this? Forums are alive with discussions on this issue. It seems that several national authorities take a dim view on empty boxes this. Guidance from European Chemical Agency (ECHA) is expected soon.

Some companies may look to invest in color printers, or due to an increase in the need for label stocks they may purchase additional black printers. There has been no major advance in printer technology to support the new CLP labeling challenge. For colour printing, companies are limited to laser printers and most chemical companies use thermal printers with black ribbons (ink).

Time Line for New Changes

Organizations must re-classify and re-label their substances by Dec. 1, 2010. To help with products that are already in the supply chain, a further two year transition period, until Dec. 1, 2012, is also available for substances that are already classified, packaged and labelled, and placed on the market i.e. already "on the shelf", before Dec. 1, 2010.

Mixtures must be re-classified and re-labelled by June 1, 2015. Similarly to substances, a further two year transition period, until June 1, 2017, is available for mixtures that are already classified, packaged and labelled, and placed on the market i.e. already "on the shelf" before June 1, 2015.

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CLP as an Agent of Change

Although there are a number of challenges when making the transition to a CLP-compliant system, the CLP provides an opportunity to consolidate and streamline processes from a global perspective. Here are 10 steps that companies can take to review their existing solutions and ensure a smooth transition.

Monitor country adoption of GHS/CLP – Stay current with legislation changes and adoption so that you can keep your plan on track. Your process needs to be able to track country-specific requirements, alert you to any changes, and assess the speed in which you can implement changes.

Maintain dialogue with stakeholders – Involve all stakeholders including sales, marketing, logistics and IT at the beginning of the assessment, and throughout the whole process, not when it is completed.

Run impact analyses on product portfolio – The ability to run an automated impact analysis and classification across the entire product portfolio at one time provides the opportunity to assess the impact for R&D, sales and the supply chain.

Set up a time line – Work backwards from the deadline and take into consideration the shelf life of your products (mixtures). If the deadline is EU 2017 (product already in supply chain) and the shelf life is five years, then the product needs to be re-labeled by 2012.

Review approach to labeling, consolidation, optimization – Consider consolidating data sources and streamlining processes.

Review purchasing agreements, stocks, labels, cans, etc. – Ensure that there are no long-term agreements in place with pre-defined delivery dates of label stock, and pre-printed packaging. Run down old stocks of pre-printed labels and packaging to minimize cost and waste.

Review label design and stock – Determine if the current design, type and stock can handle CLP changes. Label designs need to maximize space to avoid companies introducing new stock keeping units (SKU) to handle the language requirements. New requirements require a solution that can provide symbols with and without borders as well as logic to combine GHS and transport symbols where appropriate.

Review the logistics cycle – Determine if the production run is for stock or order, introduce new label concepts, re-labeling when destination known, etc.

Review IT infrastructure for labeling and hazard communication – The key to ensuring accuracy is consistency. Guarantee that the data sources driving the label are reliable and consistent. Changes in the underlying data set for the formula or SDS should be able to be handled at the same time. Hazard communication needs to be driven from one platform or from one consistent framework.

Determine costs – The sooner you start to digest the impact of the CLP on your business and especially labeling, the lower the cost will eventually be to your company as more solutions will be available to you.

The Persistence Of Time

With REACh Stealing the Spotlight, Many Have Forgotten About CLP

Forgotten Regulation – Walking in the footsteps of Reach the 2008 EU Classification, Labeling and Packaging (CLP) Regulation (Regulation (EC) 1272/2008) has received less attention than it deserves from authorities, supply chains and senior management, who are still trying to cope with the massive resource and business implications of Reach. Andrew Fasey explains why despite the pain, businesses stand to gain from putting in place comprehensive compliance strategies for the EU regulation on classification, labeling and packaging of substances and mixtures (CLP).

Andrew Fasey
founder, Protection Through Knowledge

The Reach and CLP work hand-in-hand yet, owing to its origins, CLP has an international dimension that is both important and fascinating and which promises a vision – one day – of a world far less at risk from the hazards of chemicals than today. However, the agents of this change are expected to be companies who may have a long way to go to understand the compliance challenges posed by CLP and its underpinning regime.

The Background

The CLP Regulation entered into force on Jan. 20, 2009, following its publication on Dec. 31, 2008 in the Official Journal of the European Communities. Although it has not attracted the political furor that Reach did, in many ways it will have as important repercussions for companies. Its requirements require rapid, co-ordinated, effective and efficient action to ensure compliance. Planning to meet these requirements effectively and efficiently, preferably in co-ordination with the requirements of Reach, will give many advantages to the companies concerned.

The Deadlines

One key difference from Reach is the very obvious international dimension. CLP implements in the EU the Globally Harmonized System for the classification and labelling of chemicals (GHS). The GHS will continue to be implemented in most countries across the globe over the coming years. Time and effort spent implementing CLP in the EU should therefore confer additional benefits on companies in improving their access to non-EU markets as well. It is therefore important for such companies to plan their implementation activities from a global perspective. Unfortunately, the lead times for many posed specifically by the CLP regulation will be short. The three most pressing and important deadlines under CLP are:

- Dec. 1, 2010 – the deadline for the (re)classification of substances in accordance with CLP.
- Jan. 3, 2011 (in practice Dec. 24, 2010) – first deadline for the notification to the classification and labeling inventory of substances placed on the market on Dec. 1, 2010. (notifications are due 30 days after placing on the market starting from Dec. 1, 2010.
- June 1, 2015 – deadline for the (re)classification of mixtures in accordance with CLP.

Safety Data Sheets

It should not be forgotten that the new requirements for safety data sheets (SDS), closely linked to CLP of course, start from Dec. 1, 2010 as well. Annex II of Reach sets out the requirements for SDS. This Annex was amended through the Commission Regulation No. 453/2010 that was published on May 31. This amendment makes very significant changes to the SDS provisions by introducing a new version of Annex II that must essentially be complied with from Dec. 1 for substances and a further new version that will be applicable from June 1, 2015 additionally for mixtures (although this basically only removes a requirement to continue to show classifications as per the "old" system under the Dangerous Substances Directive and Dangerous Preparations Directive). It should be noted that the "new" SDS rules for mixtures can also be applied from Dec. 1, as long as classifications under DSD/DPD are shown as well as those arising from application of CLP.

CLP – The Bottom Line Hits

CLP will impose a variety of costs on companies depending on their business, its scale and location, and on the position in the supply chain. The following activities will be required by most companies and will need to be resourced:

- Inventory preparation and updating
- Systematic reviews of requirements from, and related to, CLP
- IT systems to manage CLP
- Reclassifying, relabeling and repackaging products
- Updating SDS
- Training (e.g. staff implementing CLP and workers using classification and labeling information)
- Following CLP and GHS developments (the GHS is updated every two years and CLP will need to follow these changes. The EU will also introduce other changes such as adding substances to the list of those that are harmonized in the EU)
- Testing for physicochemical properties of substances and mixtures if this information does not already exist (NB. this is a requirement now but it is often overlooked).

Piecemeal CLP Compliance – The Risks

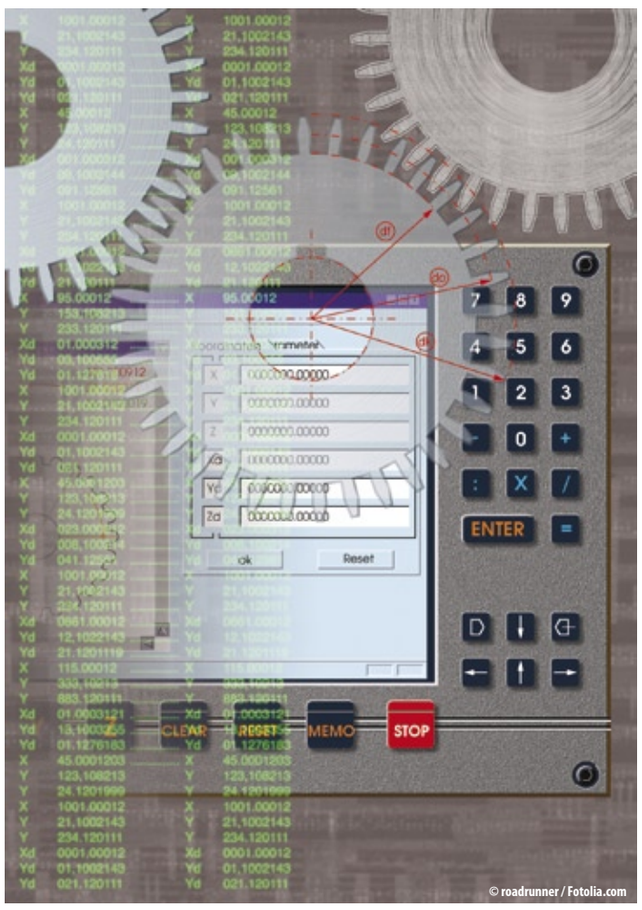
In a short article, it is not possible to tell companies everything they should do to ensure effective and efficient compliance. It is sadly far easier to inform them of what might happen if they fail to do a good job:

Continued Page 18

Time To Update?

Control System Migration Strategies

Automation – Migration could be the biggest single issue facing automation end users today. ARC estimates the value of the installed base of automation systems reaching the end of their useful lives at approximately $65 billion. This represents a big opportunity for both end users and suppliers.



Larry O'Brien
Research Director, Process Automation

Dave Woll
Vice President, Consulting Services

Process automation suppliers have significantly expanded their migration offerings compared to seven years ago. This is the case both for migrating from competitors' systems and for migrating from a legacy system to a new system from the same supplier. It has also become apparent that migration is no longer strictly a distributed control system (DCS) issue, but has grown to encompass other types of systems. These include quality control systems (QCSs) in the pulp and paper industry; supervisory control and data acquisition (SCADA) systems for oil and gas; water and wastewater; and power distribution applications; burner management systems; and other automation platforms.

Users can take any of a number of different approaches when evaluating potential migration suppliers. For many end users, migration represents a significant enough step change to warrant a complete review of all the supplier offerings in the marketplace. ARC advocates that you be just as rigorous in your approach for selecting a migration supplier as you would for control system selection. One thing end users should take into account is the potential supplier's ability to provide a solution that minimizes downtime and risk, while providing a tangible business value proposition that will have a positive economic impact on your business. No matter how smooth the implementation may have gone, if you simply end up with a like-for-like functional replacement, you failed to exploit an excellent opportunity to improve business performance.

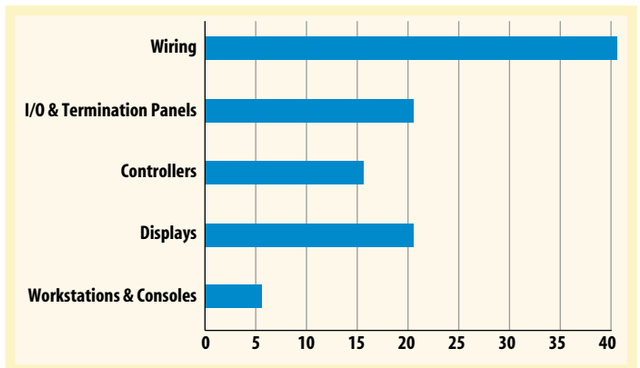
Process Automation System Lifecycle

DCSs were first introduced in 1975. While the lifecycle of these systems can be quite long, this varies from component to component. The lifecycle of DCS hardware components, such as wiring and I/O, can be 30 years or more. Controllers have a slightly shorter lifecycle, but also tend to last upwards of 20 years or so. The workstation and application layer of the system has a much shorter lifecycle. Most major suppliers announce major version changes of their HMI and operator software every eighteen months or so. HMI workstations may not be able to run the latest OS after only a few years and must be regularly replaced.

Due to these different lifecycles for various system components, most older installed systems today represent an amalgam of older I/O and wiring infrastructure, combined with not-quite-so-old controllers and newer operator workstations, servers, and related applications. The closer you get to the I/O and wiring infrastructure, the more difficult it is to articulate a business value proposition for control system migration.

When Is The Right Time to Migrate?

It's becoming more and more difficult to justifying capital spending on automation as end users increasingly focus on getting the most out of their installed assets. Any automation project today requires a compelling business case. ARC has categorized several scenarios where migration is required. Like other capital assets, automation assets have a lifecycle. At the end of that lifecycle, it becomes necessary to plan and execute a system migration. Any or all of the following situations can mark the end of the lifecycle:



Average DCS component lifecycle in years.

Reliability Issues

Reliability threatens operational continuity and threats can emerge in two ways.

Basic repair: frequency and criticality of failures. An increase can indicate the end of the lifecycle.

End of Support: Suppliers regularly obsolete or replace products with functional equivalents, or in the worst case, their businesses fail. Any of these can trigger end of life planning.

Unsupportable Opportunity

The capability of automation assets continuously increases and legacy assets often cannot satisfy new business opportunities. Many times, these opportunities become evident when functional requirements expand beyond fundamental manufacturing. When the existing automation cannot satisfy these new requirements, it may be time to consider migrating to automation assets that can.

Of course, the case for migration is most urgent when the old system reaches the point where an impending plant shutdown or incident is a real possibility. The system may be so old that replacement parts and support are unavailable or are extremely limited and cost prohibitive. The old system may not support many of the available new technologies that provide real economic advantages, such as plant asset management (PAM) applications, fieldbus, advanced production management applications, and Ethernet-based control networks.

Even worse, the old system can be burdened with a high volume of custom code and custom point-to-point integration that make long term support cost prohibitive, as companies struggle with shrinking labor resources and a lack of qualified personnel. The veteran who understood all the custom code in place (probably because he/she wrote it), will retire and be replaced by a worker who knows only open technologies and standards.

Of even greater importance is the opportunity cost associated with supporting an outdated system. This is the cost of a business opportunity missed when your system is not advanced, flexible, or functional enough to take advantage of a swiftly emerging or fleeting opportunity. Having an old or outdated system installed can actually result in direct losses. This is especially true if the end user lacks the visibility into plant operations that enables him or her to prevent abnormal situations and avoid supply chain disruptions. An inflexible system hinders the ability to react quickly to shifts in market demand.

Primary Migration Alternatives

Several approaches to migration exist in the marketplace today. These approaches usually vary according to the level of functionality to be provided in the target automation system. When choosing a migration approach, there are several possibilities, each with their own particular strengths and weaknesses. Usually, the first consideration is whether to stay with the incumbent supplier or move to a different supplier. Staying with the current supplier is, in many cases, the easiest migration to perform, especially if the incumbent remains a good business partner.

Five basic migration approaches and combinations are possible: replacement, gateways, I/O connect and wiring kits, I/O substitution, and encapsulation. How much of the system you want to replace will largely dictate the approach. The decision to stay with your existing supplier or migrate to a new supplier will also influence the approach you ultimately choose.

Replacement

The first and most obvious is the bulldozer style of migration. This eliminates all existing control system equipment and replaces it with new equipment. This is the most costly in terms of hardware, software, labor, downtime, and training. It also involves the greatest amount of risk, because you cannot go back to the old system if the new system does not perform as anticipated.

Gateways

Gateways are a well-established way of linking one control system to another. From a functional view, gateways can project added functionality; both from the legacy system to the target system and from the target system back to the legacy system. From a logical view, gateways perform protocol translation and throughput normalization.

I/O Connect and Wiring Kits

Many suppliers offer to migrate to a new system while preserving the user's existing I/O terminations and field wiring. Cabling solutions, otherwise known as wiring kits, involve mapping I/O from the existing termination assemblies to the new system through the new I/O. Suppliers also offer direct I/O bus interfaces that allow users to keep their legacy I/O while moving to a new control platform. While this preserves the user's investment in legacy I/O terminations and infrastructure, installation can take a long time and involves an increased footprint and possible problems in I/O mapping.

I/O Substitution

An alternate approach is to offer I/O cards that fit the installed system's form factor, allowing the user to migrate to a new system with no changes in wiring, installed cabinetry, or hardware infrastructure. This can be a very cost-effective option, but not one offered by all suppliers.

Encapsulation

Most suppliers also offer a software component solution that provides code translation or object wrapping. These solutions can be based on technologies such as OPC, or more proprietary in nature. This approach is functionally similar to a gateway. Suppliers with OPC offerings usually add their own proprietary extensions that provide additional security and/or reliability.

Supplier References Are Critical

Process automation system suppliers clearly understand the importance of their installed base. All the major suppliers focus on retaining their installed base by making sure that they have a path forward from their legacy system to their latest process control technologies. Some have a bigger challenge than others in this respect due to multiple system offerings, largely a result of industry consolidation. Ultimately, all suppliers want to get to an automation platform that is both scalable and "future proof."

However, the point at which existing users begin to consider migrating to a new platform also represents a point of vulnerability for suppliers. Even if the user is generally satisfied with their existing system supplier, it is likely that they will at least explore migration options from competing suppliers.

From the user's perspective, when considering migrating an existing control system to a different supplier's platform, it's important to look under the covers. Users should ask the new prospective supplier for specific references from other users who have performed similar migrations and diligently follow up on these by discussing the implementations with those references. Be sure to ask what they liked and what they didn't like, and learn about potential pitfalls that could be avoided with their own implementation.

And, for that matter, it certainly couldn't hurt to ask for references from other users, even when considering migrating from one system to another within the same supplier's lineup.

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Total Hopes to Sell Lindsey Refinery by Year-end

French oil company Total has received offers for its UK Lindsey refinery and hopes to sell it by the end of the year, Chief Executive Officer Christophe de Margerie, said. "We have some offers, we're working on it. We'll talk about it when the moment is right but for the moment the target is that we sell it at the end of the year," de Margerie told journalists on the sidelines of a conference organized by French employers' union Medef. Referring to the wider market de Margerie said he thought the oil price was "at the right level," while gas prices were low. "That is a concern for long-term investments but at the same time when you invest today, it is to produce in 8 to 10 years time," he said. ■

Merck Postpones Dutch Closures

U.S. drugmaker Merck & Co. postponed the planned closures of some Dutch operations announced in July while it negotiates with executives and workers on potential alternatives.

Merck said in July it would shut eight research sites, including three of the unit formerly called Organon in the Netherlands, as part of its restructuring programme after its merger with Schering-Plough. ■

Safe Flow Measurement

Corrosive Chemicals Pose Challenges

Flow Challenge – Measuring the flow of chemicals can prove very difficult if the underlying manufacturing process is not handled or controlled properly. The often corrosive nature of such liquids challenges conventional measurement methods based on insert-type sensors, which may ultimately jeopardize the quality of the end-product. This was the challenge facing a chemical company in China when looking for a number of flow meter technologies to be used in one of its Chinese manufacturing plants slated for expansion.

The upgrade that the chemical company planned would affect a facility that manufactured glyphosate at an annual production rate of 20,000 tons. With the expansion, another 50,000 tons would be added to the facility's output, making it the largest glyphosate manufacturing facility in Asia. Glyphosate it is one of the most widely used herbicides and is commonly used to kill weeds and plants in industrial as well as home use. Although not the case at this facility, glyphosate can also be used to manufacture water treatment chemicals, flame retardants, and lube oil and paint additives.

Precision Essential to Product Quality

One major step in glyphosate manufacturing is to make dimethyl phosphate in which phosphorus trichloride (PCl_3) is used. As part of this process, PCl_3 and methanol are pumped at a set ratio through two separate lines to a reactor where a chemical reaction under vacuum conditions takes place. This process, which is called esterification, leaves behind only dimethyl phosphate.

The quality of the final glyphosate product is directly related to the precision of the injection ratio between the PCl_3 and methanol. One of the major problems with PCl_3, however, is its aggressive nature, which makes it challenging to control:

- PCl_3 is highly flammable and generates toxic hydrochloride fumes when burning
- When in contact with air, PCl_3 becomes very corrosive
- In an uncontrolled or poorly controlled environment, PCl_3 crystallizes easily
- PCl_3 becomes explosive when in contact with water or acid

Due to these chemical properties of PCl_3, it had been difficult for the chemical company to find a flow measurement technology capable of obtaining the desired results in regards to precision and reliability while maintaining the required degree of safety in the production process.

With a non-intrusive clamp-on flow meter, contact with the medium is avoided, alleviating some of the issues normally associated with measuring highly corrosive chemicals.

Manual Flow Control Leads to High Raw Material Consumption

In the past, mechanical insertion-type flow meters had been used whose gears were easily corroded by the chemical. This would result in crystal build-up with poor or failing meter performance as a consequence. To remedy the situation, the meters had to be frequently removed for cleaning, forcing the manufacturer to rely on manual flow control. That, in turn, caused much higher raw material consumption compared to what could be obtained by automating the process and also created fluctuations in product quality.

Although the chemical company had considered using clamp-on ultrasonic flow meters, which would normally be considered an optimal solution for such an application due to the non-intrusive installation method, only narrow beam ultrasonic flow meters had been used to conduct tests. The results were not promising, primarily because of the low flow rates of 0.1–0.15 m/s (0.3–0.5 ft/s), small diameter pipes in the DN50 (2 in.) range, and the presence of aeration in the chemical. All of these factors prevented the narrow beam clamp-on ultrasonic flow meters from performing optimally, forcing the company to discard the technology as a viable option.

Testing Before Committing

For the facility expansion project however, the clamp-on ultrasonic flow measurement technology was given a second chance. Siemens offered to conduct a test that would demonstrate how precise and reliable measurement could be obtained while allowing for the esterification process to be fully automated. The means to achieve this was the Sitrans FUS1010 clamp-on ultrasonic flow meter.

The dual channel meter was tested for one month under various conditions. With reference flow volumes ranging from 186 to 744 m³/m (6,570 to 26,275 ft³), the Sitrans FUS1010 was able to measure with an accuracy of up to 0.44 percent of flow rate. The chemical company was very satisfied with the results, especially when taking the low flow rates, small pipes and aeration conditions of the liquid into consideration.

Wide Beam Vs. Narrow Beam Measurement

What makes the wide beam technology so suitable for chemical applications is that the resonant frequency of the pipe wall is utilized to achieve a strong ultrasonic signal. Upon installation, the transducers broadcast signals with varying frequencies. The aim is to find the frequency that best matches the pipe wall. When found, the signal is transmitted into the flowing media with the wall of the pipe acting as a waveguide. This method allows for a low transmit voltage of approximately ± 15 volts and produces a focused, coherent signal that covers a large axial area (fig. 1). Because this technology makes use of a wide beam it is much more resilient to aeration and suspended solids that may exist in the fluid. It would simply require a much higher concentration of particles or higher percentage of aeration to disturb the signal to a point where measurement will be impacted.

Typically, this does not occur even with fluids containing particles in the ten to 12% range.

The narrow beam method, on the other hand, which is also known as shear mode, generates a high but narrow energy acoustic signal, typically 1 MHz, which is received by the opposing transducer (fig. 2). The elevated transmit voltage combined with the single transmit frequency often produces a high level of noise. This is ultimately present on the receive signal, producing a poor signal to noise ratio, which will diminish performance.

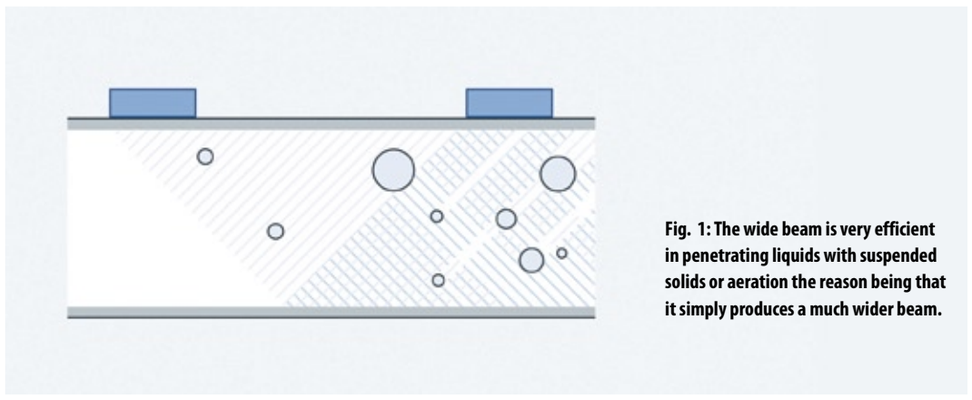

Fig. 1: The wide beam is very efficient in penetrating liquids with suspended solids or aeration the reason being that it simply produces a much wider beam.

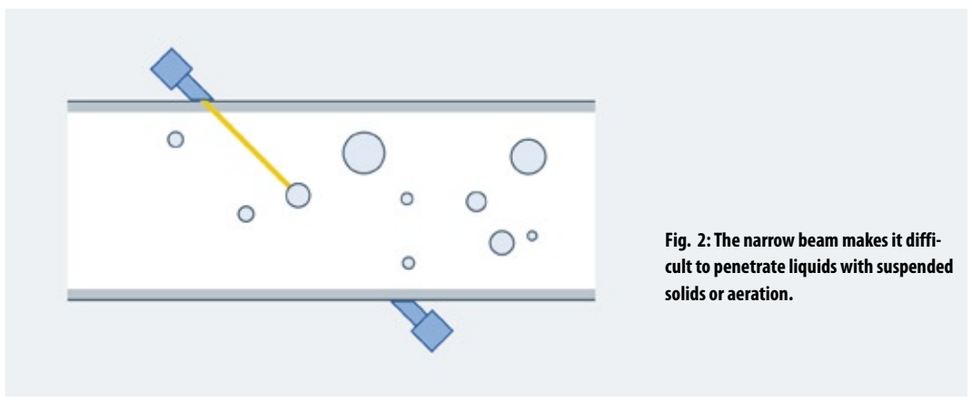

Fig. 2: The narrow beam makes it difficult to penetrate liquids with suspended solids or aeration.

Reaping The Benefits

For the chemical company, the determining factor was the clamp-on ultrasonic flow meter's ability to deliver on the precision and reliability parameters through its use of the wide beam transit time technology.

Accuracy, however, was not the only important benefit of the Sitrans FUS1010. With a dual channel flow meter they could measure both PCl_3 and methanol using only one flow transmitter, ensuring additional benefits. First and foremost, it reduces the total investment at each measurement point because only one meter is needed to measure on two pipes. It also maintains the system's integrity since the same supplier's flow meter delivers the complete solution. This facilitates the elimination of any errors and increases measurement repeatability and accuracy.

Another benefit that the chemical company was able to obtain using the Sitrans FUS1010 clamp-on ultrasonic flow meter was the measurement of the aeration percentage of the chemical. This information was used to identify process conditions in real-time, which aided in the selection of the optimal location – with less aeration – for the meter installation, and also the optimization of the process. Additionally, the clamp-on ultrasonic meter could be installed without opening the pipes or stopping the process, eliminating costly manufacturing down-time and subsequent system re-optimization.

Optimized Manufacturing Process

In the glyphosate manufacturing process, a varying ratio of PCl_3 and methanol will yield a differing end-product quality. By installing several clamp-on ultrasonic wide beam flow meters, the Chinese chemical manufacturer was able to improve the accuracy of the raw material injection ratio into the reactor, optimizing the manufacturing process and the product quality while reducing raw material consumption. All in all, the Siemens solution gave the chemical company an increased economic return and overall satisfaction.

Rocky Zhang

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IBC with EVOH Barrier also Ideal for Transport of TDI

PRODUCT Schütz has over the past few years developed some innovative new production techniques and products that have opened up new applications for IBCs (intermediate bulk containers). First and foremost, IBCs can now be used as a substitute for steel packaging. In this context, Schütz and Bayer Materialscience have successfully demonstrated in collaborative testing that the Schütz IBC with EVOH barrier is also suitable for the transport and storage of the hazardous substance TDI (toluene diisocyanate).

This particular isocyanate, like the chemically similar MDI (methylene diphenyl diisocyanate) is chiefly used as a raw material in the production of polyurethane, end products of which include foam mattresses and car bumpers and dashboards.

While MDI has been transported in composite IBCs for years, until now steel drums were the main option for TDI. The reason for this was the chemical behaviour of the HDPE inner bottles. In contact with TDI, namely, HDPE can swell by up to 13%, which in turn alters its profile of properties by up to 20%.

Schütz and Bayer MaterialScience – one of the foremost producers of TDI and MDI – have now discovered that this problem can be eliminated by using IBCs with an EVOH barrier integrated into the container wall.

Swelling Reduced to a Minimum

Swelling is reduced to a minimum, on the one hand, while on the other the ethylene and vinyl alcohol-based copolymer provides reliable permeation protection. This means that volatile ingredients are prevented from escaping into the atmosphere through the container wall and at the same time that filling goods are shielded from environmental influences, such as oxygen, penetrating it. Consistent quality is the result.

Moreover, users benefit from all the familiar handling and logistical advantages. By using composite IBCs instead of steel drums, they can save time and money during the filling and emptying of IBCs and also during all loading and transport processes. The container has the filling capacity of five drums but only takes up as much room as four. What's more, filling products can be hermetically discharged via the bottom outlet valve. The containers are naturally also included in the Schütz Ticket Service, which guarantees collection of emptied IBCs for reconditioning.

The innovative Security-Layer Technology developed by Schütz is what originally pointed the way for the new generation of EVOH IBCs. This extrusion blow-moulding process, during which six material layers can be processed simultaneously, was what first made it possible for a barrier to be sandwiched between two carrier layers of HDPE.

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Waste Not, Want Not

Getting on the Cutting Edge of Responsible Pharma Packaging

A Real Solution – An environmental revolution is underway that will impact communities, governments and businesses across the globe. Conservation and management of finite resources are at stake as we address the "perfect storm" of rising energy prices, societal and customer expectations to go green. The healthcare industry is no exception, and packaging will play a key role in providing solutions, as it represents upwards of 30–50 % of the overall waste stream. As manufacturers and suppliers position for the future, a clear understanding of customer requirements including return on environment will not only have a profound impact on package design, but present significant opportunity for those on the cutting edge of this revolution.

Kevin Mulligan
PTIS Packaging and Technology Integrated Solutions

Packaging performance in sustainability and environmental excellence are increasingly referenced by investors as leading indicators for management quality and long-term shareholder value throughout the entire supply chain. Performance based packaging metrics are the foundation that can be directly mapped to sustainability efforts, including associated impact on profitability, capital cost and increased revenue. When done correctly, suppliers, manufacturers, distributors and end users can share success with sound corporate environmental stewardship, profit improvement and growth.

Sustainability Scorecards Start With the Customer and End User

The use of sustainability scorecards has been widely recognized as the foundation of environmental preferred procurement (EPP) practices. Companies such as Wal-Mart, Procter and Gamble, and IBM have effectively and dramatically impacted package design criteria within retail and consumer markets utilizing these tools. Kaiser Permanente, the largest hospital group in the U.S. (spends more than $1 billion each year on medical products), expects to do the same by leading environmental stewardship initiatives within the healthcare community. Kaiser projects to roll out the first healthcare sustainability scorecard in conjunction with the Broadlane Group (key supply chain partner) by September.

What the Healthcare Sustainability Scorecard Measures

It is important to first understand that the healthcare sustainability scorecard is mapped to actual product use and from that, specific scores are provided for each supplier. These scores will then be included in the overall decision making process that will provide an environmental benchmark included in the procurement decision making process. More than 30 groups of specialty clinicians at Kaiser Permanente for example are responsible for selecting medical and pharmaceutical products.

"This score factors into clinicians' decisions-along with product performance and cost," said Robert Gotto, Kaiser's procurement director. Gotto believes the scorecard is a powerful tool. "It gives you detailed product information at the point when our clinicians are evaluating products, and they have the detailed information to make informed decisions."

This is a fundamental shift from the prior decision-making process where knowledge of packaging, chemical composition and environmentally friendly processes are unknown.

The healthcare sustainability scorecard will focus initially on a spreadsheet that suppliers fill out for each of their products, and it looks at 10 criteria. Six of those criteria relate to specific chemicals, and the other four involve the recycled content of the packaging. Based on a numbering system, an environmental factor to differentiate products and suppliers will be established.

Healthcare Scorecard is a Good Start

"Green washing" or misleading marketing claims can damage credibility and in serious situations, result in litigation. The use of sound metrics based on a clear understanding of the voice of customer and waste stream dynamics will not only avoid costly mistakes, but position organizations to reap benefits with increased profitability, sales growth and positive corporate perception. The healthcare scorecard is a good start, but much more is needed as we progress into the future.

The use of an acceptable life cycle analysis (LCA), one that is generated on mathematical modeling, and includes all appropriate factors associated with cradle to cradle metrics, is the foundation. Software applications such as the Wal-Mart model, Sustainable Packaging Coalition model continue to expand and improve. The ability to provide an objective assessment that supports a properly weighted average on all environmental factors will be key.

It will also be important to recognize and adjust to the dynamics of a changing waste management stream. The impact concerning waste to energy, biodegradability, recycling and landfill options can dramatically change design decisions and render a package as less than environmentally friendly if not done correctly. Maintaining a good understanding of voice of the customer, and evolving changes in the waste stream will be vital to an organizations success.

Use Sustainability For Market Edge

The medical waste stream represents significant cost to hospitals and end users to dispose of it properly. As hospitals embrace EPP, they expect to see cost savings, better regulatory compliance and enhanced corporate social responsibility for sustainable packaging. And they want it done right. Packagers who respond can gain a marketplace advantage. The following steps should be considered as part of an effective strategy:

1) Develop a mission statement for sustainable packaging

- No matter where you are along the packaging supply chain, make it part of your company environmental policy by taking the following actions:
- Get senior management to buy in.
- Make it part of standard operating procedures and incorporate as part of the new product.
- Development process, cost reduction and compliance requirements.
- Work collaboratively with other functional disciplines to support the strategy across your organization.

2) Develop a legislative benchmark and compliance strategy

- Understand the legislative requirement in all global locations where you sell products and packaging.
- Set action plans focused on compliance. Work with regulatory bodies across the globe as well as industry groups to develop sound legislative policy and positions. That is especially true for areas where your organization anticipates future requirements.

3) Continue an ongoing engagement with voice of the customer

- Understand strengths, weaknesses, and opportunities within the challenges of waste management. Do that for your organization, and do it for your customers. Know their waste management processes, trends and challenges.
- Understand present and future direction. That gives you the basis for developing effective strategies to better meet these evolving needs. In doing so, you enhance the opportunities to increase revenue, lower cost and prove the basis for good corporate citizenship.

4) Build metrics, corporate goals and competitive benchmarks on LCA modeling

- Be concerned about the perception of "green washing"-non-legitimate labeling and marketing claims.
- Use LCA models to support your efforts. They help you focus on source reduction and sustainable package material choice; identify sustainable manufacturing processes and equipment; impact the supply chain; and identify shared opportunities in cost savings with suppliers, distributors and end users.

Eliminate or Change Materials That Create Environmental Deficiencies in Medical Waste

Look to replace PVC and plasticizers. Use materials that are inert or non-harmful in common waste management technologies such as landfill, incineration, chemical disinfection, autoclave and microwave systems.

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In The Matrix

France to Use Datamatrix System for Pharma Traceability

Safety First – France is adopting the Datamatrix system to meet new regulations on the traceability of pharmaceutical products to increase patient safety. Avery Dennison is at the forefront of the Datamatrix barcoding technology that will become the accepted standard across France in January 2011. Other European states, such as the UK, Germany, Spain and Italy are looking to introduce similar regulations to improve consumer safety. 2D Datamatrix barcodes are able to store large amounts of information (up to 2,300 alphanumeric characters) on a small label. This makes it ideal for the small products and packaging often used for pharmaceuticals.

As of Jan. 1, new regulations created by the AFSSAPS (French Agency of Sanitary Safety and Health Products) will establish an improved coding standard for the French pharmaceuticals market. The new standard is designed to improve the traceability of medicines distributed in France and to increase consumer safety. From now on, a Datamatrix barcode containing the new CIP 13 standardized GS1 code, a batch number and the medicine expiry date will be printed on the production line as a replacement of the current French pre-printed CIP 7 standard.

As a result, quality of traceability will move to a higher level. The Datamatrix code will contain a unique number printed on each box, in accordance with the new principle of serialization. Avery Dennison is one of the first suppliers to propose complete Datamatrix integration solutions. These solutions will enable any pharmaceutical manufacturer to fully comply with the new regulation and improve traceability along their whole supply chain.

Improving the Distribution of Pharmaceutical Products

This regulation derives from the need to increase the control of the supply chain of medicines in order to guarantee the safety of patients. The aim of the new standardization is to improve the efficiency of batch recalls, to reduce errors, to combat counterfeiting and reimbursement fraud and to increase the transparency of the distribution chain. From 2011 onwards, manufacturers, distributors, pharmacies and hospitals will be required to trace products by an electronic receipt notice (EDI).

Valérie Marchand, health sector manager of GS1 France explains: "The new regulation will enable pharmaceutical companies to know quickly and accurately what they have supplied, both to the distributors and to the hospitals, but traceability often stops there. The strong point of this new regulation for the supplier is that it will send the information included in the Datamatrix code electronically. It will allow automatic integration by the various players in the traceability information chain, while also improving product monitoring and enhance flow management. In a nutshell, the regulation improves the traceability of products from the production chain to the patient's bed."

A Possible European Standardization

France and Turkey are the first two countries to adopt the Datamatrix system in their traceability regulations. What has become an official regulation in France could become a rule shared by all of Europe in the future, given that EFPIA (European Federation of Pharmaceuticals Industries and Associations) recommends the adoption of the Datamatrix system to GS1 standards as a common traceability standard. Moreover, Germany, Spain and Italy also envisage adopting the Datamatrix system in the future.

Advantages of the Datamatrix System

The Datamatrix marking system was chosen because the new regulations require three types of information: the new CIP 13 code, the batch number and expiry date of the medicine. If stored on a conventional uni-dimensional barcode, this amount of information would need a large printed area, making it impractical for many smaller medicine packages. The serialisation number will be added over time. Datamatrix marking has a large storage capacity and minimal physical dimensions, making it ideal for this application. This system facilitates the automation of product monitoring in the supply chain to allow batch recalls or automatic detection of out-of-date products. Finally, its cost remains competitive (marking cost between 0.1 to 0.2 cents).

Pharmaceutical Companies Must Adapt Their Supply Chains

Marchand said: "The pharmaceutical manufacturers will be obliged to install new printing systems for the Datamatrix marking. It is a necessity to satisfy the new regulation criteria."

As such, the French and international manufacturers who wish to distribute medicines on the French market will have to acquire appropriate equipment in order to comply with this new regulation. The difficulty of implementing this new marking lies in the correct integration of new printing and control system.

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Read the full interview with GS1 France Heathcare Manager Valérie Marchand here: www.chemanager-online.com/en/tags/GS1

chemanager-online.com/en/tags/pharma-packaging

Process R&D

Chemical Development and Scale Up in the Fine Chemical and Pharmaceutical Industries

Scale up – When I left university after my PhD and started my career in industry as a development chemist, I encountered many applied aspects of my job that were completely new to me. And like most people in those days I learnt "on the job" gathering information and knowledge from my older, more experienced colleagues. But nevertheless I still made mistakes. Some years later in 1989/1990 I came across a course on chemical research and development that had just been developed by Dr Trevor Laird who had formed the company Scientific Update. Dr. Laird had been head of process research and development at Smith, Kline and French's Tonbridge site, but had the foresight to see that there was a real need for applied training for chemists and chemical engineers starting work in process research and development (R&D) to stop new entrants making the same mistakes as he had made when he started out.

Dr. Will Watson
Scientific Update

From lab scale to large scale

There are many changes that can affect a reaction when it is scaled up, but one of the most significant is time and particularly mixing time. Mixing times typically change from a 1–2 seconds in the lab to 0.5–1 minutes on large scale. The result is that when one component is being added to a reaction there will be a significant difference between the local concentration at any one point in the reactor compared to the average concentration. Other average parameter/local parameter differences that also affect the reaction care temperature and pH either of which can affect the reaction selectivity and so the yield and purity of the isolated product.

Process R&D departments fulfil a vital role during the commercialization of new chemical products (pharmaceutical, agrochemical, flavour, fragrance etc). The key requirement is to devise a synthesis that can be operated safely and economically on production scale, but in addition they will often have to deliver batches of material (from a few hundred grams in the early stages to 100's of kilograms or even tonnes during later development) for further studies such as formulation, toxicity investigations, clinical trials for pharmaceuticals, field trials for agrochemicals, or further chemical transformations.

Converting a synthetic route used to make gram quantities of a chemical to a process for manufacturing tonne quantities is a topic about which much is known, but where the "tricks of the trade" are handed down within companies. There is little shared experience between chemists in different companies, and the result is a lack of awareness of what is involved in chemical development – the skills and techniques needed to efficiently scale-up chemical processes. Since many processes require chiral synthesis or use chiral catalysts, where control of conditions and optical purity are critical, the development chemist who transfers these processes to plant needs to be aware of the techniques which will lead to efficient scale-up.

Knowledge And New Ideas

The training course on "Chemical Development and Scale Up in the Fine Chemical and Pharmaceutical Industries" that Dr. Laird developed gives an overview and introduction to the subject. The course consists of 14 lectures and 5 interactive problem sessions and concepts and techniques are illustrated by a wealth of real-life examples. The lectures are designed to cover all the main topics and are organized in a logical order to follow the pattern of a typical process/project.

The first topic is Route Selection. A review on the Costing of Chemical Processes follows and the course moves on to a detailed lecture on Development and Optimization. In this section approaches to improvement in the yield and selectivity of particular steps using standard chemical techniques is discussed along with studying the effect of changing the order of steps and/or telescoping two or more steps together. A lecture on Solvent Effects deals with the choice of solvent or solvent systems, but also discusses neoteric solvents such as ionic liquids, supercritical fluids, and fluorous solvents.

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Statistical Methods of Optimization is an introduction to an alternative approach to the optimization of chemical reactions and processes. Methods covered include the Simplex Method, Modified Simplex Method, Factorial Design, Fractional Factorial Design, Path of Steepest Ascent, and Response Surface Modelling. A brief discussion of commercially available software packages is also included. In Analytical Issues in Chemical Process R&D quality issues are discussed. The main areas covered are sampling, methodology, specifications, impurity control, and finally quality assurance including Good Manufacturing Practice, Process Validation, and Quality by Design.

Work-up is arguably one of the most important topics since a significant amount of development time is spent on product isolation and purification. The lecture on The Importance of Work-Up discusses quenching reactions, filtration and product isolation. This leads in to An Appreciation of Chemical Engineering Principles which does not try to teach chemists to be chemical engineers but rather to show them the sorts of areas where their chemical engineering colleagues can help them solve problems or preferably to engineer them out before they occur. An interactive session dedicated to issues of heat transfer and mass transfer follows before thinking about how to approach the first pilot plant batch in "Planning For Scale Up".

"Crystallization and Polymorphism" also includes some discussion of salt forms and hydrates and solvates. "Chemical Development of Enantiomerically Pure Compounds" surveys the various approaches to producing single-enantiomer products concentrating on resolution/crystallization and asymmetric catalysis but also including some discussion on biocatalysis.

The final two topics are "Thermal Hazard Testing and Runaway Reactions" and "Waste Minimization and Effluent Control". "Thermal Hazard Testing and Runaway Reactions" contains an overview of testing equipment available for assessing thermal hazards of reactions and individual compounds as well as a discussion of problems that have encountered in the past and a discussion of which functional groups to beware of. "Waste Minimization and Effluent Control" is essentially about green chemistry issues. Participants are encouraged to think about the whole process when looking waste minimization and not just to think about individual reagents or yields, with the most efficient processes being those that generate the least waste.

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Infobox:

Training course on "Chemical Development and Scale Up in the Fine Chemical and Pharmaceutical Industries"
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EU Agency Allows Access to Drug Side Effects Data

The European Medicines Agency (EMA) has agreed to provide access to studies about drug side effects, following criticism over data secrecy from the European Ombudsman.

The move could help people hoping to take legal action against drugmakers and highlights the pressure on healthcare regulators to make more information about drug safety available to the public.

A spokeswoman for the agency said that the London-based watchdog would release the information requested about Roche's acne drug Accutane by an Irish citizen whose son committed suicide "within the next few weeks." The EMA had argued that European transparency rules did not apply to serious adverse reaction reports, given the need to protect patient confidentiality. But, in a change of heart, the organization has now agreed to release such reports, after first deleting personal data that would allow identification of individual patients. ■

Air Products Signs Contract with Russian Petrochemical Company

Air Products today announced a contract to supply Voronezhsintezkauchuk, part of Russia and Eastern Europe's leading petrochemical company Sibur, with a new on-site air separation unit (ASU).

The ASU will have the capacity to produce up to 3,000 m/hour of gaseous nitrogen when on-stream in 2012, plus up to 16,000 m/hour of dry compressed air. In addition to providing Voronezhsintezkauchuk with all of its industrial gas requirements, Air Products will supply liquid product to the Russian market.

As part of this agreement, Air Products' first with a state-owned Russian firm, the company will own, operate and maintain the ASU to be located at Voronezhsintezkauchuk's site. ■

BASF to Build Dispersions Plant in Huizhou

BASF will invest in a dispersions plant in Daya Bay Petrochemical Industrial Park in Huizhou, China. With an annual capacity of 100,000 tons, the new plant will produce XSB dispersions for the paper industry and acrylic dispersions for industries such as coatings, construction, printing & packaging and adhesives.

The facility will benefit from local availability of raw materials and proximity to key customers, who serve Asia's fastest-growing consumer markets. Production is scheduled to begin in the first quarter of 2012, subject to government approval. The investment is part of BASF's growth strategy for Asia Pacific, which has the goal of doubling sales by 2020.

"This is an important step for BASF in Asia, following the establishment of our paper chemicals division in 2009. The investment strengthens BASF's commitment to the paper and board industry, with South China offering one of the fastest-growing markets in the region. With this facility, we are well positioned to support our customers' aspirations for growth and success in the South," said Engsoo Chew, senior vice president, paper chemicals Asia Pacific. ■

Evonik to Expand Production Capacities in China

Demand for triacetonamine derivatives (TAA derivatives) has kept rising for several years. Evonik Industries is taking advantage of the economic opportunities afforded by this situation and is considerably expanding its production capacities for these special derivatives in China. The foundations for a new plant will be laid as early as this year.

Currently, Evonik produces the derivatives in a joint venture Evonik Tianda (Liaoyang) Chemical Additive at the Liaoyang site in northeastern China. The existing production capacities are to be moved within the Liaoyang region to the Aromatic Site (LAS), one of the country's largest petrochemical sites. Furthermore, production will be significantly increased. Full production is scheduled to commence in the fourth quarter of 2011. ■

Lonza Acquires Vivante GMP Solutions

Lonza enters the viral based-manufacturing market with its purchase of Vivante GMP Solutions. The acquisition advances Lonza's strategy to broaden its biologics custom service offering for the growing viral vaccine and gene therapy markets.

Based in Houston, TX, Vivante is a custom manufacturing organization dedicated to producing GMP viral-based therapeutics. The company's viral-vaccine production services will be enhanced by Lonza's established expertise in expression technologies and large-scale manufacturing platforms. Additionally, Vivante's experience with pre-clinical through late-stage supply of viral vector-based products will compliment Lonza's growing cellular and gene therapy process development and manufacturing capabilities. ■

Chemicals – Custom Manufacturing
Examining the relationship between pharma and CMOs
Page 17

Chemicals – Catalysts
A look at the importance of catalysts in all areas of chemicals
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Chemicals – Excipients
Learn about the ins and outs of what gives pharmaceuticals their form
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‘More Talking, Less Walking’

CPhI Opens in Paris with a New Layout

Same show, new look – The CPhI has established itself as the definitive trade show for the pharma ingredients industry over the last 21 years; the show has grown from 250 delegates at the first show in 1990 to a mega-event that covers 50,000 m² and hosts more than 1,400 exhibitors. While many in the industry complain that the show has gotten too large, its organizers, UBM Live, say it reflects the growth seen in the sector over the last two decades. In addition to the CPhI, the parallel shows P-MEC, ICSE and BioPh help break the three-day event into manageable dimensions. Brand new this year are the six exhibitor zones within the CPhI, which are hoped to give delegates more time for fruitful conversation and less achy feet from unnecessary walking. Brandi Schuster asked UBM Live brand directors Annemieke Timmers (CPhI) and Haf Cennydd (ICSE, P-MEC & BioPh) about the trends in the industry and their expectations for the show Paris show, Oct. 5–7.

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CHEManager Europe: What have been the most significant trends you’ve witnessed since last year’s CPhI? What are the exhibitor numbers looking like compared to 2009?

A. Timmers: The predominant trend that we have witnessed in the pharma ingredients sector over the past 12 months has definitely been the market shift to generics as result of healthcare legislation changes in both the EU and U.S. As we have had generics companies exhibiting at our events for many years, this trend doesn’t necessarily have any immediate effect on our exhibitor profile.

Last year, the events hosted 1,808 exhibitors from over 125 countries and regions and the show has grown further since then, suggesting that pharma companies have a sense of renewed optimism and confidence regarding the future business outlook and state of the global economy.

H. Cennydd: Both visitor pre registrations and exhibitor numbers are looking good for the 2010 events. Typically, outsourcing thrives during tough economic times, as companies take steps to rationalize their production and R&D assets, and we estimate that the ICSE event will be around 10% larger than last year with visitor pre-registrations also running at around 10% higher than 2009. Within pharmaceutical contract services, two of the fastest expanding areas of outsourcing are undoubtedly Packaging and Contract Research, and as a result we have introduced dedicated zones to cater for exhibitors and visitors in these sectors at this year’s event.

P-MEC will also see around 10% growth in exhibitors this year and a notable shift in exhibitor demographics, with the event now featuring instrumental analysis, measuring and testing technologies, materials testing, quality control and laboratory equipment, as well as “traditional” large-scale capital machinery with which P-MEC has become associated.

With BioPh, we again expect the event to continue to grow as the convergence trend between bio and major pharma shows no signs of abating.

The economy is finally starting to pick up again, and most of the big chemical players have seen significant improvements in their balance sheets. What have you been hearing from your end?

Haf Cennydd
brand director, ICSE, P-MEC and BioPh

H. Cennydd: The feedback that we have been getting is cautiously optimistic and this is reflected in the continued growth of the events.

CPhI is divided into six different product zones. What was the impetus behind this? How did the exhibitors respond?

A. Timmers: The zones – APIs, Custom Manufacturing, Intermediates, Fine Chemicals, Excipients and General – were introduced as a result of extensive exhibitor and visitor research. They have been introduced to facilitate navigation of the event, and help visitors to easily find exactly what they are looking for, leaving them with “more talking, less walking” time.

The exhibitor feedback has been great, and they have been universally pleased to have a choice of exhibition space which more accurately reflects their company profile. The Initial zones reflect basic ingredient product areas, and we will be looking to further refine them for 2011.

Will this also be reflected within the parallel shows at the CPhI?

Annemieke Timmers
brand director, CPhI

H. Cennydd: Again, as a result of visitor and exhibitor surveys, we have also introduced zones within our ICSE event. The Packaging zone features companies that provide packaging solutions within various stages of pharmaceutical processing, from bioprocess vessels to anti-static film. The CT & CRO zone will not only cover clinical trials, but also pre-clinical, clinical research, phase 1–4 clinical trials and contract research organisations.

The CPhI has gotten into hot water in previous years when dubious companies were allowed to exhibit. Are there any measures in place to insure the quality of exhibitors doing business on the floor? How can visitors protect themselves from such companies?

A. Timmers: UBM Live has specific terms and conditions for exhibitors across our global portfolio of CPhI, ICSE, BioPh and P-MEC events. We stress to all exhibitors their need to verify their specific entitlement to display goods in the host country and to seek appropriate legal advice if they are unsure:

We take worldwide trends in protecting patents very seriously and support all appropriate industry efforts to maximize product certification, regulatory and IP compliance and enforcement, which are in turn key to the integrity of our event brands. Additionally, exhibitors need to keep in mind that even if they did not make or do not own the goods, they may still be legally responsible for their import, display and promotion.

UBM’s general conditions covering goods display specifically exclude: “… any counterfeit goods … or goods which infringe any third party’s intellectual property rights”. Also excluded are any goods: “Prohibited or restricted by local laws or regulations where the exhibition takes place.”

Under our general conditions, we reserve the option to remove displayed goods which the company or relevant authority, such as a government agency or inspector, deem to be in breach of relevant IP rights, or which are prohibited or restricted under the hosting country’s national or local laws.

Responsible and ethical trading is vital for the industry. While UBM has no regulatory function, we are acutely aware that our exhibitors and visitors expect the reassurance that comes from taking a very clear position and response should exhibits raise IP or compliance issues.

How do you respond to criticism that the show has gotten too large?

A. Timmers: Our events precisely mirror growth in the industry sectors that we serve and represent. By breaking the events out into the separate brands- CPhI Worldwide for Pharmaceutical Ingredients, P-MEC Europe for equipment, machinery and technology; ICSE for contract services and packaging; and BioPh Europe for the biopharma sector – then further breaking CPhI and ICSE into specific product zones, we are responding directly to such market feedback. We hope that the introduction of these measures will enable visitors to plan their attendance in advance and maximize the use of their time during their week in Paris.

About CPhI

Paris Nord Villepinte

CPhI worldwide
where intelligence gathers

Oct. 5 – 7 2010

Opening hours
Tuesday 5 Oct.: 09.30 – 17.30
Wednesday 6 Oct.: 09.30 – 17.30
Thursday 7 Oct.: 09.30 – 16.00

Sign up before Oct. 1 to get free access to CPhI.
For detailed exhibitor list, floor plans, all events and much more, visit www.cphi.com.

► www.cphi.com

chemanager-online.com/en/tags/cphi

Who's Who in Fine Chemicals

An Analysis of the Industry's Top 10 Players

Looking back, moving forward – The fine chemical industry has gone through a few difficult periods in the last decennium. More recently, however, the market has improved quite a bit. In this article, we will have a look at the top 10 companies in the fine chemical market. In order to be able to put things in the right perspective it is interesting to look at the situation in the early 2000s first.

Jan Ramakers
Jan Ramakers Fine Chemical Consulting Group

In 2001 (fig. 1) the three largest producers, DSM, Degussa, and BASF were very close to each other, each of them having fine chemical sales in the $1.8-2.0 billion range. Also in that year, the top five companies had a combined market share of 12.3%; the combined market share of the top 10 was 16.7%. Looking at the current situation (fig. 2) the first impression is that the industry has concentrated compared to eight years before.

However, closer look shows that this is not the case.

In 2009 the market share of the leading company was 3%, whereas in 2001 the market share of the leading company was 3.5%.

The top five had a combined market share of 10.4%, which is less than the 12.3% they had in 2001. Also, the combined market share of the top 10 in 2009 was 13.2%, down from 16.7% in 2001 and only slightly higher than the top five in 2001.

So the net result of all the buying and selling of businesses and companies since 2001 has not really increased the degree of concentration of the fine chemical industry. On the contrary, instead of being more concentrated, the fine chemical industry is more fragmented now than it was eight years ago. The increasing importance of fine chemical producers from India and China is thought to be one of the main factors behind this development.

A Closer Look at the Top 10

1) BASF

As the leading fine chemical producer in 2009, Germany's BASF also happens to be the largest chemical company in the world with production sites in 41 countries. The product portfolio of the company ranges from chemicals, plastics, performance products, agricultural products and fine chemicals to crude oil and natural gas. The company's main site in Ludwigshafen is the world's largest integrated chemical complex. Over the last decade, BASF has invested significant amounts of money into the development of its Verbund strategy: optimal integration of processes and businesses. This has created a highly integrated company.

2) Lonza

The second largest company is Lonza. This company is quite different from BASF, not only in size but also because it has always viewed fine chemicals as its core business. At the end of 2006, the company divested its polymer intermediates business and since then almost all of its revenues have been generated from fine chemicals. In recent years, Lonza has invested heavily in strengthening its position in the biotechnology area.

Biotech manufacturing facilities were built and/or expanded at the Visp, Switzerland, and Slough, UK, sites in 2004 and 2005, followed by a large number of acquisitions and investments in the biotech area, including: UCB Bioproducts, Cambrex's Bioproducts and Biopharma segments; Genentech XE "Genentech"'s mid-scale mammalian biopharmaceutical production plant in Spain; large-scale commercial mammalian cell culture manufacturing facilities in Singapore; a large scale production plant for antibody drug conjugates; and some others. With that, Lonza has positioned itself as a leading player in the biotech/biologicals area.

In 2008, it entered into a partnership with Novartis for the development and manufacture of its biological pipeline, and into a joint venture with Teva, one of the largest generics companies for the manufacture of biosimilars.

Currently, the company is streamlining its organization. The focus of its small molecule manufacture will be increasingly shifted to Asia.

3) Evonik

The next company on the list is Evonik. Evonik's fine chemicals business is part of its Chemicals Business Area, which formerly traded as Degussa. The company positions itself as a producer of specialty chemicals. Its fine chemical operation mainly revolves around the custom manufacturing business. The company divested its Seal Sands, UK, site in 2008 and it acquired Eli Lilly's Tippecanoe, U.S., API manufacturing facility – including a long term supply agreement – in 2009.

In April 2010, Evonik opened a new plant for the manufacture of APIs in Nanning in the Guangxi province of China. The plant has been set up in collaboration with an (unnamed) European pharmaceutical company for which Evonik will produce various APIs under a multi-year contract.

4) DSM

DSM, the leading fine chemical company in 2001, has streamlined its fine chemical portfolio over the past few years, which included some divestments and site closures in the pharma area in 2004–2006. One of the major reasons for this was the extremely competitive situation that developed in the market for semi-synthetic antibiotics, mainly from Asian producers, which had a heavy impact on DSM's business in that segment.

In 2007, the company decided to focus more on Life Sciences and Materials Sciences; it has since divested several of its commodity chemicals businesses and closed down or divested some smaller fine chemical manufacturing operations.

In May 2010, DSM Biologics signed preliminary agreements to enter a partnership with the Australian government to design, build and operate the first major Australia-based mammalian biopharmaceutical manufacturing facility, which will be located in Brisbane.

DSM ranked fourth in 2009.

5) Sumitomo Fine Chemicals

Sumitomo Fine Chemicals, the highest ranking Japanese company, merged with the fully owned Sumitomo subsidiary Sumika Fine Chemicals in 2003. After that no other major acquisitions were made.

6) Saltigo

The next one on the list is Saltigo, formerly the fine chemical business of Bayer. The business has certainly benefitted from its independence, as well as the subsequent realignments. Being independent from Bayer, one of the leading pharmaceutical companies as well as one of the leading agrochemical producers, made it easier for Saltigo to attract custom manufacturing business from the agrochemical and pharmaceutical industries.

In May 2010, Saltigo entered into a cooperation agreement with Syngenta, a leading agrochemical company. Syngenta is investing some €50 million in expanding several Saltigo facilities in Leverkusen to significantly enhance its capacity for manufacturing active agrochemical ingredients. Saltigo supplies the active ingredients and intermediates produced in those facilities exclusively to Syngenta.

7) SAFC

SAFC, the fine chemicals business of Sigma-Aldrich and the seventh largest producer of fine chemicals in 2009, has a clear focus on the pharmaceutical market. The company has shown a rapid growth to its current sales level over the past few years, largely as a result of a number of acquisitions. In 2004, it acquired Ultrafine (UK), a chemical contract services provider for drug development, and Tetrionics (U.S.), a specialized producer of high-potency pharmaceutical intermediates and APIs (HPAPIs). In 2005, it invested in the high potency plant, almost doubling its size.

In the same year it acquired JRH Biosciences (U.S.), a supplier of cell culture and sera products to the biopharmaceutical industry, and Proligo (U.S.), involved in nucleic acids and oligonucleotide synthesis. 2006 saw the acquisition of Iropharm (Ireland), involved in the manufacture of APIs, and Pharmorphix (UK), involved in research services for the pharma industry. In 2007, the company acquired Epichem (UK), involved in high-purity chemicals for the electronics industry. The Pharmorphix facility was expanded in 2007. Since then, the HPAPI capability was expanded a few times as well as the biologics capability of the company.

8) Albemarle

Albemarle showed good growth in the first few years after 2001, partly fuelled by acquisitions: Atofina's bromine fine chemicals business in 2003 and DSM Pharmaceutical Products' generic API business that was operated out of South Haven, U.S., in 2006. After that, growth stalled for a while but recently the fine chemicals business seems to be picking up the pace again.

9) WeylChem

WeylChem was formed in 2005, when International Chemical Investors Group of Germany acquired part of Rütgers. The deal included the pharma fine chemicals business of Mannheim-based Rütgers Organics and its U.S. affiliate, which specialised mainly in agrochemicals. Since its formation, the company has acquired a number of other businesses, including Albemarle's Thann, France, facility; the Cork, Ireland, and Landen, Belgium facilities of Cambrex; Clariant's custom manufacturing business; and and Miteni.

10) Groupe Novasep

Last but not least, the number 10 on the list is Groupe Novasep. The company is organized in two strategic business units: Novasep Process (focused on purification engineering) and Novasep Synthesis (focused on chemical and biochemical synthesis)

Novasep uses the combined strength of the business units to manufacture advanced intermediates and API's for custom manufacturing services to the pharma industry and other fine chemical industries. Sériphram, part of Novasep Synthesis, is involved in the manufacture of highly potent compounds. In 2009, the company acquired Henogen (Brussels, Belgium), a contract manufacturing organization offering bioprocess development and manufacturing services ranging from cell bank to supply of clinical products.

Pharma Significant for Fine Chemicals

The pharmaceutical industry has been the main market for fine chemicals for many years. As a matter of fact, the relative importance of pharma for fine chemicals is still increasing, and in 2009, pharma accounted for some 66% of the fine chemical market. Consequently, developments in the pharma market have a large impact on the status and developments of the fine chemical market.

In recent years the number of highly complex APIs with multiple chiral centres on the market has increased significantly. Typically, the manufacture of the vast majority of these products requires one or more biotechnological steps. Obviously, companies like Lonza and SAFC seem to be in a very good position to benefit from this development.

Another interesting development in the pharma market is the increasing importance of high potency APIs, and SAFC's acquisition and expansion of one of the leading HPAPI producers has put them in a good position to benefit from this development.

Most of the companies in the top 10 are fairly heavily involved in custom manufacturing. After a period of decline, the market for custom manufacturing has emerged from the doldrums and started to grow again.

Bright Future

The future of the market for fine chemicals looks brighter now than it has done for quite a few years. Custom manufacturing options are improving, as are opportunities in biotechnology and at the biotechnology/classic chemistry interface. At the same time the competitive intensity is likely to increase further, mainly from the increasing number of producers from China and India. To be successful in this market the ability to form manufacturing partnerships with clients, rather than being a supplier, will remain of vital importance.

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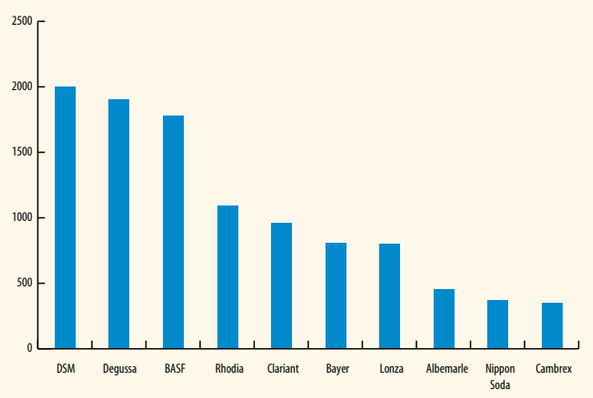
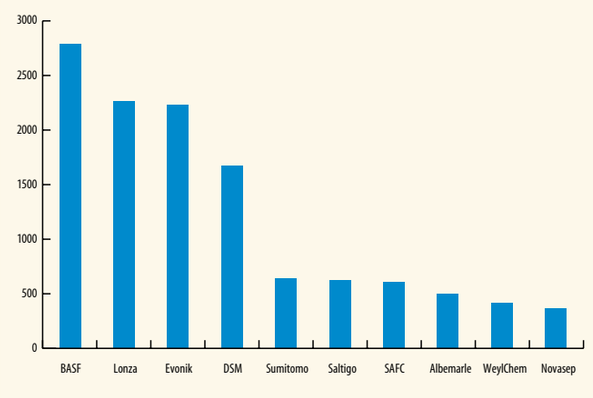
Top 10 Fine Chemical Companies 2001 Figure 1
Sales in 1.000 $



Source: The Fine Chemical Benchmarking Service © GIT VERLAG

Top 10 Fine Chemical Companies 2009 Figure 2
Sales in 1.000 $



Source: The Fine Chemical Benchmarking Service © GIT VERLAG

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‘Layer By Layer’

Clariant’s Streamlining Bears First Fruits

Turning Point – Business is looking up for Clariant; the Swiss-based specialty chemicals company posted an 18 % increase in sales in local currencies year on year and reported growth across all businesses and regions. However, this does not mean the company is in a festive mood – Clariant is in the midst of a sweeping restructuring and remains cautiously optimistic about the rest of 2010.

Patrick Jany
CFO of Clariant

The company added a third round of sites that will be closed or consolidated under its Project GANO. The pigments site in Tianjin, China, will be consolidated; activities from there will be moved to Clairant’s largest Chinese site in Hangzhou. Pigments production will be stopped altogether in Onsan, South Korea. Other sites that have been earmarked for closure or partial closure include locations in France; the UK; Mexico; Germany; Switzerland; Brazil; and India.

Brandi Schuster spoke to Clariant Chief Financial Officer Patrick Jany about new developments within the company’s restructuring strategy.

CHEManager Europe: what was behind the decision to consolidate pigments activities in China and South Korea?

P. Jany: It is a part of our global review of our production sites. As far as pigments are concerned, it’s not a question of geography, rather a question of productivity. We are concentrating our focus on our larger and more efficient production sites; Tianjin is one of our oldest units, and of our older we will be transferring the production to our largest Chinese site in Hangzhou.

How many job cuts will come with the relocation of the Tianjin site and the closure of the Onsan site in South Korea?

P. Jany: Between 200 and 300 positions will be eliminated in China, and about 130 in Onsan. We expect the consolidation to be wrapped up by the beginning of 2011.

These site closures don’t mean that Clariant is decreasing its pigment capacity …

P. Jany: There is always a small amount of capacity loss; in the end, we will be better utilizing our capacity. There will be no discontinuation of products – they will just be made at a different location.

Will the consolidation in China have any effect on Clariant’s Hoecht site, the company’s largest site worldwide?

P. Jany: Not specifically. It is a part of the total review of our sites. It’s just another step, and we will be announcing the third wave of plant and site consolidations at the end of Q3 or early in Q4. That will be the final review of our production sites.

What regions will be affected?

P. Jany: It’s too early to make any statements regarding regions or total number of jobs. However, the total dimension of this last review will not be as significant previous announcements.

In what regions is Clariant looking to increase its capacity to make up for closures elsewhere?

P. Jany: In some areas, such as in textiles, we are definitely looking to move closer to the customer market in Asia, which is also reflected in the Swiss closures we announced in February. This translates into increasing capacity in India and China.

As far as our other business units are concerned, we are really focusing on the most productive sites. In general, it’s clear that we are expanding new and existing capacities in places like India, China and Brazil, because we have to follow the local growth. And these are certainly the main areas of growth for the coming years.

This is now the third wave of announcements under the GANO plan. Is this a plan that has been evolving over time or is it something has been set in stone from the beginning?

P. Jany: It is absolutely an evolving model. We have always said that 2009 and 2010 would be restructuring years. The effort of reducing our selling, general and administrative – SG&A – costs is undergoing the same review as our production sites. Layer by layer, we have been reviewing the cost structure and determining where there is potential for optimization.

Where else will cuts be made?

P. Jany: The review of our costs will be going on until the end of the year. This year we will be reducing about 500 full-time equivalents. In the first six months of this year, we have reduced 268 jobs, and we will be below 17,000 by the end of the year.

The cuts themselves will be made all around the world. There are some small and specific projects that are being done in every country; there is no single initiative. We are optimizing the processes and structures all around the world.

We are reviewing smaller sites all around the world – and quite a few are being closed – to concentrate our efforts on our bigger and more efficient sites.

How far along is Clariant with the closures that were announced in November and in February?

P. Jany: Things are proceeding very well in determining product transfers and so on. It takes one to two years to close a site, and even up to three years for bigger site. Therefore, this effort has been booked into 2009/2010, but the actual closures will take place in 2011 and 2012 and possibly also in 2013.

What kind of company will Clariant when all is said and done?

P. Jany: We will be much more focused on sustaining our results, further improving processes, having our permanent improvement initiatives throughout the company to ensure that this base provides a solid platform for growth.

We have a good market position, we have good products and we plan on growing organically through business optimization.

And acquisitions?

P. Jany: We are also always considering small acquisitions – if they make sense in either a geographical or technical context.

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Responding To Change

Redefining the Relationship Between Pharma and CMOs

New Start – Major changes are impacting the pharmaceutical industry: the financial crisis, hard hitting government finances and health care budgets throughout the world, as well as patent cliff effects exacerbated by inadequate R&D productivity levels. Traditional business models applied by the pharmaceutical industry are being undermined, forcing change within the sector that also could spell out sweeping implications from the pharma CMO sector.

To respond to these challenges, pharmaceutical companies are increasingly confronted with the imperative for maintaining revenues to increase while also increasing access and affordability. Within this frame, some industry observers are predicting a further downgrading of the pharmaceutical industry to a simple AA (affordability and access) as opposed to its rapidly fading AAA (guaranteed returns and steady growth) status. If this holds true, the industry would evolve at an accelerated pace towards a model characterized by:

- Massive consolidation of the supply structure;
- Downscaling of R&D activities as the emphasis shifts from new chemical entity (NCE) development to reformulation and product life extension;
- Massive surge in the share of generics; and
- Pruned product lines – eventually only a couple of APIs in each therapeutic category being maintained.

Evolution, Not Revolution

We are likely to witness is – rather than a revolution – a gradual evolution scenario for the pharmaceutical industry. These developments are mainly a continuation of a process that began in the late 1990s. The recent economic crisis acted more as a revelator than a trigger for these developments:

- The focus within consolidation and mergers amongst companies has shifted from securing access to complementary resources to cost synergies as a tactic to protect the bottom line.
- R&D programs are redirected and reassessed, with the focus moving away from the quest for blockbuster products to specialist products. Companies are also being more selective in their development decisions, rationalizing their pipelines while placing increasing emphasis on lifecycle management.
- New organization models being explored to find a more appropriate balance between growing size and the imperative to maintain entrepreneurial behaviour.
- More attention is devoted to costs, which leads to the downsizing of own M&S as well as industrial operations.
- Business development efforts are being redirected towards emerging demand areas and assembling full- product lines to meet the requirements of the therapeutic areas targeted – a move dictated by the need to offer a complete range of solutions to the patient as opposed to single molecules.

What Does It Mean for CMOs?

The implications of these developments on the pharmaceutical CMO sector are substantial, resulting in increasing business volatility patterns.

In particular CMOs are confronted with:

- Smaller average project size and tighter budgets, combined with unpredictable timelines;
- High staff turnover within the customer organization – jeopardizing thereby value of personal relations, making the creation of goodwill between the vendor and the customer organization an elusive concept;
- Increase leverage application from customers as they try to pass the burden down value chain;
- As the flows of new projects dries up, new sets of players are entering what was traditionally Western CMO territory – a development actively encouraged by several customers;
- Evolving customer requirements – as an example in molecule building: the demand for organic synthesis is stagnating while biomanufacturing is still growing; also, product tonnages tend to decrease, mirroring the smaller markets targeted by the NCEs being developed; and
- Low delivered prices and values are absolute musts.

These developments are hard the CMO sector hard, and several players are reported to be struggling. The situation for CMOs focusing on dosage form manufacturing is not much better – CROs focusing on earlier stages of the pharmaceutical product creation process also struggling. Problems that have arisen include project cancellations, postponements and price-volume reductions, all of which lead investors to reassess the prospects of the business.

The Future of Western CMOs?

It is important to note that the aggressive behavior of pharmaceutical companies with their CMO or CROs vendors is nothing particularly new. The sole real novel factor in the current situation is the volatility patterns. In fact, the situation CMOs are facing today represents an intensification and acceleration of trends that have been observed over the last decade or two. Factors behind this include globalization, cuts in healthcare budgets and financial turmoil.

Also, the situation of flux that several CMOs/CROs are facing is now is not very different from what was seen 10 years ago with the advent of the CMO bubble.

At that time, a rush of new entrants scrambled to take a position in the pharmaceutical CMO/CRO space, which was viewed by some as a harbinger of prosperity and continuing growth.

These prospects lured many new entrants, who often acquired CMO/CRO activities to set up a base in the field – AlliedSignal, Honeywell, Clariant, PPG, Rhodia are just a few. However, many of these players (who were all invariably jockeying to reach a $500 million + size) have been forced to exit the scene after suffering major losses. These setbacks have been largely self-inflicted: Many of these new entrants failed to properly understand the dynamics of the industry; its intrinsic lumpiness; the continuing quest for value characterizing pharmaceutical companies who are not eager to share their comfortable high margins with their vendors.

Old Recipes For New Success?

CMOs are taking an active part in the industry consolidation, a larger size often being associated with increasing resilience, as well as enhanced bargaining power in regard to ever-larger pharmaceutical giants – the benefits of such a move being all but clear, as size tends to go in parallel with:

- The loss of efficiency and of responsiveness – one of the pitfalls often encountered by mega pharmaceutical groups resulting from mergers amongst pairs; and
- The failure to diversify risks, rather creating increasing dependence on key products and customers.

CMOs can also broaden the range of services offered to the pharmaceutical industry, for example combining capabilities in molecule building with formulation or developing full service research and development platforms. However, the viability and need for this have yet to be tested. This is a major issue being represented by the breadth and diversity of skills having to be mastered under a same roof.

In the quest from new traction, some players are considering moving outside of their home turf – for example, API producers moving into dosage-form generics or setting up an Asian base. The benefits here will depend on the company’s ability to leverage synergies in order to avoiding moving in untested waters – a fail-safe recipe for disaster.

The Right Track

The key for success can be found by gaining insights in what it will take for vendors to be successful in the evolving environment. It is important to keep in mind that the pharmaceutical industry will continue to evolve with:

- Continuing volume, but not necessarily value growth;
- Growing convergence between innovators and generic marketers as the boundaries between the two become more diffuse; and
- Pharmaceutical companies continuing to insist on maintaining a firm control as overall project managers and supply chain orchestrators.

This will imply for vendors:

- Fewer but more sophisticated and more complex to serve customers ; few will be willing to move to a virtual mode of operations for R&D or supply chain – all, however, will continue to have multiple sourcing requirements;
- Continuing unpredictable product life cycles; and
- Diminishing turnover and volumes associated with any given contract.

In the end, success for vendors will hinge on:

- Reaching a certain size – differing depending on the segment of activity considered – large enough to reach critical mass – whilst small enough to operate efficiently
- Develop a balanced – yet coherent business portfolio avoiding critical customer or product dependencies
- Being able to conduct business in all parts of the world being comfortable dealing with different cultures
- Continue to focus and excess on internal operations whilst striving to exceed customer expectations avoiding moving in unrelated areas.

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The Cornerstone Of Chemistry

Evonik's Catalyst Business Sets Technology in Motion

Essential – At the heart of most chemical reactions is a catalyst, and given their complex nature, it's not always an easy task to find the right one. As a global supplier for catalytic system solutions, Evonik has been working to establish itself as a leader in the field, most recently through building a new plant in China and acquiring assets in Germany and India. Brandi Schuster and Dr. Michael Reubold spoke to Dr. Wilfried Eul, Senior Vice President of Evonik's catalyst business, about the company's recent strategic moves, opportunities in the market and technological progress.

CHEManager Europe: Dr. Eul, in February, Evonik bought H.C. Starck's catalyst business; in June, you also took over Indian Ravindra Heraeus' precious metal powder catalysts business. How are you integrating these businesses into Evonik's catalysts group?

W. Eul: From H.C. Starck we bought the activated base metal catalyst business, and from Ravindra Heraeus in India we have acquired their precious metal powder catalyst business. With H.C. Starck we have entered into a toll manufacturing agreement during the transition period – they will continue to manufacture the catalysts at their site in Laufenburg, Germany, until we have transferred all of the production formulations to our plant in Hanau, Germany. We expect this to be completed by early 2011.

Will Evonik need to build new capacity for these catalysts?

W. Eul: No – we have sufficient capacity to integrate the business. Nevertheless, we also acquired some special technologies and some special catalysts which will complement our portfolio of technologies and gives us more flexibility in terms of applications for serving the customer base with activated base metal catalysts.

And the Ravindra Heraeus business?

W. Eul: The acquisition of the Ravindra Heraeus precious metal powder catalysts business was the second step of a deal we did with Heraeus in 2005, when we acquired major parts of their corresponding North American and the European precious metal powder catalysts business. As part of the transaction we have established a partnership with Heraeus covering a significant part of our global precious metal recycling from spent catalysts.

We did not acquire any production assets in India, just the customer list. Ravindra Heraeus will toll manufacture all the catalysts we need in the Indian market, and they will also do the precious metal recycling from spent catalysts.

What are the advantages of having a partner who takes care of your precious metal recycling?

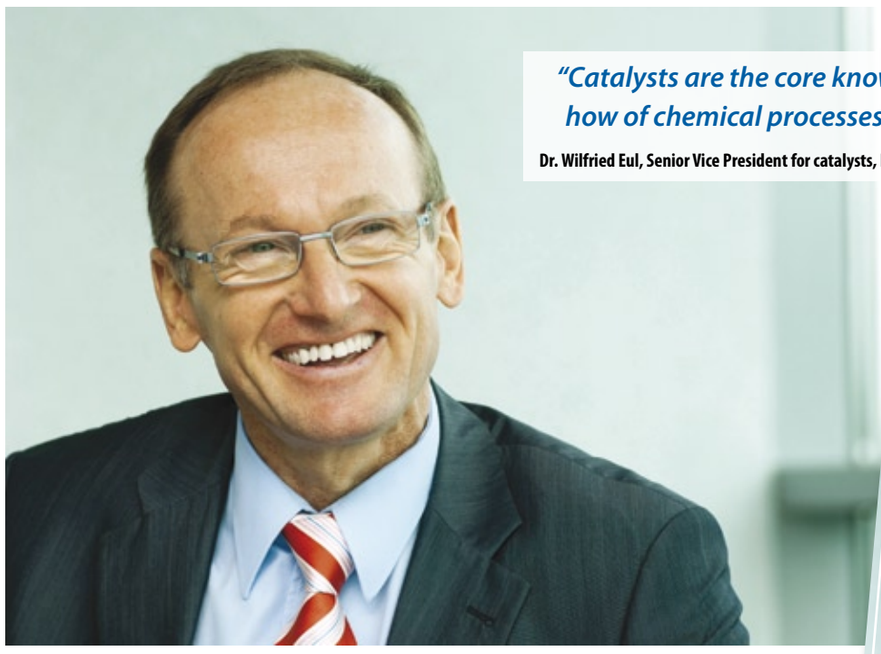
W. Eul: In precious metal powder catalysts, it is important to close the precious metal loop in the country or region and offer recycling services via a reliable and experienced partner to the customers. In many countries or regions of the world it is a difficult undertaking to import precious metals or precious metal catalysts and then to export the spent catalysts – which are very often considered hazardous waste – for recycling of the precious metal. It is therefore important to have a closed precious metal loop in big markets such as India, China, North America, Europe, etc.

This also means it is important to have the catalysts produced in the same country where you recycle the precious metal.

How important is the Asian market for your business?

W. Eul: The worldwide growth rate for precious metal powder catalysts is about 2–3 %. In China and India we see double the growth rate, thanks to their booming fine chemical and pharmaceutical markets – the main outlets for these catalysts. Leading pharmaceutical companies are shifting their production into Asia, and they require the suppliers to follow them.

We also just recently opened our new facility for precious metal powder catalysts in Shanghai. Here we also work together with Heraeus, which enables us to have a closed loop for precious metals in China. The new facility allows us to cater the Chinese market directly from a local source.



"Catalysts are the core know-how of chemical processes."

Dr. Wilfried Eul, Senior Vice President for catalysts, Evonik

With the recent acquisitions and investments in Asia we accomplished our mission to offer state of the art Precious Metal catalyst technology accompanied by a full Precious Metal Loop in all developed and emerging regions on the planet.

Many industry sectors, such as fine and specialty chemicals, have been concerned for years about Asian competition becoming stronger, and many fear that their intellectual property could be compromised.

W. Eul: The situation is somewhat different in the catalysts business. Catalysts are really the core know-how of chemical processes, and companies are very careful when choosing their partners. Very few Western or Japanese customers would give any catalyst know-how to producers or into regions where they have concerns about the IP security.

How can a company do business in Asia and still have peace of mind that their IP is safe?

W. Eul: For Evonik, it is important that our staff is loyal, and this is achieved by selecting them carefully and treating them well. Secondly, we have implemented mechanisms to protect our know-how. However, local companies in Asia are starting up and may try to pick up know-how wherever they can find it. They may catch up with us, mostly with standardized products, but in catalysts it takes longer than in the production standard chemicals – and we have to maintain the speed of innovation to stay ahead.

What are your expectations in homogeneous catalysts, which are also part of your portfolio?

W. Eul: The market is still in a formation stage and requires very specific tailor-made catalysts and significant screening and testing resources. Successful applications will be best developed by entering into partnerships.

For CX-coupling reactions and asymmetric hydrogenations, we have teamed up with Solvias, a leading company in providing customer solutions to the life sciences industry. We have granted them in 2008 an exclusive license for our catACXium and catASium product families.

A hot topic is olefin metathesis, which has emerged as a powerful tool that is opening unique industrial routes for the production of petrochemicals, polymers, specialty chemicals and pharmaceuticals. Core asset here is an unambiguous and firm IP position, a transparent customer friendly, and a royalty-free business model as Evonik offers it for the catMETium product family. In such emerging markets you also need the determination and power to protect your own IP-rights to the benefit of the customers. Recently we settled a patent issue with Elevance Renewables Sciences and turned this into a cooperation in the field of generating specialty chemicals from an oleo chemical natural feedstock.

The demand for olefin polymerization catalysts is also increasing, especially now that polypropylene is being substituted for more and more other polymers in different applications. Has this lead to a demand for new catalytic technologies?

W. Eul: Yes. The polyolefin market is growing at a rate of about 5 % p.a. This has translated into an increase in the demand for Ziegler-Natta catalysts and catalyst components. This is a very complex technology, and customers demand a lot of innovation and support. There are also new technologies based on metallocenes and single-site catalysts. We are working with customers on an exclusive basis in this area of polyolefin catalysts to help them developing improved or new generations of catalysts.

So this field is growing as much as the life sciences sector?

W. Eul: Yes. There is a lot of new polypropylene or polyolefin capacity coming on stream in the Middle East, China and India. According to industry experts, we may see significant overcapacity in the market at some point, but until today the growth rate is still strong.

What other areas are important for your customers?

W. Eul: Something very important for our customers is our service in high-throughput catalyst preparation for fixed-bed catalysts and high-throughput catalyst screening. Here we help customers to identify the optimal catalyst in a short period of time. This is the basis for fast tracking catalyst development projects and moving quickly into up-scaling and production within a given timeline.

How have high-throughput screening and other new technologies given a boost to catalyst development?

W. Eul: Today you can screen a number of catalysts and /or enhance their performance in a relatively short period of time, much faster than it was possible 15 or 20 years ago. Back then, it took years to improve a catalyst – now, each time you change a fixed-bed catalyst in your production plant you may already have an improved catalyst generation. There is a large number of parameters that have to be screened in order to find the right catalysts or improve existing catalysts – in the end, finding the right one is the art of combining good science with the unavoidable trial and error approach.

How is your production set-up for fixed bed catalysts?

W. Eul: We are well known in the market for taking customer developed catalyst recipes with challenging time lines through our scale-up plants to commercial manufacturing at one of our sites. A versatile set-up of equipment capacities and catalyst manufacturing technologies from 100 kg to several thousand tonnes per year give us sufficient flexibility. Our toll manufacturing business for established catalysts allows leveraging large scale capacity and technological competence.

Are fixed-bed catalysts an area in which you see chances for growth?

W. Eul: There is good growth potential in the fixed-bed/continuous process catalyst area. Evonik has leading positions in certain catalyst application fields for chemical or petrochemical production processes. We are expanding our technological spectrum to generate more value for our customers. You can either develop such technologies on your own, you partner with a customer or you acquire a company who has already the market access or the know-how for a certain catalyst technology.

So Evonik is constantly working on new developments, yet always has an eye out on the market?

W. Eul: We do both. We focus on new catalyst developments in areas such as bio based chemicals, either on an exclusive basis with selected customers, or as a technology platform offering the catalysts to the general market. Developing new technology platforms takes a lot of time and resources. Therefore we constantly look for partnerships or acquisitions in relevant technologies or market access.

Are there any potential acquisitions on the horizon for Evonik?

W. Eul: We are constantly looking for potential acquisitions – if they have the right size and the right fit, be it technology, market access or regional set-up. At the same time, we are focused on organic growth through developing and manufacturing catalysts growing with the general market and convincing the customers with the competitiveness and quality of our products and our services.

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The Persistence Of Time

◀ Continued **Page 10**

- Non-compliance could lead to fines, imprisonment, loss of reputation and loss of markets in the UK, EU and globally. The introduction of CLP will lead to increased enforcement activity (coupled with Reach) and the publication of the classification inventory will provide far greater transparency over the activities and regulatory compliance of companies. Already the EU member states have agreed a second coordinated enforcement project starting early in 2011.
- If companies are not "joined-up" in their approach, there is the risk of reinventing the wheel in each country as GHS is implemented. This is a waste of resources and could potentially lead to different decisions being taken in different markets for the same product.
- The failure to have effective systems in place could mean that accurate implementation measures are not in place, changes are not tracked and acted upon and the impact on downstream legislation missed. A failure to implement one piece of legislation implies that other failures in related legislation will subsequently be discovered with potentially serious implications for the company.

What Your Company Should Be Doing

To reduce the risks from piecemeal or non-compliance, companies should be doing some or all of the following:

- Joined up working across organizations is essential, the following parts of the business, for example, should work together:
  - National
  - EU
  - Global
  - REACH team
  - Regulatory specialists
  - Environment, health and safety (EHS)
  - Legal
  - Procurement
  - Sales
  - R&D
  - Others
- Resources are needed to ensure effective and efficient implementation; what, where and when. It should be recognized that CLP and GHS will change and evolve over time – work on CLP should not be considered to be a one-off exercise.
- Training will be needed to help ensure that those workers applying CLP and using classification, labeling and packaging information understand the new system.
- Consider preparing a vulnerability assessment to see where CLP (and GHS) may have most impact on your business.
- Up-to-date inventories are needed of all products coming into, through and out of the company to ensure that CLP is fully addressed. Remember there is no tonnage threshold for the classification and labeling inventory, the scope of CLP is different to that of Reach and exemptions are relatively few. The inventory should be a living document as products in the supply chain and associated quantities and corresponding duties will change over time.

CLP and GHS may have a greater impact on companies globally than Reach. They should not therefore be seen as the poor relation of Reach. Careful consideration needs to be given to the steps needed within a business to ensure effective and efficient implementation to minimise the downsides and maximise the business benefits.

Infobox

Andrew Fasey and Mark Blainey are the authors of a new Chemical Watch report – Managing CLP Compliance: The Essentials for Business – which offers an easy-to-read, step-by-step guide.

As well as dissecting the EU CLP Regulation to show how it works, the authors explain the implications for companies, with messages aimed at senior management to explain why they should release resources to maximize the benefits from compliance. The report also presents advice written specifically for the report by the European Chemicals Agency plus comprehensive references and corporate case-studies looking at existing compliance strategies, making it a truly practical tool.

A 20 % discount is available to CHEManager Europe readers (discounted price €197). Contact lorna.m@chemicalwatch.com stating "CHEManager offer." Also see contents summary at www.chemicalwatch.com/clp.

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Here To Stay

The Significance of Catalysis in the Pharmaceutical Industry

A Challenging Business – **The medicines supplied to patients are the final result of a very lengthy process (commonly about 10 years) and a huge investment both in monetary terms (exceeding $1 billion) and in staff effort (a drug project of decent size will easily involve hundreds of experts covering various scientific, technological and clinical areas). In spite of the resources available to at least the major pharmaceutical companies including all the experience and knowledge, the business continues to be haunted by a very low success rate. Thus, out of 10 projects taken into preclinical development, on the average merely one will survive all the way to the market.**

Hans-Jürgen Federsel
Senior Principal Scientist,
Astrazeneca

The Drug: A Complicated Piece of Construction

Looking into the manufacturing process for making a drug ready for use by patients, two discrete stages will become visible. Firstly, the creation of what is commonly known as the active pharmaceutical ingredient (API), which is the chemical compound – often an organic molecule of medium to high structural complexity – where the pharmacological effect resides (this assumes that we are focusing small molecules as opposed to biomolecules, such as antibodies or proteins). At first glance, you might think this is all it takes to produce a drug product, but the fact is that the API is just an intermediate on the way to the final drug. Instead, a second step is required where the formulated product is achieved, that is when the active compound is "dressed up" as a tablet, an injectable, an ointment or in inhaled form. In short, this involves adding various components described as excipients which will provide features such as stability, powder characteristics, taste masking etc. In other words, drugs delivered to patients represent highly sophisticated materials that have been achieved in close cooperation between chemistry, engineering and pharmacy to arrive at a final product that has to prove its efficacy and safety in rigorous clinical and toxicological studies.

Sustainability – A New Paradigm in the Chemical Industry

One of the elements in the renowned Principles of Green Chemistry is the area of catalysis. Alongside the other 11 topics listed, catalytic chemistry is seen as a major contributor to ensure that the technologies applied and the way of operating is following the philosophy of reducing the footprint of mankind in the environment. In this sense, catalysis will also play a key role in creating a sustainable society going forward. The aim will be to use the available feedstock of raw materials as efficiently as possible, hand in hand with an outspoken ambition to minimize waste emanating from chemical processes, which obviously can be, at least in part, achieved by recycling of spent solvent and recovery of catalysts.

Various measures to describe the efficiency of chemical reactions, for example the frequently utilized E-factor (defined as quantity [kg] of feed materials per quantity [kg] of product out), is an extremely good eye-opener that will help draw the attention to bottlenecks and weaknesses in a process, regardless if it is constituted by a single step or a multi-stage procedure, which then can be addressed and hopefully improved.

Homing-in on Synthetic Chemistry: Catalysis as a Major Tool

While catalytic transformations and processes have been a mainstay in the chemical industry for a very long period of time, it is only fair to say that pharmaceutical companies generally speaking have acted more as laggards. The root causes for this are manifold, but a major factor has undoubtedly been the lack of drivers forcing the business to change gears and start applying catalysis in a more consistent manner. Key contributing factors in explaining this reluctance are arguably the special circumstances under which pharma operates, namely on a heavily regulated, monopoly-type market where huge corporations dominate the playground by virtue of their strong IP and patent protection for own products. This situation effectively eradicates all competition, in the ideal case at least until the drug goes generic, and, hence, the need for implementing more challenging and complex technologies (of which catalytic chemistry is one) by the sheer fact that there is no or only limited competition to take into account.

Nowadays, such attitudes have changed thoroughly under the influence of multitudes of reasons, for example: cost of goods where authorities, markets, and payers are demanding lowest possible prices for ethical drugs; a general buy-in across the business that manufacturing processes should utilize best methods and techniques available at a given point in time; a realization that many of the complicated molecular architectures represented by today's drug compounds cannot be achieved sustainably by "traditional" approaches; and, last but not least, due to the aforementioned commitment to green and sustainable processes.

We are now witnessing how the pharmaceutical industry at large is keen on a broad application of both conventional catalytic technologies as well as front-line novelties to solve their problems. Many of the current flagship products in commercial use rely heavily on catalytic transformations. Against this backdrop, and by virtue of the rich repertoire displayed by the full breadth of catalytic methodologies at hand, the standing of catalysis in pharma R&D and large scale manufacture has never been as strong as today. A few examples will serve as nice illustrations in demonstrating the versatility and the power of catalytic technologies.

Catalytic Breakthroughs – Illustrative Case Stories

One of the few catalytic transformations operating in an asymmetric mode that has actually survived through all phases of R&D and made it onto the market is the manufacture of esomeprazole, the active ingredient in AstraZeneca's antiulcer drug Nexium. Best currently available estimates give the number of commercial processes relying on asymmetric catalysis to less than 20, which, however, does not reflect a poor utilization of this approach but more so that most of the industry's drug projects will fail along the path before reaching launch as was already alluded to earlier. The unique features with this method (fig. 1) is the unsurpassed performance in terms of chemical yield and stereochemical purity achieved by using a groundbreaking combination of a titanium catalyst and a simple amine reagent (Hünig's base). Reliability and robustness are other key characteristics of the process that has been thoroughly validated by producing tens of tons of material per annum for more than a decade.

The fact that catalysis can be obtained not only with various types of metals is nicely illustrated by the olefinic nitration, constituting a critical step in the sequence leading to robalzotan, a compound developed for the treatment of depression which, unfortunately, had to be discontinued. In this case, elemental iodine (I_2) is applied in order to activate the double bond before expulsion as HI which is accountable for re-generating the double bond. While the literature procedure required a huge excess of I_2, this created major problems in the work-up, and therefore a catalytic alternative had to be constructed.

The clue to this problem was realizing that in order to install a catalytic cycle, the iodide formed as part of the process had to be re-oxidized to I_2, and this was found to be conveniently achieved by adding an oxidant in situ (a mixture of per-acetic acid and hydrogen peroxide in water/acetic acid, marketed under the brand name Oxystrong 15). With this profound process modification the loading of I_2 could be reduced from superstoichiometric amounts (3 mol eq.) to just 20 mol-%, which, concomitantly, enabled a much less burdensome isolation of the nitrated intermediate (fig. 2) in the robalzotan synthesis in considerably enhanced yield (70–75 % vs. 45 %).

Over the past 30–40 years, we have been witnessing a formal explosion of coupling methodologies – for example Heck, Suzuki, and Buchwald-Hartwig – which all in all have provided valuable tools that allow ever more complicated structures to be synthesized in a straightforward and direct way. Originating from academia, many of these new procedures have withstood the test on large scale, albeit some only after considerable modifications and optimizations. A case in point is the AR-A2 project (abandoned in phase II due to side-effects), which was aimed at developing a novel antidepressant (profiled as a 5HT1B antagonist), where one of the critical steps was the attachment of a heterocyclic moiety onto the core part of the molecule, a chiral aminotetralin.

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A Reliable Partner

Custom Manufacturing is Built on Trust

Partnership – The name of the game is focusing on core competencies – and this is something custom manufacturers have been able to benefit from over the last several years. This trend has set the scene for the industry's CMOs to show off their services. CMOs offer such services as API contract manufacturing; custom purification and separation; exclusive synthesis; and much more. Brandi Schuster asked some of this year's CPhI exhibitors the following questions:

- *What do you consider to be the biggest* **trends** *in custom manufacturing?*
- *Many pharma companies are looking to concentrate on their* **core competencies** *and are outsourcing manufacturing services. How has your company benefited from this trend? Do you see this trend shifting or changing in any way?*
- *What role does* **location** *play when it comes to custom manufacturing. How do you see competition from eastern companies who may have a better cost position?*

Dr. Andreas Stolle
Head of Business Line Pharma
Saltigo

Dr. Christian Dowdeswell
Sales Director
Dishman Group

Mark Cassidy
Director of Global Sales & Marketing
SAFC

Roger-Marc Nicoud
President and CEO
Groupe Novasep

Trends:

A. Stolle (Saltigo): As far as I see it, there is a big trend to offer custom manufacturing out of Asia.

This is partly driven by increasing focus on delivering sustainable competitive prices and partly by investments into future markets. Established custom manufacturers are either buying or building assets, while some like Saltigo, are expanding their activities with well established Asian companies where a variety of successful projects have already been jointly performed.

After years with of high growth rates, CMOs now need to adapt their traditional way of doing business to the new directions dictated by the market. While maintaining the pressure on continuous cost of goods reductions, customers are, for example, looking for new ways of inventory management, smaller campaigns and shorter lead times. Having an Asian supply base with an advantage on low-cost production is a dominating trend to better manage this challenge.

Also, Asian suppliers are investing heavily to move away from pure raw material supply to offering compounds higher in the value chain. Customers are willing to work with and train this type of company in order to participate in the low-cost offering and to establish local suppliers for the future.

Another trend in the industry I have noticed is that customers are to looking at the overall project and not just at the next milestone or budget – and so do custom manufacturers. The key drivers of such a long-term vision could be risk sharing and cost of goods. Bearing that in mind, Saltigo has a long track record of delivering value to its customers by not just simply supplying the material but also sharing the risk and thus reducing development timelines, as well as providing innovative solutions for long-term cost reductions.

C. Dowdeswell (Dishman Group): There is increasing demand for high potency APIs (HPAPI) primarily as a consequence of the growth in oncology R&D. In addition, there is a growth in the number of HPAPIs being produced at large volume. This is mainly due to the improved tolerability of products and a trend towards oral formulations requiring higher doses. There are a number of significant volume APIs, which although not strictly be classed as highly potent, require high containment for production. The number of companies that have appropriate facilities for the production of HPAPI at large scale is relatively limited, although a number of companies, including Dishman, have been attracted to this area in recent years.

M. Cassidy (SAFC): In recent times, there has been an on ongoing imbalance between supply and demand, resulting in a greater level of price pressure, as CMOs competed with each other for market share – this was particularly the case with regard to product manufacturing using general chemistry capabilities and generic products.

CMOs, such as SAFC, operating with an increasing proportion of their business concentrated on niche, specialized capabilities such as high potency, viral vaccines and antibody drug conjugates, have performed well relative to the general market. Our strategy of investment in these areas is helping us to sustain performance in difficult market conditions.

The outlook, however, is brightening for CMOs, with the imbalance correcting itself, due both to the re-emergence of venture funding and as CMOs increasingly support big pharma's manufacturing requirements.

But major pharma is not just shedding manufacturing fixed costs – we also have seen the divestment of R&D assets. Pharma companies are increasingly looking to the biotech sector to in-license development candidates. For SAFC, these biotech firms have been an important part of our business for many years, and we are well positioned to supply continuity of support in the development of these products as they transition into big pharma.

R.-M. Nicoud (Novasep): For a number of years, the pharmaceutical market has been undergoing profound changes, and we are not at the end of it. Although significant consolidation has occurred, a lot is still to come. On the supply side, the offer is considerably scattered, and this is not going to last for ever.

The main trends in API custom manufacturing are driven by the general pharma market evolution. For mature APIs, it is linked to the growing generic segment, which is being boosted by the so-called "patent cliff". For new drugs, the trend is towards more potent and more targeted medicines. More active, lower volume APIs are also more and more complex, and therefore more expensive to make. The manufacturing of these increasingly complex molecules often requires very specific chemical reactions and a combination of advanced technologies to obtain the required purities with acceptable recovery yields. Also, the manufacture of the increasing number of highly potent APIs (HPAPIs) requires specifically designed manufacturing plants and operations.

Core Competencies:

A. Stolle (Saltigo): In big and medium pharma, we have seen the trend to go back to a "preferred supplier model," with mostly all of their products outsourced. A key reason is the complexity of the business, but it is also due to reduced resources and staff cuttings. These companies tend to work with only a few, well-established suppliers with a long track record. Saltigo has clearly benefited from that trend with our best customers. These companies are turning to us as a partner of choice if commercial products are being transferred from internal production to external suppliers.

C. Dowdeswell (Dishman Group): Dishman has shown continued growth, which has been clearly driven by the increase in outsourced manufacture and has shown 30% year-over-year growth over the last five years, with this trend set to continue.

And the realization of asset strategies is ongoing. While some companies have been very public and aggressive in moving out of the production of API to focus on R&D, formulation and marketing, a number of other major players continue to review their own strategies. There is undoubtedly more rationalization to come.

The companies that have benefited most from this rationalization in the CMO sector have been those who focus on developing and maintaining strong relationships with their customers. The CMO sector suffers from a lack of differentiation among suppliers, with a common standard for production facilities and the use of similar technologies and chemical processes. Investing in customer service to ensure that relationships continue to develop is key here. Asian companies do not have a reputation for strong customer service in general; however Dishman has been very active in this area and has used the experience of its Western assets, such as Carbogen Amcis, to build strong project management and customer service teams.

M. Cassidy (SAFC): Many of our customers have exited from non-core activities and as part of this process, and they have carefully identified the best strategic partners to fulfill their manufacturing needs. SAFC has been able to support its pharma partners throughout these structural changes in order to serve their needs effectively, particularly where we have differentiating capabilities such as high potency, viral vaccines and bioconjugation.

We do not envisage that this process will revert, since these were tough strategic choices made in light of strong market forces. Also, there is now sufficient expertise, competency and competition in the custom manufacturing sector to ensure that customer needs are well served.

R.-M. Nicoud (Novasep): It is true that a number of big pharmas are increasing the outsourcing of their existing APIs and advanced intermediates. A significant portion of this demand is or will however be outsourced to Asia. Conversely, it is also true that several big pharmas are trying to cut their costs through the rationalization of their assets, and are re-insourcing some API or intermediate productions to fill their idle manufacturing capacity.

Therefore it would be far too optimistic to claim that the general outsourcing trend benefits the western contract manufacturing industry in general. As a matter of fact, the industry is facing major challenges and only the most innovative and efficient players will survive the years to come. Since its inception, Novasep has developed an original business model based on a combination of advanced technologies such as chiral expertise, hazardous chemistry, HPAPI handling and chromatography, and we generate a considerable and increasing portion of our business with a combination of these technologies, which enable us to capture manufacturing opportunities of complex new chemical entities. As far as existing/mature products are concerned, we are successful in capturing the outsourcing decisions of our customers when we are able to move the value chain up, for instance insourcing an advanced intermediate that we were previously making in China, and proposing to our customer an innovative manufacturing solution for the last step(s) of the synthesis, enabling substantial cost reduction with additional process intellectual property protection for our customer.

Location:

A. Stolle (Saltigo): Ideally, CMO companies have a global asset base. At the moment, decisions for Eastern suppliers are clearly based on costs and the strategy to invest into emerging markets. However, the need for simplified supply chains, coupled with predicted prices increases in Asia, will lead to shift the decisions in some instances back towards local suppliers.

C. Dowdeswell (Dishman Group): While competition from Asian suppliers has long been a consideration for European CMO, the pharmaceutical industry has been slow to capitalize on the potential, and currently less than 10% of the value of outsourcing spend is directed towards Asia. Typically, pharmaceutical companies will view an Asian supplier as a post launch second source of supply and source only intermediates in the run up to launch.

Dishman was the first Asian CMO to produce an API for launch, some nine years ago, but there remain few examples of this. However, pharmaceutical companies have worked hard with a number of Asian suppliers over recent years and look set to start to increase pre-launch outsourcing of regulatory starting materials (RSM) and APIs.

In addition, the fastest growing markets for pharmaceuticals are in Asia, and there is a trend to produce drugs that target diseases found in the region, which will also lead to an increase in the production of API (and drug formulation) locally.

M. Cassidy (SAFC): First of all, it is important to carefully distinguish between the various Eastern countries and the individual companies, since there is a wide spectrum of performance. If we speak generally, then the intensity of competition between Eastern and Western CMOs varies according to a number of factors.

Firstly, the size of the customer – the Western emerging pharma or biotech customer base is often less comfortable with, or do not have the resources to source from the East compared to a larger pharmaceutical company.

Secondly, the West is generally considered more attractive for certain types of product, for example, more complex new chemical entities versus more general chemistries and generic products in the East. Also, products that require high technology, manufacturing expertise, such as high potency or antibody drug conjugates tend to stay with the proven, specialist players in the West.

Finally, the choice of outsourcing manufacture to the East often varies according to the stage of synthesis. Earlier, non GMP products are more commonly outsourced to the East rather than late stage intermediates and APIs.

Interestingly, at SAFC, we have witnessed an increasing number of late phase projects returning to the West, where the previous supplier had been located the East. The reasons behind this have been cited as quality, reliability and communication. While cost remains important to our customers, they are increasingly looking at total cost, which factors in the cost of potential failure.

R.-M. Nicoud (Novasep): You know, the cost advantage provided by eastern companies, which is real in the short term, will be substantially reduced in the long term. Also, at the end of the day, people do business with other people. Therefore the performance of our service to our customers (which includes cost of course, but also many other parameters), reciprocal trust and the quality of the relationships that we entertain with them are key in maintaining and growing our business. Closer locations, shorter travel time and less jet lag as well as common or close cultures are part of this complex equation. Western Europe offers some advantages for European and US customers in these respects.

Custom Manufacturing

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The Other Side of the Coin

What do companies look for in a custom manufacturer? Jörg Decker-Conradi from Bayer Healthcare fills in

What do you consider to be the biggest trends in custom manufacturing?

J. Decker-Conradi (Bayer HealthCare): We at Bayer HealthCare (BHC) look for suppliers which are reliable and meet the increased quality and regulatory requirements as well as provide the opportunity to develop into a strategic partner.

In our production, quality and safety standards are of utmost importance. Therefore, we regularly and stringently audit our CMOs to ensure our standards are rigorously met.

Looking into the CMO market, we are observing an increase in the number of CMOs due to more and more Asian companies entering the market. This provides us with a choice of best quality at attractive market conditions. Within the different CMO market segments we see a significant expansion of the bio-pharmaceutical CMO market.

Many pharma companies are looking to concentrate on their core competencies and are outsourcing manufacturing services. How has your company benefited from this trend? Do you see this trend shifting or changing in any way?

Jörg Decker-Conradi
Bayer Healthcare

J. Decker-Conradi (Bayer HealthCare): We have a clear focus at BHC: Make what is strategic and value-adding; buy everything else.

Compared to other research-based pharmaceutical companies, we believe to have a balanced approach between in-house and external production with an outsourcing ratio of more than 30%. The main reason for that is the structured make-or-buy process BHC has in place. Within this process, procurement checks with cross-functional teams any investment in own capacities against external opportunities. This results in more business opportunities with dedicated CMOs that offer a special or niche technology or particular expertise in certain well-established technologies. The benefits for BHC are: better control of expenses; freed funds for investments in other areas; professional supply for niche technologies; participation in volume benefits for small volume products; and reduction of complexity within our own sites. There is a clear trend that more and more Asian CMOs, especially from India, participate in our bids. And these suppliers offer additional services beyond simple supply.

What role does location play when it comes to custom manufacturing. How do you see competition from eastern companies who may have a better cost position?

J. Decker-Conradi (Bayer HealthCare): Location of manufacturing is essential for the manufacturing cost structure. This is one reason why we established a strategy to increasingly source within the regions, where the markets are. Since growth is expected especially for the Emerging Markets, manufacturing/sourcing will in future play a more important role in these countries. Herewith we gain an increase of flexibility and responsiveness to markets needs.

While we presently see only limited opportunities for global drug supply coming from CMOs in Eastern European, we see an increased necessity to fulfill local demands from local manufacturing activities in these countries.

Coming Home

Fine Chemicals Are Enjoying a European Revival

Reliability – Complexity is nothing new in the field of fine chemicals, which include everything from advanced to pharmaceutical intermediates. Many within the field also say they have noticed the Asian trend is reversing, with many companies once again turning to trusted Europe-based companies with strong track records of reliability and supply chain security. Brandi Schuster spoke to Dr. Andreas Meier of Solvay Flour prior to the CPhI.

What are today's main trends in fine chemicals in terms of chemistries, synthetic routes and reprocessing?

A. Meier: The trend towards increasingly larger and more complex synthetic components is becoming stronger. Manufacturers are making use of synthetic building blocks with more functional groups to be able to produce increasingly complex active ingredient molecules as easily as possible. Fluorine-containing building blocks are becoming more and more important because fluorine in the molecule increases efficacy. It makes active ingredients more stable and increases membrane permeability. However, fluorine chemistry requires very special know-how and equipment. Active ingredient manufacturers like to buy that expertise together with the entire molecule. We are noticing that customers who used to buy simple molecules, such as TFAC (trifluoroacetyl chloride), are now changing to more complex molecules like ETFBO (4-ethoxy-1,1,1-trifluoro-3-butene-2-one).

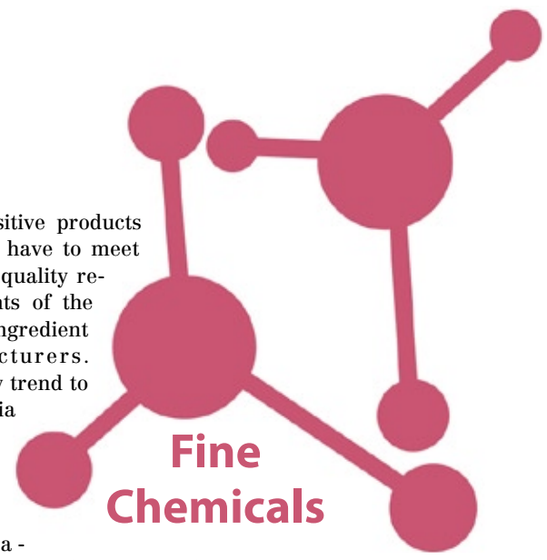
Dr. Andreas Meier
Head of the Regional Business Unit Europe and Managing Director
Solvay Fluor

How did the fine chemicals business fare over the course of the economic downturn?

A. Meier: The highroad through an economic crisis is reducing spending to an absolute minimum. In the fine chemicals industry, as well as in other areas of the business, we have observed that customers are postponing investments and projects and reducing stock. We are glad to observe an excellent order situation since the spring of 2010. Now it looks as if everyone is trying to make up for the time lost during the economic crisis.

How do you compete with price pressure from competition from the East?

A. Meier: Asia has not really been a strong competitor for knowhow sensitive products that also have to meet the high quality requirements of the active ingredient manufacturers. The early trend to go to Asia is being reversed. The great pharmaceutical companies once again appreciate European manufacturers in order to protect their know-how and to be on the safe side regarding warranty claims, quality and supply chain security.



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Here, There, Everywhere

Many Companies Offer a Wide Range of Services

One-Stop-Shop – There are many players in the industry who are household names; the companies who are masters in their own areas or who are able to provide their services to almost all corners of the pharmaceutical industry. Brandi Schuster interviewed Dr. Matthias Grehl, Vice President of Umicore prior to the show.

What market trends have been keeping you busy this year?

M. Grehl: The recovery of the economy allowed Umicore to pursue its goal of sustainable value creation with concentrating its activities into four focused business groups: catalysis, energy materials, performance materials and recycling.

Precious metals chemistry (PMC) strengthened its presence in the life science and chemical industries with scaling up new precious-metal based APIs and catalysts such as Ruthenium-based olefin metathesis catalysts, used in the synthesis of key pharmaceutical intermediates or in the synthesis of chemicals out of renewables, or such as platinum based APIs, known as powerful anti-cancer drugs. We also expanded into solar with scaling up Ruthenium dyes for DSSC, the technology developed by Dr. Michael Grätzel at the Ecole Polytechnique Federale de Lausanne (EPFL), as well as into the electronic industry with launching high purity precious metal based chemicals.

Dr. Matthias Grehl
Vice-President
Business Unit Manager Precious Metals Chemistry, Umicore

Experts say that the recession is coming to an end? How are things looking on your end?

M. Grehl: Umicore's performance in the first half of 2010 improved substantially compared to the first half of 2009, and was also well up compared to the second half of 2009. This was indeed due to the recovery in the main markets of the advanced materials and precious metals products and catalysts businesses, coupled with the positive impact of cost reduction measures.

PMC also benefits from the return of the steady growth in markets such as automotive and specialty chemical industries as well as from its expansion into the new markets and technologies.

What has been the biggest challenge for your company over the last year?

M. Grehl: These were actually two: Maintaining the growth during the crisis and keeping on track with the construction of our new metal-based API plant in Argentina. Thanks to the diversity and the fidelity of our customers, we kept growing in 2009; and thanks to the dedication of our team we can now support the internationalization of our Pt-API customer base with an Argentinean production facility fulfilling the latest quality standards and regulations.

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Here To Stay

Continued Page 19

Thus, is was shown that the catalyst loading of this Pd-catalyzed transformation could be reduced to <1 mol-% and by further refinements of the reaction conditions, the overall yield was close to quantitative as demonstrated on 125 kg pilot plant scale (fig. 3).

Outlook: The Direction of Catalysis in the Future

Against the backdrop of today's already established position as a key technology capable of ensuring that challenging chemical structures are successfully delivered in an efficient manner, the catalysis field is, most likely, bound to undergo further significant and pronounced developments going forward, as seen from a pharmaceutical industry perspective.

A confirmation of its continuously strengthened role as a tool of increasing versatility is the fact that estimates indicate that one step out of an average of eight required to synthesize an API will be catalytic. While existing methodologies such as coupling reactions, transformations in heterogeneous systems and asymmetric hydrogenations among others will stay on as the dominating ones, new additions will be seen in changing stoichiometric reactions to their catalytic counterparts. Thus, it can be hoped that such standard reactions as de-methylations, amide formations and preparation of certain fluorine-containing motifs will see new opportunities in the near future.

An interesting development can also be expected at the interface between chemo- and bio-catalysis (based on enzymes), possibly with opportunities for organocatalysis (small organic molecules as catalysts) which constitutes an area showing a strong upwards trend. Moreover, switching to less-precious metals (for example to Fe and Cu) is something that might boost catalysis at large, if nothing else then from a cost point of view.

Finally, the emerging topic of predictive catalysis that will allow the user to quickly home-in on the best catalytic system has a lot speaking for itself as it has the attractive feature to enable process development to occur much faster. The same argument can be applied to catalysis in flow systems – an area of considerable hype nowadays – as this brings with it a fast progress from laboratory experimentation to a large scale manufacturing scenario. At any rate, catalytic technologies are here to stay and their importance will only increase in the foreseeable future.

References are available from the author upon request.

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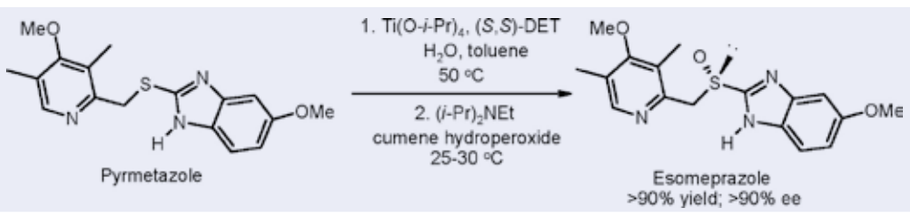

Fig. 1: The power of asymmetric catalysis demonstrated by the sulfoxidation reaction taking the pro-chiral sulfide pyrmetazole to the drug substance esomeprazole with unsurpassed efficiency.

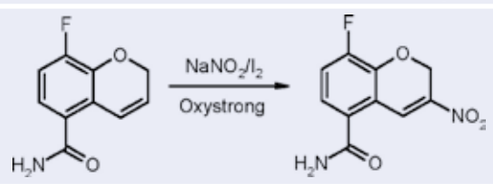

Fig. 2: Conducting a nitration as part of the synthetic pathway to robalzotan using iodine as catalyst (20 mol-%) and a mixture of per-acetic acid and hydrogen peroxide (Oxystrong 15) as oxidant.

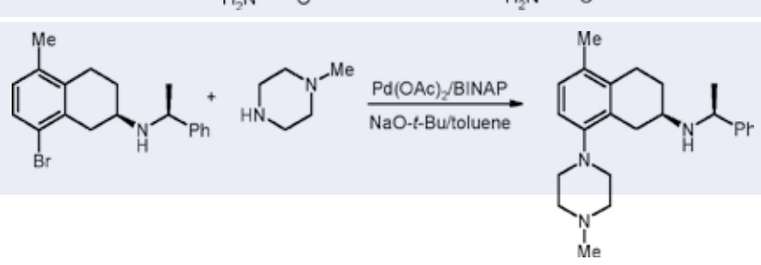

Fig. 3: Connecting a heterocyclic building block (N-methylpiperazine) to an aromatic framework using the Buchwald-Hartwig protocol with palladium(II) as catalyst (<1 mol-%); a key step in the sequence leading to the antidepressant AR-A2.

Expect High Performance

API Manufacturers Face Many Hurdles in Business

No Headache – Active pharmaceutical ingredients (APIs) are something that anyone who has ever had a headache has come into contact with. These days, the worldwide market for APIs is being influenced by changes within the pharma industry, including more demand for patent-free drugs and an increasingly complex regulatory environment. Manufacturers from the East are also putting pressure on Western players. CHEManager Europe asked some of this year's CPhI exhibitors the following questions:

- *What do you consider to be the biggest* **trends** *in APIs and intermediates right now?*
- *What role do* **generic APIs** *play for your business, if any?*
- *What is your* **strategy** *for competing with API manufacturers from the East?*
- *How do you see the growing interest in* **biopharmaceuticals***? Does your company have any plans in this direction?*

Dr. Andreas Dietrich
Head of Pharma Chemicals and Business Operations
Boehringer Ingelheim Pharma

Dr. Heinz Sieger
CEO
CU Chemie Uetikon

Trends:

A. Dietrich (Boehringer Ingelheim): The pharmaceutical industry has seen a number of changes in market trends over the past years. Mainly an increased pressure on profitability due to local healthcare cost reduction measures and, consequently, the balancing trend of outsourcing manufacturing and production process improvements through process excellence initiatives to lower cost in response.

Within these macro trends, we currently see several factors influencing the field of APIs and intermediates. Firstly, manufacturing overcapacity puts pressure on pricing during a time of rising cost and regulatory complexity. We believe that overcapacity is caused by a number of issues. New producers entered the market in particular in Asia. Ongoing major pharma restructuring and divestiture activities seldom eliminate production capacity. The existing assets are often sold to new owners who are trying to keep capacity utilization high to manage operating cost effectively. In addition, the long-term trend for new product approvals remains currently softer than intended. Hence, less capacity for new products is needed. In summary, capacity supply outstrips capacity demand and respective market prices fall.

Secondly, the need for a dual- or multiregional production site strategy remains important. This movement is driven by a number of concerns, including geopolitical aspects that make companies consider hedging their supply chain security. In particular, a sole dependence on an exclusive Asia manufacturing strategy will be carefully looked at.

Thirdly, the newer generations of APIs tend to be more potent, which creates an increased need for special manufacturing set-ups, like a containment solution for manufacturing. In addition, production processes tend to be more complex. Consequently, associated lower volumes often require smaller equipment.

Fourthly, regulatory and quality requirements will continue to grow, thereby raising the complexity and cost for a business, independent of an already existing product or a new product. The respective maintenance and upkeep requires continuous investments to ensure that analytical and quality standards are always up-to-date.

H. Sieger (CU Chemie Uetikon): The worldwide market for APIs and intermediates will be very much influenced by the changes within the pharma industry that are resulting from strong cost pressure, an increased demand of patent-free drugs and the shift from the developed to the E7 emerging markets – China, India, Brazil, Russia, Indonesia, Mexico and Turkey.

Due to the demand of cheap patent free drugs, a situation has been created, where a high percentage of APIs – which comes from non-EU sources such as India and China – do not always comply with the European Quality standards. As a consequence, an alarming increase of falsified APIs that threaten public health can be observed. A latest example is the clopidogrel case with the API produced in India and a recall of the drug from the market.

To resolve this unacceptable situation, the instruments that guarantee

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the enforcement of existing legislation have to be adjusted. We therefore appreciate the European Parliament and the Council's amendment to Directive 2001/83/EC, which now contains wording against falsified medicinal products, including falsified APIs.

Generic APIs:

A. Dietrich (Boehringer Ingelheim): Generics currently make up only a smaller portion of our focus and respective portfolio. We focus on specific, mostly innovative, APIs where together with our customers we seek good technological, launch, regulatory support and commercial fit. However, in case of a fit with our manufacturing capabilities, we have been quite successful with generics.

H. Sieger (CU Chemie Uetikon): APIs for generics are a substantial part of our growing pharma business, with a range of our own products as well as products that are produced under exclusivity.

Strategy:

A. Dietrich (Boehringer Ingelheim): In order to compete in today's marketplace, we have to offer superior manufacturing reliability, a better product quality and a fast time to market. In addition, it is advantageous to be extremely familiar with local and regional regulatory requirements. In this area, we certainly consider ourselves a leader that demonstrates the needed operational know-how in our day-to-day activities and engagement with our customers.

We know what is expected from us working successfully with regulators and how to provide superior service to safeguard intellectual property rights. In case of product launches, customers who have chosen us always have valued our ability to scale up and launch production quickly while operating efficiently and reliable within a complex regulatory environment.

Ultimately, our customers value our expertise and our competence of being a reliable and high quality supplier. Many customers consider these attributes sufficient to pay a premium for a Western based producer.

H. Sieger (CU Chemie Uetikon): Without a level playing field, competition is always most difficult when price is the only criteria.

But when price is not the only reason behind a purchase decision, then customers – particularly those from pharma – prefer the compliance, the expertise and an excellent track record of a reliable CMO supplier. Customers become convinced that sustainability is favored instead of short-term profit optimization.

Biopharmaceuticals:

A. Dietrich (Boehringer Ingelheim): Boehringer Ingelheim has more than 25 years experience in development and manufacturing of biopharmaceuticals like monoclonal antibodies, therapeutic proteins and also DNA for gene therapy or vaccination. Our two large scale manufacturing sites in Europe offer contract development and manufacturing services and can produce biopharmaceuticals from cell culture technology as well as from microbial and yeast systems. Both sites have multiproduct facilities which can supply the global market and are compliant with the major regulatory authorities like the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMEA) and the Japanese Ministry of Health, Labor and Welfare (MHLW).

The biopharmaceutical market has been growing constantly and is expected to grow with around 5 % per year, which is five times higher compared to the pharma market. This highly attractive market will offer also in the future opportunities for the contract manufacturing business at Boehringer Ingelheim. We also expect increasing demand for biopharmaceutical products coming from emerging markets like China and India.

H. Sieger (CU Chemie Uetikon): There is absolutely no doubt about biopharmaceutical's success story; they will soon make up to 50 % of new drug approvals.

Already in 2007, we took over a Bio-CMO in Ireland, a former spin off from the Dublin City University. After investing in SUB technology – single-use bioreactors – and downstream equipment, we are now offering mammalian cell-culture service and are working on different bio projects, including monoclonal antibody projects. This activity perfectly extends our small molecules business with the big bio-molecules technology.

chemanager-online.com/en/tags/apis

Securing Each Step

Excipients Manufacturers Adhere to Standards and Goals

A solid base – Like nearly all aspects of public and private business, healthcare management organizations and national governments are feeling price pressure, and many look to mitigate this by saving money when it comes to drugs. This pressure gets passed along the value chain to the manufacturers of excipients, who strive to provide the highest-quality products to their customers in a world where the regulatory framework is unclear. Brandi Schuster asked some of this year's CPhI exhibitors the following questions:

- *What do you consider to be the most* **pressing issues** *in excipients right now?*
- *What are the current* **trends** *and requirements from pharma manufacturers and formulators?*
- *What is your opinion on* **GMP** *for pharmaceutical excipients?*
- *What is your* **strategy** *for competing with excipients from the East?*

Bodo Fritzsching
Head of Sales & Technical Services Pharma
Beneo-Palatinit

Burghard Freiberg
Senior Vice President Life Science Solution
Merck KGaA

Dermot Pearson
Marketing Director
Novozymes

Pressing Issues

B. Fritzsching (Beneo-Palatinit): There is an increasing cost-sensitivity within the pharmaceutical industry. While costs of clinical studies, regulation and quality assurance have been increasing over time, healthcare management organizations and governmental bodies are urged more and more to save money when buying drugs. As a consequence also excipients – particularly commodity standard excipients – are under price pressure in all segments of the industry.

Pharmacopeial monographs and drug regulations are lacking harmonization resulting in different requirements and various testing procedures requested by the European Directorate for the Quality of Medicines & Healthcare; the United States Pharmacopeia – National Formulary; and Japanese Pharmacopoeia-Japanese Pharmaceutical Excipients monographs. A single ingredient can only be approved in different regions around the world after it has fulfilled all of them. Although being essential, such a variety of procedures causes extra cost as well as hurdles for market growth.

B. Freiberg (Merck): As I see it, two requirements are particularly strong right now: functional excipients and risk mitigation.

Functional excipients can extend profitability and boost the efficacy of existing products by tailoring them more closely to customer needs. Pharmaceutical companies are recognizing the value of excipients more than ever, particularly when it comes to physical characteristics of increasing the flowability and compassibility of the tableting blend. Other characteristics of the drug such as efficiency, safety, stability and storage are also supported by using the right excipient. For example, new coating and disintegrant formulations can provide gradual release of active ingredients. That's a key product differentiator – to that effect, demand is growing fast.

Risk mitigation, of course, is more important than ever before. We still have no EU guidelines for excipients, so

the best policy for manufacturers is to source supplies from a company with a good reputation for quality. That's the only way to get the consistent purity they need – plus, of course, fast, secure and reliable deliveries. At Merck, we secure every step along the entire process chain – we audit our suppliers stringently and repeatedly, and we only work with companies who share our standards and goals.

D. Pearson (Novozymes): Pharmaceutical manufacturers and formulation scientists strive to achieve optimal, robust drug dosage forms through the use of well-characterized excipients. Excipient choice can influence development timelines and acceptance of final drug products, thus influencing costs along the entire product lifecycle.

Required characteristics that determine excipient selection include functionality; material quality; product consistency (preferably through GMP manufacture); safety; regulatory compliance; secure sourcing; and cost. Raw materials derived from animal sources have also become a concern for formulation scientist due to risk of contamination of the final drug product with animal-derived adventitious agents.

The International Pharmaceutical Excipients Council Europe (IPEC) believes that along with manufacture to GMP principles, the availability of a drug master file (DMF) is critical to demonstrate the safety and efficacy of a new excipient. Currently in Europe, there is no such master file system in place for "novel excipients" that restricts excipient manufacturers' confidentiality due to lack of protection of intellectual property, as there is no option but to provide the master file-type information to the excipient user. As a consequence, few new excipients may be introduced, limiting European patient's access to improved medicines and placing Europe at a competitive disadvantage.

Trends

B. Fritzsching (Beneo-Palatinit): Under the light of drug development and excipient costs, the industry is looking for more highly functional excipients that fulfill different needs: They should help to reduce development times as well as production and formulation costs. Also they should be in accordance to all regulatory and quality requirements as well as available around the globe.

Since these excipients may also play an important role in the drug effectiveness as well as the safety and storage stability of the drug product, they are interesting to all segments. With special focus on over-the-counter drugs but also standard generics, highly functional excipients help to improve formulations by providing functionalities which had not been offered by the excipients used in the original formulations: The possibility to reformulate a drug into a different, faster acting dosage form (e.g. from tablet to sachets for direct oral application) or the opportunity to reduce the tablet size by using a filler-binder diluent excipient such as galenIQ (pharmaceutical grade isomalt from Beneo-Palatinit) are just two examples.

GMP

B. Fritzsching (Beneo-Palatinit): Pharmaceutical companies are obligated to secure the safety of their drug products in order to protect the patient. A traceability of all excipients and manufacturing steps is substantial. We regard the manufacturing of our excipient range galenIQ under cGMP standards as mandatory and therefore have been producing galenIQ under these standards since the very beginning.

Moreover, as a member of the International Pharmaceutical Excipients Council (IPEC), we are following the IPEC-PQG (Pharmaceutical Quality Group) cGMP guidelines for pharmaceutical excipients, as we are deeply convinced that these guidelines help to increase and maintain safety within the market.

B. Freiberg (Merck): As a quality-oriented company, Merck is fully committed to GMP. That's why we made a significant investment in our brand-new GMP plant in Darmstadt, Germany. The entire facility is designed to ensure the highest possible standards of quality and safety. And with three production lines, we're confident we can keep pace with demand for years to come.

D. Pearson (Novozymes): The manufacture of excipients according to GMP principles is critical to assure safety, quality and consistency not only of the excipients but also the final drug product. GMP is a requirement for almost every component of the drug, including the API and packaging materials.

The current lack of requirements for GMP principles to be applied to the manufacture of excipients seems to be counter-intuitive with the GMP requirements for APIs, as excipients can often make up a greater constituent of the final drug product.

Concerns over contamination of the drug products with viruses or transmissible encephalopathies (TSE) and the risk of substitution or contamination of the excipient with erroneous material have seen a push toward GMP requirements for excipients. Recently, the International Conference on Harmonization GMP standard ICH/Q7A4. Directive 2004/27/EC specifically mandated the implementation of GMP for "certain excipients" including, excipients prepared from materials derived from a TSE-relevant animal species and excipients derived from animal sourced material.

Manufacturing according to GMP principles ensures batch to batch consistency at the highest quality standard. Novozymes is committed to product safety and quality and therefore applies GMP principles in the manufacture of their excipient products.

Strategy

B. Fritzsching (Beneo-Palatinit): There might be nothing wrong with many excipients from the East. Over time, most excipient suppliers from the East will meet all standards and requirements, since the market demands strict implementation of GMP standards.

However, it not just the excipient as such that makes the difference; it is the continuous improvement of services and trustful excipient functionality, high quality standards, IP protection and service package which makes an excipient supplier superior. This is in particular true for multifunctional excipients.

B. Freiberg (Merck): Simple: Instead of importing low-grade ingredients, we export our own high standards instead. Take China, for instance: Their own exports may not always be of the finest quality, yet when it comes to excipients, the standards they set for the domestic market are surprisingly strict. In fact, they are as equally demanding as in the West.

D. Pearson (Novozymes): Over recent years, there have been concerns regarding the quality and safety of excipients manufactured in China.

Novozymes has over 20 years experience in operating facilities in China, being the first Western biotech company to establish a wholly owned operation in the area. We have recently started construction of a hyaluronic acid (HA) facility which will be the world's first HA manufactured in an animal-free, solvent free environment. The facility will be run in full compliance to ICH/Q7 guidelines for API manufacturing and will represent a state of the art facility for HA cGMP production.

Quality and safety of Novozymes products is paramount and significant measures are taken to ensure that they are not compromised by manufacturing locations. Selection of the highest quality raw materials, equipment, and highly skilled, international personnel is also crucial to the success of the manufacturing facility no matter where the location.

On completion of the facility, the U.S. Food and Drug Administration (FDA), as well as other international regulatory agencies will audit prior to operation with customer audits also expected.

It is through regulatory compliance and manufacturing to the highest quality standards that ensures product safety, quality and consistency.

Excipients

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Lonza Signs Manufacturing Deal with Glaxosmithkline

Swiss drugs industry supplier Lonza will manufacture a number of drug compounds for Britain's Glaxosmithkline, in a sign demand for the Swiss group's products is recovering. Lonza said it would support the ongoing development of GSK's biopharmaceutical pipeline by supplying manufacturing capacity for five early stage monoclonal antibodies.

Lonza will initially manufacture clinical trial batches of five compounds currently in Phase 1 and 2 for GSK, it said. The group did not give any financial details of the deal.

The Basel-based group, which has moved away from specialty chemicals to focus on higher-margin pharmaceutical ingredients, had said its business was set to recover further as clients from the pharmaceuticals industry placed more orders. ■

Carbogen Amcis and Eirgen Announce Partnership

Carbogen Amcis, a Switzerland-based pharmaceutical process development and active pharmaceutical ingredient (API) manufacturing company announced a new strategic collaboration with Eirgen Pharma, an Ireland-based company that specializes in the manufacturing of solid-dose high-potency products. The companies will work together to provide timely and flexible manufacturing of highly potent active ingredients and solid oral-dose products for the treatment of cancer.

"Due to the improved side-effect profiles of many new classes of highly potent API, more oral-dosage forms are being developed and product volumes are increasing. Carbogen Amcis' strategic alliance with Eirgen allows the company to provide the market with a combined service offering to reduce the number of management interfaces and improve the speed of drug development," said Charlie Johnson, high potency business manager for Carbogen Amcis. "We selected Eirgen Pharma as a preferred partner for its solid-dosage high-potency products. We value the company's strong reputation for providing quality service, using a state-of-the-art infrastructure and maintaining a strong emphasis on the safe handling of highly potent materials."

The strategic alliance with Carbogen Amcis will encompass integrated services, spanning from high-potency API supply to solid-dose packaging. ■

Complexity Within Biosimilars

Gold Mine or a Dead-end for the Generic Industry?

Hard to Copy – Market data shows that sales of biotech products are worth billions of dollars worldwide – just the sort of prospect that normally brings generic manufacturers rushing in to take advantage. Usually, patent expiry is followed by a flood of low cost generics that lead to prices falling by 80–90 %, but this has not happened yet with biological products. Why not?

Peter Wittner
Interpharm Consultancy

It is partly due to the great complexity of the products and the difficulties in copying them accurately. In addition, Europe has set high regulatory standards for proving equivalence and the U.S. has only recently created legislation for a biosimilars pathway.

The Potential Market

Estimates suggest that sales of Biological product in 2010 will exceed $100 billion worldwide with over $60 billion of that coming from the U.S. alone. Figure 1, based on figures from a presentation at the Biosimilars India conference in 2009, demonstrates that this could grow by 10 % in 2011.

While many of these products still benefit from patent protection, several others have lost exclusivity in Europe and the normal pattern is for patent expiry to be the trigger for a flood of copies to hit the market with the almost inevitable plunge in prices, but this has not happened yet. Where there have been copies they have struggled to gain market share (fig. 2).

As an example erythropoietin lost patent cover in the EU in 2007, but still they had worldwide sales of $5 billion in 2009. In the past, generic companies have happily copied products with much smaller turnovers – so what is different here?

The Problem With Biosimilars – Equivalence

Biosimilars are very different animals from small molecule generics. Their enormous size brings with it much greater complexity and thus a much bigger headache for generic companies trying to prove that their copy is similar to the original. Atorvastatin, for example, had a molecular weight of around 500 whereas a product like Peginterferon has a weight in the region of 40,000.

With small molecule generics, a simple bioequivalence study on about 24 volunteers is generally adequate to convince the regulator of the product's equivalence to the original. In regulated markets, this is not enough for biologicals; the regulators want to see a package of clinical studies to demonstrate that the copy is sufficiently similar to the original to be used for the same indications.

Another barrier to overcome concerns is immunogenicity. Companies registering biosimilars have to demonstrate to the regulators not only that their product works in the same indications as the original, but also that it is just as safe and no more likely to cause an immunological response than the original.

The problem of demonstrating equivalence is a real issue in European countries and the other regulated markets that have copied the European Medicines Agency's (EMEA) approach to biosimilars. The EMEA started issuing guidelines for biosimilars in general in 2006 and has added specific substance guidelines over the years since then. As a result, there are several copies based on filgrastim, erythropoietin and somatropin available in Europe, but this is far from the dozens of copies that normally flood into the market for other products.

The situation is worse in the U.S., where no such guidelines yet exist, although the enabling legislation has finally been passed. Until now, though, companies have needed to create virtually a complete copy of the originator's regulatory documentation so that only a handful of biosimilar products have reached the market.

In less regulated parts of the world, however, the market has opened up more with an abundance of biosimilars available. Biosimilars are often bought on tender and used in place of the product that was previously supplied. There appears to be frequent substitution due to the lower regulatory barriers and the acceptance that originals and Biosimilars can be interchangeable.

Interchangeability

It is this issue of interchangeability that has proved a major barrier to biosimilars in Europe and is likely to do the same in the U.S. when the regulatory pathway is in place. Put simply as an equation reflecting the mindset of the regulators:

For small-molecule generics: A = B
For biosimilars: A ≠ B

What this means in practice is that the European regulators have stated that the grant of a marketing authorization to a biosimilar does not mean that it is interchangeable with the original, rather it is merely sufficiently similar to be used as an alternative. As a result, prescribers are reluctant to switch a patient from the original brand on to the copy, despite any possible cost savings. In addition, most EU countries have specified that biosimilars should be prescribed by brand name rather than an International Nonproprietary Names (INN) chemical name, thereby precluding the possibility of switching or substitution by the pharmacist.

What appears to be happening instead is that prescribers in European countries are tending to only use a biosimilar product on a newly diagnosed patient. This acts as a very effective barrier to deeper market penetration, as the substitution that is the norm with standard generics is just not happening. As a result, biosimilars seem to have only taken a few percent of the market so far.

The significance of this barrier is that most of the sales of biological products take place in those relatively high-priced EU and U.S. markets where the barriers exist. Consider figure 3, which shows the breakdown of sales of leading biological products. Since worldwide sales of Enbrel amounted to $6.6 billion, these two zones account for 75 % of world sales. Similarly for Remicade, sales worldwide total $5.9 billion so that here, too, the EU and U.S. accounted for 75 % of the world total.

When biosimilars start to reach the U.S. market in significant numbers, and this is dependent on the FDA creating a mechanism and guidelines, it is quite probable that the same mentality that prevails in Europe will be the case in the U.S.

This is why companies selling biosmilars really need to find a way to overcome the interchangeability issues in both the EU and the U.S. The new U.S. legislation provides guidance on what is required to prove equivalence rather than just similarity, but only time will tell whether the FDA ever accepts a copy as being 100 % identical to the original and thus interchangeable.

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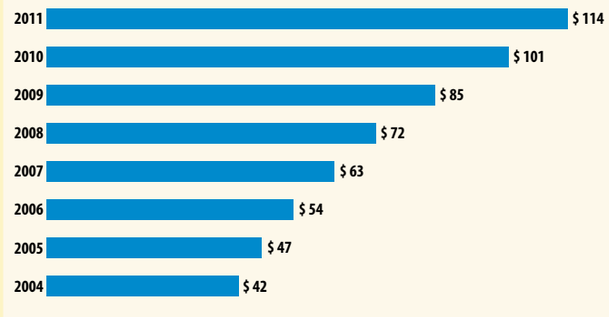
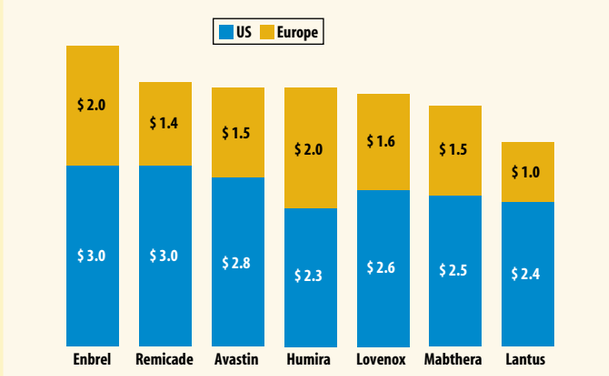
Biological sales 2004-2011 Figure 1
Sales in $ bn



Source: Presentation at Biosimilars India 2009 © GIT VERLAG

Biological products 2009 in EU/US Figure 2
Sales in $ bn



Source: IMS © GIT VERLAG

Brand	Generic	Company	2009 Sales	2008 Sales
Enbrel	Etanercept	Amgen / Wyeth	$ 6.580	$ 6.490
Remicade	Infliximab	Centocor / Schering Plough	$ 5.934	$ 5.335
Avastin	Bevacizumab	Genenetech / Roche	$ 5.777	$ 4.484
Rituxan / MabThera	Rituximab	Genenetech / Roche / Biogen-IDEC	$ 5.653	$ 5.099
Humira Pen	Adalimumab	Abbott / Eisai	$ 5.488	$ 4.521
Epogen / Procrit / ESPO	Epoetin Alpha	Amgen / Ortho / Janssen-Cilag / Kyowa Hakko	$ 5.033	$ 5.123
Herceptin	Trastuzumab	Genentech / Roche / Chugai	$ 4.890	$ 4.384
Lantus	Insulin glargine	Sanofi-Aventis	$ 4.185	$ 3.130
Neulasta	Pegfilgrastim	Amgen	$ 3.355	$ 3.318
Aranesp	Darbopoetin	Amgen / Kyowa Hakko	$ 2.871	$ 3.334
Source: La Merie report – Top 20 Biologics 2009			$ 49.766	$ 45.218

Fig. 3: Leading Biological Products 2009

Umicore Obtains License From Japan Science and Technology Agency

Umicore has signed a license agreement with Japan Science and Technology Agency expanding its technology offering to the nobel-prize winning asymmetric ketone hydrogenation technologies of professors Noyori and Ikariya. Under the license, Umicore is allowed to market Ruthenium diammine and diphosphine Ruthenium diammine catalysts on an industrial scale.

"With this technology expansion we are able to give our customers access to JST's extremely powerful technology," says Dr. Matthias Grehl, vice president BU precious metals chemistry. "Our customers can use these catalysts in their vessels to transfer ketones into chiral alcohols. This license complements our current intellectual property for chiral ligands and catalysts for example those of the MeOBIPHEP or Josiphos type."

The agreement underlines the strategic focus of Umicore precious metals chemistry on emerging applications for organometallic precious metals chemistry in general and in homogeneous catalyst technologies in particular. Besides chiral catalysts, Umicore precious metals chemistry develops catalysts for metathesis applications and for C-X coupling reactions, and provides innovative solutions for precious metals separation and recovery for homogeneous catalysis processes. ■

Evonik to Expand Production Capacities in China

Demand for triacetonamine derivatives (TAA derivatives) has kept rising for several years. Evonik Industries is taking advantage of the economic opportunities afforded by this situation and is considerably expanding its production capacities for these special derivatives in China. The foundations for a new plant will be laid as early as this year.

Currently, Evonik produces the derivatives in a joint venture Evonik Tianda (Liaoyang) Chemical Additive at the Liaoyang site in northeastern China. The existing production capacities are to be moved within the Liaoyang region to the Aromatic Site (LAS), one of the country's largest petrochemical sites. Furthermore, production will be significantly increased. Full production is scheduled to commence in the fourth quarter of 2011. ■

Helsinn Installs –80 °C Reactor

HOME STORY Helsinn strives to have a state of the art facility that fulfils the growing needs of all of its customers. In 2009, the company realized that a –80 °C reactor was something that had become a necessity. The engineering group, led by Marco Soardi, drew up the plans and received approval from upper management for the 800,000 CHF investment that has been officially up and running since mid-August. The team who worked on this project has moved quite efficiently – it only took seven months from approval to fully operating after the commissioning and validation phase.

The project was divided into two areas. The first part was a new cryogenic plant for the generation and distribution of a utility fluid at –90 °C. The previous technology at Helsinn did not allow the company to go so low. This was done by installing a liquid nitrogen storage tank unit outside of the facility.

The second part was the installation of a new R51 Synthesis Reactor with a relevant heating/cooling unit suitable for new products to be processed in these conditions. The new reactor has a net volume of 2,500 l and is a double half-coil. It is made out of Hastelloy HC2000, which is an innovative nickel-based material. The temperature operating range is from –80 °C to +140 °C. The pressure operating range is from full vacuum to +9 Barg.

A 2,500 L Hastelloy Reactor with a high cooling capability up to –80 °C allows a high versatility to perform reactions with very strong reagents. Usually very low temperatures are needed when using alkyl halide bases such as hexyl lithium, butyl lithium, lithium diisopropylamine, as well as alkylating agents such as Grignard reagents and also for reductive agents (e.g. with lithium aluminium hydrid). A wide set of organometallics reactions are driven by low temperatures and these processes are fundamental in the synthesis of pharmaceutical molecules. In the coming months the low temperature reactor will be used for the manufacturing of the third party projects and for the synthesis of Helsinns' product Netupitant.

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BASF Further Invests in Catalysts

BASF has initiated a number of capital investment projects to enhance the company's manufacturing operations for copper-chrome catalysts at its production sites in Erie, Pennsylvania, and Elyria, Ohio. These multi-million dollar investments are aimed at reengineering, retrofitting and further automating the catalysts manufacturing environment at both sites. The operational improvement projects will be completed in phases through the early part of 2011. BASF's Erie and Elyria sites produce a wide variety of base-metal catalysts, which are primarily used in petrochemical and oleochemical processing.

In addition, BASF dedicates significant ongoing investments in research and development, production facilities and personnel to deliver leading-edge fluid catalytic cracking (FCC) technology and technical service to its global refining customers. The company's stepped-up R&D investment is delivering innovative new products in response to market needs, providing users with greater flexibility and improved FCC economics. Over the past 20 months, BASF has introduced several FCC catalyst and advanced co-catalyst solutions as well as a new Multi-Stage Reaction Catalyst (MSRC) manufacturing platform. Greater development of the MSRC platform will further accelerate and enhance delivery of new, higher performance FCC catalysts. In 2011, the company will also start up a state-of-the-art FCC catalyst pilot plant at its Iselin, New Jersey, research facility to be used for customer support and advanced catalyst development. ■

DSM Launches R&D Outsourcing Services

In response to the increasing interest of pharmaceutical customers to outsource the development of robust low-cost manufacturing routes, DSM is offering focused and flexible stand alone route scouting services under the InnoSyn trademark. DSM's route scouting capabilities lead to significant cost savings by the reduction of synthesis steps or redesign of synthesis routes.

The InnoSyn route scouting team supports research and development, and the implementation of economical and scalable routes. Unique value creating solutions are provided by integrating the full range of enabling DSM competencies such as biocatalysis, homogeneous catalysis, organic synthesis and continuous chemistry using for example micro reactors. These capabilities to rapidly screen a wide variety of catalysts speed up feasibility studies for chemocatalytic and biocatalytic steps.

Recent success stories have introduced new efficient enzymes, such as pharmaPLE, lyases, transaminases, dehydrogenases and new, easily accessible homogeneous catalysts for asymmetric hydrogenations, aromatic substitutions, and oxidations. Furthermore, a safe and clean nitration reaction was implemented under cGMP for manufacturing of an API based on DSM's micro reactor technology.

InnoSyn services are based in DSM's R&D facilities in Geleen, The Netherlands and utilize DSM's wide range of technology and production sites across Europe. Oliver May, Ph.D., Business Manager InnoSyn route scouting services commented, "Due to the reduced focus and resources in process R&D within our customers' operations there is an increasing demand for developing flexible and robust 'technology packages' ready to implement at large scale." Dr. May will be speaking at the CPhI Worldwide conference in Paris on Tuesday October 5th at 1 p.m. ■

AkzoNobel Expands Salt Production

AkzoNobel inaugurated its new salt plant in Delfzijl, the Netherlands. This €25 million investment was officially opened by Werner Fuhrmann, president of AkzoNobel industrial chemicals. The expansion has been combined with the conversion to full scale production of mTA industry salt – also of the other salt plants in Delfzijl. mTA, a complex of iron and meso-Tartrate, is a unique biodegradable anticaking agent for salt, enhancing the CO_2 footprint of the chlorine industry.

The new salt plant adds an annual capacity of more than 300 kt which increases AkzoNobel's production capacity in Europe to six million tons of evaporated salt in total. The plant applies mechanical vapor recompression (MVR) technology where in a one step evaporation process the primary fuel is electricity instead of steam. ■

Imagination Over Experience

Exploring new Innovations in High Functionality Excipients

Inventing The Future – The modern tablet development usually includes three basic formulation techniques – direct compression, dry compaction and wet granulation. Depending on the API, characteristics and the desired dosage, one of these formulation approaches is used. Direct compression is the most preferable method due to the low development costs, simple solvent free procedure and a much shorter time-to-market compared to the other methods. Disadvantages of this technique are powder flow difficulties, segregation, poor content uniformity and lubricant sensitivity.

Edmont V. Stoyanov
JRS Pharma

Growing pressure to reduce the production costs and improve the product performance is driving the pharmaceutical companies to look for new solutions. The majority of the tablet formulations include too much and often overdosed conventional excipients: diluents (lactose, powdered cellulose); binders (microcrystalline cellulose, povidones); different disintegrants (croscarmellose, sodium starch glycolate, PVPP); glidants (silicon dioxide); and lubricants (magnesium stearate, sodium stearyl fumarate). The resulted multi-component mixtures of materials with different particle size and shape and bulk density tend to segregation and poor formulation uniformity.

Discussion

Nowadays, the innovation is focused on the development of high functionality excipients (HFE), a synergistic consolidation of two or more conventional excipients that show a synergistic functional performance and overcome the simple blend of its individual components in all technological parameters like flow, compressibility, disintegration, content uniformity and drug dissolution.

Just a co-processing of two or more ingredients is not enough to get high functionality. Every single component of the new formed composite should perform better compared to any other dry mixture or granulated powder with the same excipients content. This requires a precise selection of ingredients and creation of an adequate particle design.

The first generation of co-processed excipients was developed 15–20 years ago. Some of these products have been on the market for a long time: Prosolv SMCC (silicified microcrystalline cellulose); Ludipress (lactose, pvp, pvpp); Cellactose (lactose and powdered cellulose); Starlac (lactose and starch); Emdex (glucose and maltodextrine). What do these co-processed excipients have in common?

- They all are based on the combination filler + binder, binder + glidant or filler + binder + disintegrant.
- Their development is focused on achieving good powder flow and compressibility.
- Not all of them are truly high-functionality excipients.
- They all are mono-particular in nature.
- They all need an appropriate lubricant to be compressed.
- Co-spray drying is the preferable co-processing technology.

The use of these new excipients brought revolutionary advantages in the tablet development. In particular, direct compression formulations were updated and simplified by reducing the number of excipients and improving the formulation efficacy. The development and production benefits of the first generation co-processed excipients include:

- Simplified tablet development – less excipients and blending steps.
- Shorter development times, which drastically reduces R&D costs.
- Low segregation risk in direct compression.
- Better compressibility leads to reduction of the tablet weight and size – better patient compliance and reduced coating costs.
- Switching from wet granulation to direct compression gives radical production costs reduction.
- Simplified supply chain management – less excipients, less controlling steps.
- Getting free manufacturing capacity.

Table 1

Wet granulation Diclofenac Sodium	**Direct Compression** Diclofenac Sodium
Diclofenac Sodium 42.0 %	Diclofenac Sodium 42.0 %
Lactose Mohohydrate 19.7 %	Prosolv SMCC 57.5 %
Microcrystalline Cellulose 21.4 %	Magnesium Stearate 0.5 %
Starch 12.0 %	
Silicon Dioxide 1.4 %	
Croscarmellose 2.6 %	
Magnesium Stearate 0.9 %	

One example for successful HFE application: Diclofenac Sodium. The original wet granulation formulation was re-worked to a direct compression formulation with silicified microctystalline cellulose.

Same tablet size and weight but much elegant direct compression formulation can be achieved with Prosolv SMCC. The high functionality excipient acts as a diluent, binder, glidant and disintegrant , drastically reducing in this case the number of necessary excipients from six to two (see Table 1). The change from the expensive wet granulation to direct compression allows additional cost and time savings.

Still, open formulation issues by using this first generation HFE are lubrication and overmixing, sticking and capping as well as the drug dissolution reproducibility with poorly soluble actives. Next generation high- functionality excipients should be able to solve these problems. But how?

Time For Something New

The old conception diluents + binder + disintegrant is not innovative enough anymore. The blind co-processing of different excipients without a clear vision will lead merely to another "me, too" product.

It's time for something new, maybe something that, up until now, has been considered to be impossible or useless: The incorporation of the only one missing excipient group to make a HFE complete – the lubricant. Limiting factors in the lubricant co-processing were reduced compressibility respective to decreased tablet tensile strength; poor disintegration (disturbed water drainage into the tablet matrix); and drug dissolution. An additional question is what will happen if we affix the lubricant level in the excipient composite? Will the lubrication be enough after adding the API? Is it possible to overcome these at first sight insolvable difficulties?

As Albert Einstein once said, "Experience is more important than knowledge, but imagination is more important than experience."

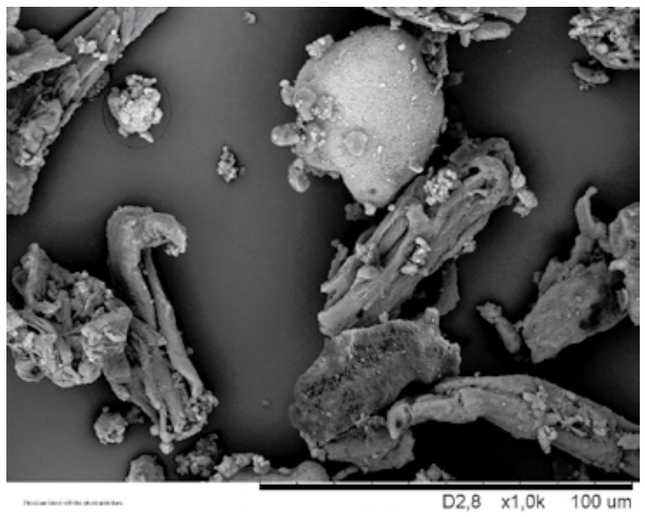

Fig. 1: Piroxicam blend with physical mixture of conventional excipients: Such dry blends trend to segregation and separation. The generated share forces by the mixing process are not sufficient to crash and attrite the piroxicam lumps which leads to very poor content uniformity of 19.59 %.

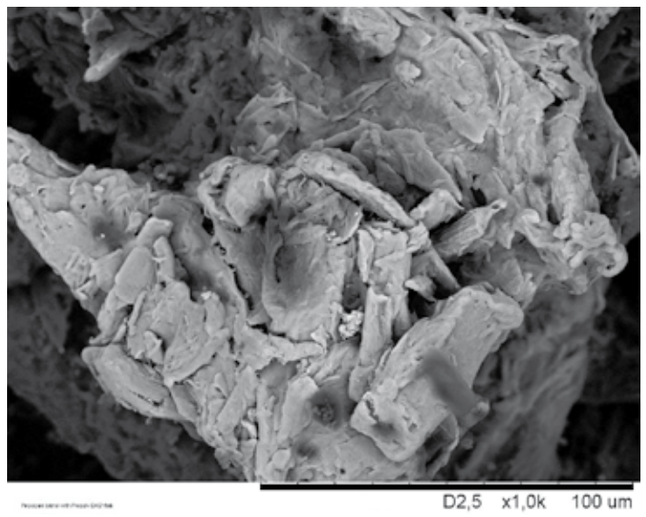

Fig. 2: Piroxicam blend with Prosolv easytab: The mono-particulate in nature excipient composite provides a superior homogeneity of the blend giving in the same mixing time an excellent content uniformity of 1.62 %.

The breakthrough is has been made. The first lubricant-coated high functionality excipient Prosolv easytab was recently developed and tested successfully in some very problematic direct compression formulations. With innovative particle design and improved functional performance this new product comprising microcrystalline cellulose (diluents and binder), silicon dioxide (glidant), sodium starch glycolate (superdisintegrant) and sodium stearyl fumarate (lubricant) showed a superior all-round functionality. The homogeneous lubricant distribution provides an excellent lubrication, sticking prevention, powder flow improvement, enhanced tablet disintegration and reproducible API dissolution without to disturb the function of the other ingredients.

To demonstrate the benefits of the new lubricant-coated high functionality excipient, a comparison with piroxicam as model API in direct compression was made. This BCS class II active (low solubility, high permeability) is a real challenge for the formulators with its poor blending properties and inconsistent dissolution results. In our study, two direct compression formulations with 5 % piroxicam were compared: one with easytab and one with the physical mixture of its individual components. The blending time 20 minutes, and the blends were compressed to 200 mg, 7 mm round-shaped tablets.

The active content uniformity was studied by using the classical analytical procedure and SEM (scanning electron micrograph) pictures of the ready piroxicam blends (figs. 1–2). Dissolution test of six randomly selected 10 mg Piroxicam tablets from the both formulations was preformed: USP Test in simulated gastric fluid (SGF).

The Next Generation

Lubricant co-processed excipients are the next generation high functionality excipients with a completed functional composition – diluent, binder, glidant, superdisintegrant and lubricant. Easy to use, simple application, robust formulation development, no overmixing, time and cost saving switch from wet granulation to direct compression and low production risk are among the advantages of this new HFE group.

How is looking the excipients future? There is no sense in trying to predict the future. As Alan C. Kay said: "The best way to predict the future is to invent it."

The new generation prelubricated high functionality excipients will simplify the drug development minimizing the formulation and production risk. The pharmaceutical industry needs reliable, cost effective and low risk production technologies which provide an optimal drug delivery and patient compliance. The creation of the lubricant-containing HFE is a considerable step forward in this direction. As every new idea this one needs time to be understood and accepted but one is sure – the future belongs to the high functionality excipients. Soon or later they will dominate the formulation development thank their outstanding functional performance.

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CPhI worldwide
where intelligence gathers

You can hear Edmont Stoyanov's presentation on high functionality excipients at the CPhI Pre-Show Conference on Oct. 4 at 5:30 p.m.

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AkzoNobel Buys Chinese Vehicle Refinish Supplier

AkzoNobel significantly boost its presence in the Chinese automotive market after agreeing to acquire Changzhou Prime Automotive Paint. Financial details were not disclosed.

Prime is one of China's largest vehicle refinish suppliers and a leader in the fast-growing mid-market segment. This sector is estimated to double in size within the next five years. Based in Jiangsu Province, the company develops, manufactures, markets and distributes automotive coatings, primarily for the refinish market.

The agreement follows AkzoNobel CEO Hans Wijers' recent announcement at the World Expo in Shanghai that the company plans to double its revenue in China to $3 billion within five years.

"This is an excellent deal involving an extremely well run business which gives us strong representation in one of China's most promising growth segments," said AkzoNobel's board member responsible for performance coatings, Leif Darner. "Our global capability, combined with Prime's marketplace knowledge, products and technical know-how, creates an enviable strategic proposition and will allow us to significantly grow ahead of the market." ■

Kemira Invests €25 Milllion in China Plant

Kemira is establishing a manufacturing facility in Nanjing, China to enhance customer service in the growing Chinese water treatment markets. The investment is expected to be at €25 million. The facility will be a state of the art regional production hub for a range of specialty process chemicals serving all of Kemira's customer segments.

The plant will be located in the Nanjing Chemical Industry Park (NCIP) about 300 kilometers northwest from Shanghai. "The NCIP chemical park is one of the state level chemical parks and gives easy access to raw materials and utilities. It also provides a good geographical position close to our targeted customer base with several modes of transportation for logistics. The location is also attractive for competent workforce," says Ronald Kwan, region head for Asia Pacific. "The Asian water chemistry market offers us ample opportunities for growth. Having a local manufacturing facility that works closely together with our R&D center in Shanghai will help us to tailor our offering to the local business needs," Kwan continues.

This investment underlines the strong commitment of Kemira to the growing customer base in Asia Pacific region. The facility will be 100% owned by Kemira, and will generate approximately 100 new employment opportunities in full operation. The building will start during 2011 and the facility is expected to be operational in 2012. ■

Roche Signs Up to $1.1 Billion Drug Deal with Aileron

Swiss drugmaker Roche Holding is entering a deal with U.S.-based Aileron Therapeutics worth up to $1.1 billion, giving it access to a new way of targeting diseases.

Aileron, which has built up a preclinical pipeline focusing on cancer, infectious disease, metabolic disease and immune and inflammatory diseases, is set to get an upfront payment of $25 million. It will receive up to $1.1 billion in payments if drug candidates are successfully developed against five targets, as well as royalties on any future sales.

The companies have not disclosed the targets, but Roche said they would be selected from its key therapeutic areas, which include oncology, virology, inflammation, metabolism and central nervous system.

Aileron is developing stabilized "stapled" peptides, a small protein, and its technology makes it easier for a drug to penetrate a cell. This can sometimes be a challenge when delivering a drug to the body. ■

Portfolio Management

The Art of Making the Right Choices

Planning Ahead – We are faced with choices in most aspects of life. In the majority of cases the consequences of our choices are relatively limited and, while we may weigh up alternative attributes, we do not do so consciously. However when the choices have serious and long-term consequences, for example the future shape of the portfolio of a pharmaceutical company, a far more systematic approach is needed. My purpose here is to take an overview of the method of choice known as Portfolio Management.

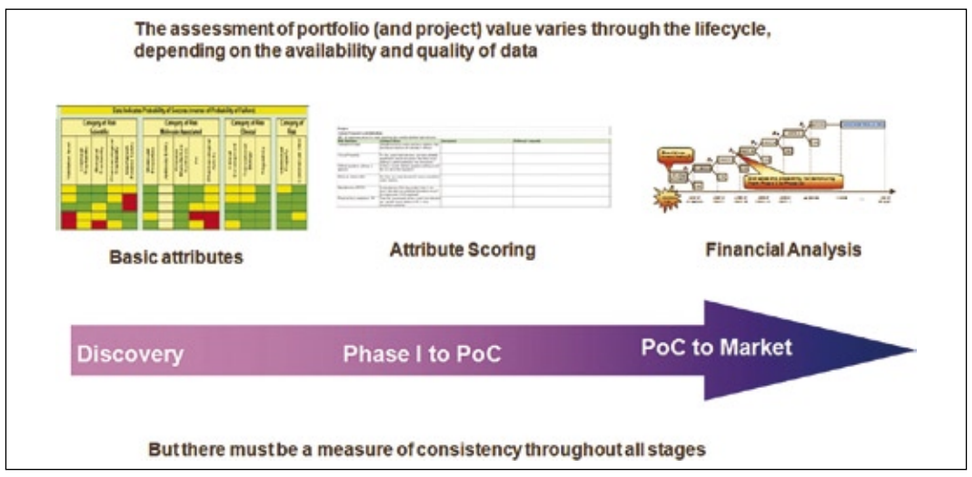
Roger Holdsworth
Director – R&D Portfolio Management
UCB

The pharmaceutical industry is at a crucial stage. Potential loss of revenue from drugs on the market and currently protected by patents is estimated to amount to between €50–70 billion between 2010 and 2015. Productivity, measured by comparing cost with the number of new entities launched, is low. To quote from a recent report from Price Waterhouse Coopers "The industry is investing twice as much in R&D as it was ten years ago to produce two-fifths of the medicines it then produced."

Although there have been some improvements in this situation over the past year, the underlying factors remain the same. For example, looking across the Pharma industry, the success rate (measured as the percentage of products reaching launch) for compounds entering the first phase of development remains at about 8–10 % and this number has not changed significantly despite major scientific advances in recent years.

We are working in a changing market place where focus on the patient is paramount. We will increasingly look at overall solutions, including diagnostics to ensure that drugs are administered to patients most likely to respond and least likely to suffer adverse effects. Devices to make administration simpler and improve compliance will be developed in parallel with the drugs themselves and this will in turn lead us into new alliances between pharmaceutical companies and device designers.

These new strategic directions are likely to lead to more complex and dynamic portfolios and in turn to a greater need for effective choices.



Evaluation of the portfolio throughout the development lifecycle

Portfolio Evaluation And Management

The function of portfolio management is clearly differentiated from project management although there are many close interactions between the two. To use a well known definition portfolio management is about doing the right projects (the definition of the word right in this context varies with circumstances). Project management, is concerned with doing the projects right (delivering the required outcome of appropriate quality on time and within budget).

Although the prioritization of projects within a portfolio is an important deliverable for portfolio management, it is not the only one. The determination of which combination of projects will deliver value in line with company strategy is a central objective, combined with the ability to look into the consequences of different scenarios.

Evaluation

Evaluation of the portfolio (and the projects within it) is in general based upon four main pillars, value, cost, risk and timing. A number of other criteria, for example strategic fit, may also be taken into account.

The way in which value is assigned to a project depends very much on where it sits in the project lifecycle (fig. 1). In the early stages a financial evaluation is less likely to be helpful because even if the primary target disease is identified, predicting the characteristics of a specific drug some 8–10 years ahead of launch will be difficult – assessing the price which might be achieved or the competitive position even more so. In many cases, therefore, we must rely on some surrogate measure of value related to the actual or required characteristics of the drug and the market into which it will be launched.

In discovery research the most significant attributes will be associated with the scientific data supporting the molecule. As a method of evaluation, the attributes can simply be color coded (green is acceptable; yellow is possible issue; red is warning) to give a qualitative feel for the potential of the candidate drug.

Later in development during phase 1 and up to proof of concept (POC) as knowledge is gained on the potential drug and the disease(s) for which it may be useful, the scientific attributes will be better defined and it will be possible to add more detail on commercial measures (size of market, potential competitive environment, time from planned launch to loss of patent exclusivity). The aim at this point is to score the attributes in some way in order to provide at least a semi-quantitative surrogate view of value.

Beyond POC, the emphasis generally moves to financial measures of which the most frequently used is risk-adjusted net present value (RANPV). The net present value summarizes the overall project value (taking into account cost and revenue) in today's money. The RANPV also takes into account the technical risk of failure to launch by reducing the NPV in line with identified risks.

Consistency

To ensure that projects within the portfolio are treated on an equable basis it is important that all the data used are based on a consistent definition of the project objectives. In addition as the evaluation of project attributes is to some extent subjective cross-checking the data with the appropriate stakeholders in advance of the analysis avoids what should be a discussion on the relative merits of different portfolio scenarios becoming a critique of the data contained in the analysis.

Moreover, it is essential to ensure that sanity checks are in place following the analysis. For example it may be that a project which is of strategic importance but not particularly high monetary value would be excluded from the optimal portfolio based purely on the numbers generated.

Outcome

Clearly any analysis is only useful insofar as it supports decision making by the appropriate group of senior managers. Clear recommendations are needed and ideally alternative scenarios should be presented for consideration. These alternatives could include, for example, taking on more or less risk or considering the scheduling of projects to optimize delivery in particular therapeutic areas. When decisions regarding what is or is not considered to be the optimal portfolio are made they need to suggest clear courses of action and be clearly communicated.

While regular set-piece analyses form part of the strategic planning cycles of most companies, the process should allow for ad-hoc reviews to examine the effect of internal and external change on the portfolio.

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Hot Melt Extrusion Technology

Growing importance in Pharmaceutical processing

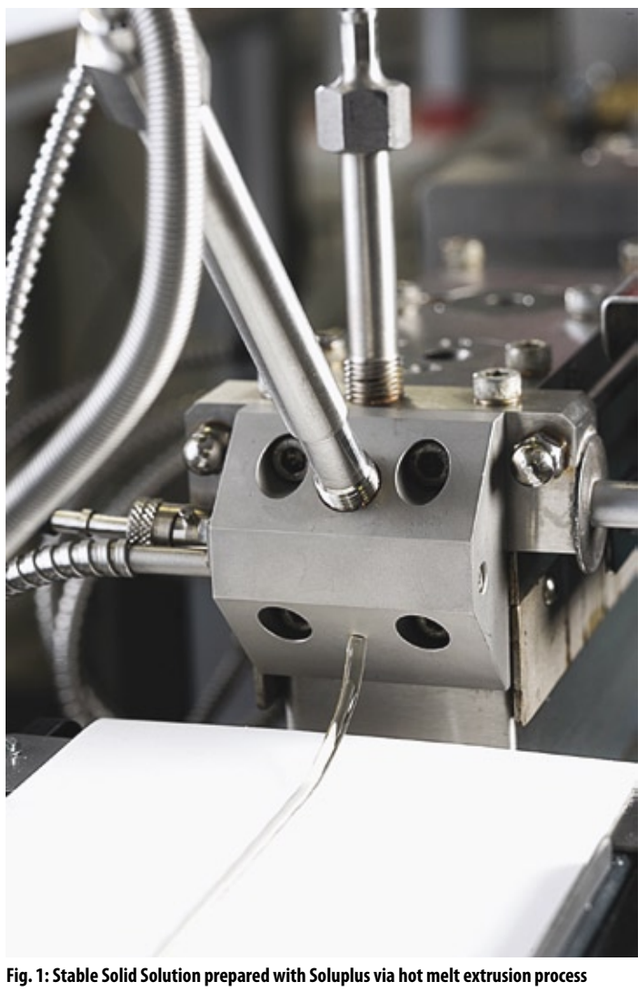

Fig. 1: Stable Solid Solution prepared with Soluplus via hot melt extrusion process

Modern Manufacturing – Hot Melt Extrusion Technology (HME) has been on a successful path in the pharmaceutical industry for solubilization and bioavailability enhancement, particularly regarding poorly soluble drugs.

Vanessa Occhipinti
BASF

HME Evolution

In other industries, such as plastic, rubber and food products, this technology has extensively been used since the1930s. About 20 years ago, the pharmaceutical industry began to employ melt extrusion as a promising solution for its solubilization of almost insoluble drugs. More than 100 articles have been published in scientific literature and the number of HME patents has increased tremendously– mainly in the U.S., Germany and Japan. It is easy to understand why the pharmaceutical industry invests in this process, since it has many advantages; no organic solvents or water are needed, shorter and more efficient processing times can be achieved, as a result of the process solid solutions can be very stable, and solubility and bioavailability of poorly soluble drugs are improved. The only relevant disadvantages are that HME may not be applicable for heat-sensitive active ingredients, they must be almost moisture free, and it requires investment in equipment and training (although the company can decide on third-party production with a firm that already possesses the necessary equipment and expertise).

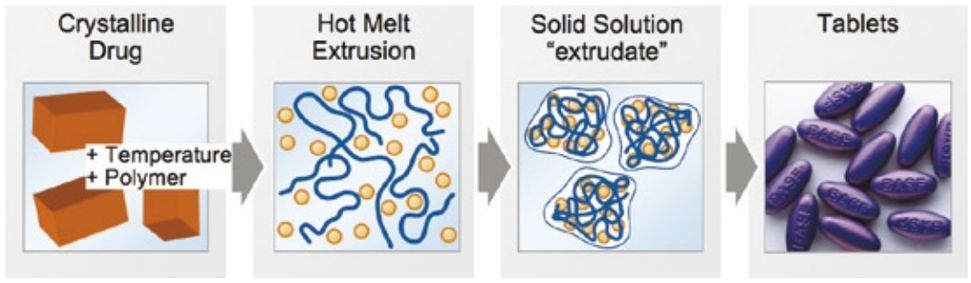

Fig. 2: Steps applied from a crystalline drug to a finished product: Real benefit to the patient

Solid Solutions

Solid solutions are similar to liquid solutions, whereas the matrix is not a liquid, but a solid. The most reliable and stable system is achieved when the drug is molecularly dissolved below the saturation point.

The practical benefit of having stable solid solutions with the drug being molecularly dissolved is the capacity to orally administer drugs that are difficult to solubilize (fig. 2).

The choice of an adequate polymer as a matrix to form stable solid solutions is crucial in HME. The polymer must have thermoplastic behavior and be stable at the extrusion temperature. Furthermore, it should have a suitable glass transition temperature between 50 and 180 °C, low hygroscopicity and no toxicity, since large amounts of polymer are used. Features such as lipophilicity and a few categories, e.g. hydrogen bonding acceptors (or donors) and amide groups, are commonly prerequisites for a high solubilization capacity. This explains why povidone and copovidone are suitable for HME. In particular copovidone is much more lipophilic than many other water soluble polymers which contain hydroxyl groups and therefore best meets the lipophilicity requirements of poorly soluble drugs. Nevertheless, other entities of different chemistry have been used for HME: polyethylene glycols, polyethylene oxides, hydroxypropyl and ethyl celluloses, acrylates and, most recently, a unique polymer with an amphiphilic chemical structure (Soluplus, fig. 3).

Pioneer In HME

Soluplus is the first excipient in the market especially designed for hot melt extrusion. Dissolution results showed a considerable enhancement in the drug release of poorly soluble active pharmaceutical ingredients, e.g. itraconazole. This study was performed with solid solutions prepared with Soluplus and compared with several polymeric matrices. The best results were achieved with Soluplus (fig. 4).

Considerable improvements in the oral bioavailability of several poorly soluble drugs, e.g. itraconazole, were achieved with solid solutions prepared with Soluplus. The bioavailability studies were conducted in beagle dogs.

A wide range of safety studies have been performed on Soluplus and the product safety is demonstrated in comprehensive documentation.

Conclusion

Most of the current drug candidates are barely soluble by regular solubilization methods and therefore not sufficiently absorbed from the gastrointestinal tract. Thus many promising drug products have not been able to reach the market because of failures in bioavailability studies. HME is now opening new doors for drugs that have suffered from this problem.

A detailed list of references can be obtained on request from the author.

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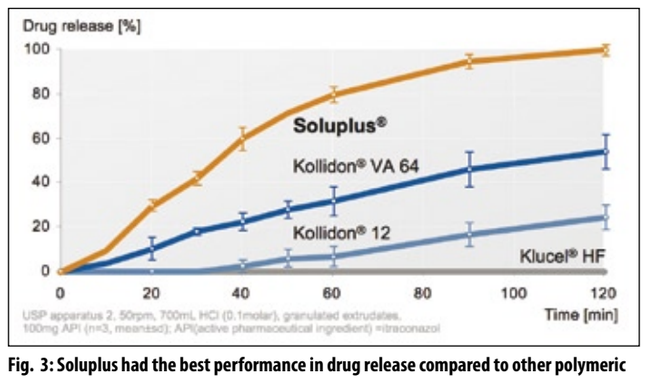


Fig. 3: Soluplus had the best performance in drug release compared to other polymeric matrices.

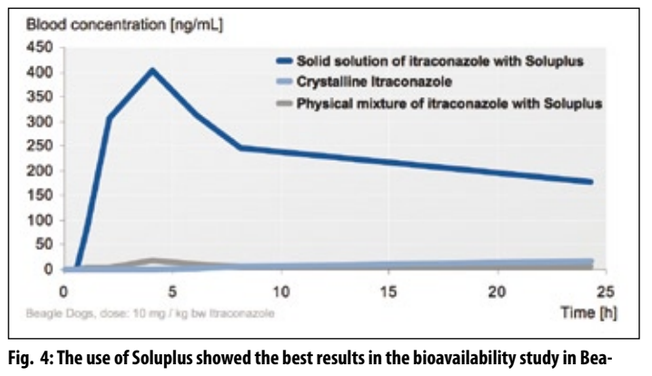


Fig. 4: The use of Soluplus showed the best results in the bioavailability study in Beagles, using different preparations of itraconazole.

Fluctuating Raw Material Prices

How to Manage Higher Costs, Inflation and Collapsing Margins

Rollercoaster Ride – Before the economic crisis, raw material prices knew only one direction: upwards. The sky seemed to be the limit. Now the situation has changed. No one seems to know in which direction raw material prices will go. They go up and down with irregularity and without any discernible pattern.

Dr. Karl-Heinz Sebastian
Bonn

Dr. Andrea Maessen
Simon-Kucher & Partners, Cologne

Companies have a hard time correctly judging the risk of strongly fluctuating raw material costs. If they pass on increasing costs only minimally, delayed or too conservatively, or if increasing raw material costs coincide with decreasing sales prices, a margin squeeze is inevitable. Highly fluctuating raw material costs and ineffective price management can greatly endanger a company's success.

Bayer, as an example, expects a loss of approximately €500 million in 2010 due to higher raw material costs. The steel industry is in a similar predicament. A price difference of €30 per ton for the remaining capacity of the year is enough to cause either a small profit gain or a huge loss for one major German steel manufacturer.

How do market players assess the current situation? Do volatile raw material costs pose a danger to the economic recovery? What determines the highs and trends of raw material prices? We asked over 250 European managers from the chemical, construction and base material industries these questions.

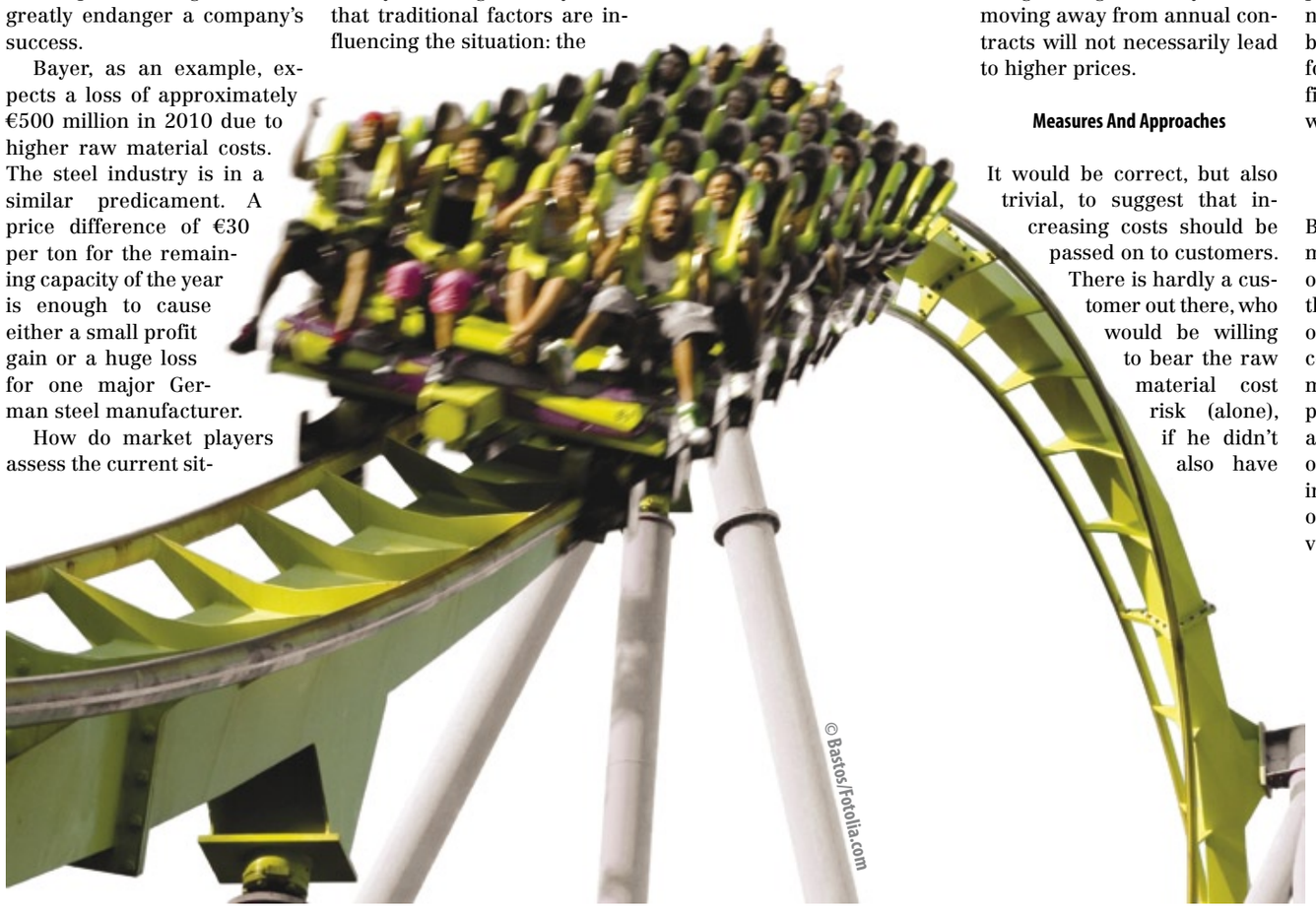
Assessment of the Current Market Situation

The price trend of raw materials with its current ups and downs is primarily driven by supply and demand, according to approximately 60% of the surveyed managers. They claim that traditional factors are influencing the situation: the crisis, the reserve level, the free capacities and the current inventory.

But there are other influencing factors at play here: speculations. In an effort to spread out their risk and take advantage of opportunities, investment funds, retirement funds and insurances are investing in the raw material market. Yet, only 40% of the responding managers believe that speculation is the cause of higher raw material costs. This emphasizes that speculators are "only" strengthening the up and down trend. They do not set a specific trend, they simply go where ever looks best.

Facing increasing volatility, companies must move away from rigid and fixed systems. Annual contracts, e.g., are no longer appropriate or up-to-date with the currently volatile raw material cost developments. 70% of the managers confirm this. Moreover, 80% of the respondents are sure that the elimination of annual contracts will further exacerbate the price dynamics.

In a dynamic market and cost environment, shorter terms (quarterly and monthly prices instead of annual contracts) allow companies to quickly and accurately assess the price opportunities and adapt prices accordingly. The gap between contract and spot prices should then start to decrease. 50% of the respondents feel that shortening the negotiation cycles and moving away from annual contracts will not necessarily lead to higher prices.



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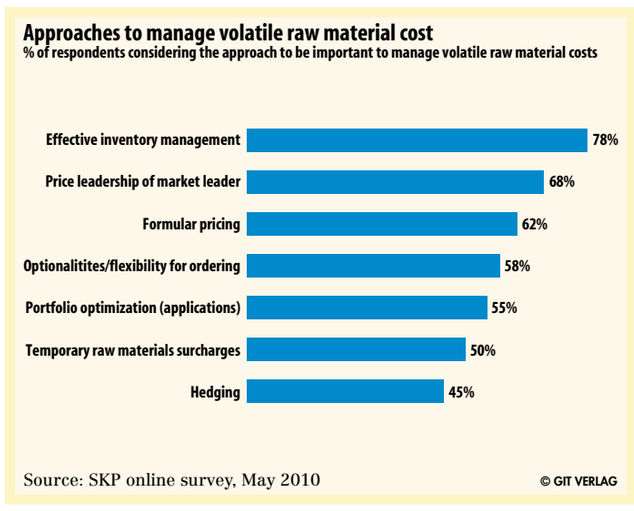
Measures And Approaches

It would be correct, but also trivial, to suggest that increasing costs should be passed on to customers. There is hardly a customer out there, who would be willing to bear the raw material cost risk (alone), if he didn't also have the chance to pass on the costs to his buyers. Since mass product buyers are usually at the end of the value chain, the acceptance of such cost increases is low. And the high competitive intensity is another reason, why the costs cannot be converted into price increases. In such cases, price formulas, like "costs up, price up," cease to work as intended. Yet, 62% of the managers are of the opposite opinion. They feel that the price formulas do work as an effective means of overcoming cost and price dynamics. This percentage is particularly alarming: formula pricing in fact turns active price management into passive "pricing-by-the-rules."

A recent case from the steel industry reveals how price formulas are not necessarily the cure-all: to increase long-term customer loyalty, major steel producers wanted to continue negotiating annual contracts – but with formulas. Most buyers fought this, as the retention of fixed prices in their contracts was what they wanted.

There Must be Other Solutions

But what are they? Inventory management, according to 78% of the respondents, is seen as the most important means of dealing with raw material cost fluctuations. 70% of the managers, the basis material producers especially, feel that active price leadership on part of the market leader is another important solution. Contract optionalities (regarding dates, volume, standards, fees, etc.) are seen by 60% of the managers as important. Only every second respondent considers surcharges as a means of managing cost and price dynamics.



Conclusions and Recommendations

Assessing the current raw material situation, including potential measures and approaches, leads us to the following conclusions and recommendations:

The (increasing) dynamics and fluctuation of raw material costs, along with the tendency to shorten contract terms, require more efficient dynamic price management from a company. Pricing processes must become faster, more transparent and more effective in reacting to changing market environments. Simple and clear pricing guidelines help to overcome the complexity of pricing. After all, not only do the monthly or quarterly contract negotiations and the cost dynamics determine the price, so do other factors: the customer size and negotiating power, the order behavior of customers and the customer value.

The higher requirements also demand that companies are able to forecast supply and demand developments and that market-leading companies practice active price leadership. Price forecasts are difficult and not always 100%, but they are not impossible. An educated guess based on an expert system is always preferable over a subjective decision based on gut feeling. This is especially relevant for market leaders who set the market tone and have to possess strong pricing competence and expertise.

Price formulas are not cure-alls. Initiating and setting price changes should not be based solely on escalation clauses. This is the responsibility of management, which should review the options of time-restricted surcharges as price-relevant factors.

Price formulas are only recommended, if raw material costs are the main or sole price driver. If all cost factors cannot be objectively assessed and indexed, then the terms of buying and selling cannot be properly matched. If other factors like inventory, demand or customer behavior are the primary price drivers, then price forecasts or decision support models would improve the price setting process.

Initiating and setting price changes is a key component of price leadership strategies.

Dr. Karl-Heinz Sebastian and Dr. Andrea Maessen

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Adhering To Quality Demands

Distributors Must Believe in the Products it Sells

Take Responsibility – Quality of products is one of the most important parameters for global players, no matter in which branch, but when it comes to healthcare, it is definitely the most important of all. To ensure the highest standard in quality, it is inescapable to employ only the best experts on the market. Dr. Alen Guy is known as such an expert, working successfully in the excipients sector for several years. In May 2010 he joined IMCD Group one of the biggest distributors in the chemical industry, as technical director of pharmaceuticals. Brandi Schuster and Philipp Praet talked to him about responsibility in pharmaceutical affairs and new trends concerning the pharma industry.

CHEManager Europe: There is no universally accepted standard defining the GMP standards required in the manufacture of excipients. While most European manufacturers adhere to the Voluntary Guidelines, others do not, which puts Europeans at a cost disadvantage. What is your take on the situation?

Dr. Alen Guy
technical director of pharmaceuticals for the IMCD Group

A. Guy: My take on this situation is that excipient manufacturers should maintain their adherence to quality demands. The pharmaceutical industry will progressively be guided towards or be required to adhere to quality by design standards and principles. To do this they will need to work with excipient manufacturers that are prepared to provide them support that will not be possible or at least more difficult from lower cost environments. Quality costs money. At the moment low-cost suppliers of goods are adhering to minimums associated with monographs. Monographs do not deal with functionality and performance or, indeed, production stability.

Using lower cost excipients will likely force manufacturers to eventually suffer higher costs in managing their production. Operators will most likely see a greater incidence of variances in manufacturing.

By using higher quality materials it should be possible to quantify more important cost savings. These can be enshrined in such areas as operational excellence and go beyond simple bill of goods accounting.

The true cost of excipients in pharmaceutical and nutraceutical manufacturing is very often really quite small. The cost of using a minimal quality excipient at low-cost may eventually run into millions of dollars over the life of a pharmaceutical product.

Excipient manufacturers that operate in high quality management of processes will minimize this impact. It should not be a case of being able to afford high quality excipients as much as believing you cannot afford not to.

How much of the burden of responsibility do distributors shoulder when it comes to product quality?

A. Guy: Ultimately, the regulations in virtually every country state that finished product quality is the responsibility of the company making the finished product. However, distributors typically supply a very large number of companies; therefore their products touch an enormous number of finished products.

Some of these products will undoubtedly reach the shelves of friends and family. A distributor must always ensure its products are neither adulterated or at risk of adulteration. The distributor must believe in the quality and performance of the products it sells. To ignore this would just make it a trader of goods.

What can you tell us about new trends within solid dose formulations and the impact they are having on the industry?

A. Guy: Trends in formulation for solid doses can begin for a variety of straightforward commercial reasons, such as lifecycle management. However, their acceptance by health authorities and patients is created by therapeutic need and adherence improvement – the ease with which the patient can take the medicine.

The continuing trend toward orally dispersible tablets – also known as ODTs – granules or films has been pronounced. It is also true that controlled release doses are increasing in popularity but this area is tightly managed analytically. The orally dispersible trend has developed towards a variety of forms such as ODTs, thin-films, chewables and dispersible granules because of the ease in swallowing these compared with many tablets. I feel that it is orally dispersible forms that are the most challenging; and the formulation difficulties are less objective and more subjective than traditional solid dose formulations.

Can you explain why?

A. Guy: In its simplest form, a solid dose tablet is formulated to have minimal tableting quality issues; meet disintegration and dissolution properties that ensure the drug is delivered appropriately and quickly; and be economically viable. Such tablets are normally swallowed with a small amount of water. They are typically produced in high-speed tablet presses, often coated and are relatively simple to make. The performance is based upon strict analytical control with all tablet samples meeting criteria for dose loading, disintegration time and dissolution of the active. This is a very objective analysis, with little margin of error, when carried out in a well-controlled environment.

A solid dose orally dispersible tablet relies upon so much more than a simple tablet that is swallowed. All the necessary requirements for a drug product are still required – dose, disintegration, dissolution etc. – but now the human element appears. Therefore taste and mouth-feel become relevant. This is no longer objective. There comes a need for people that are expert in marketing and consumers to be present in the development process much earlier than otherwise expected. This can be unsettling for formulation and development groups.

The excipient choices for these forms are informed as much by how they taste and feel as to how they flow or compact. It is at this point that formulation gets tricky and formulators need more help. It is arguable that pharmacy is reverting to its roots and that the personal touch is becoming more apparent again.

What kinds of excipients lend themselves to such formulations?

A. Guy: These include polyols, sugar-based granulations, flavors, texture enhancers, disintegrants and coatings. The way these excipients interact is vital to understand, but once the product is working in production and the patients like them, they can become very difficult to dislodge from the segment. People become aware of how their medicine tastes and will notice even very subtle differences. Such differences may make the product less palatable, or even present the patient with some doubt as to its stability and performance.

Who stands to benefit from this?

A. Guy: I am excited by this trend as it could truly provide products that are easier to administer to difficult patient groups such as pediatric, long term care or the elderly. The number of people in these segments is growing and medicine needs to be more effective and adhered to in order to make our welfare system more cost-effective. Solid-dose formulation that includes orally dispersible forms to a much greater extent can have a profound effect on our healthcare provision.

► www.imcdgroup.com

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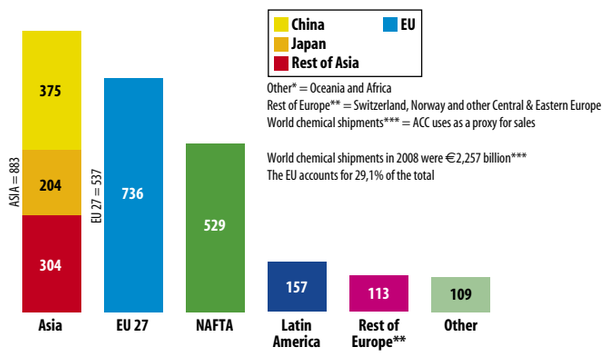
The State of the European Chemical Industry

Geographic breakdown of world chemicals shipments Figure 1
2008
Chemicals shipments (€ billion)



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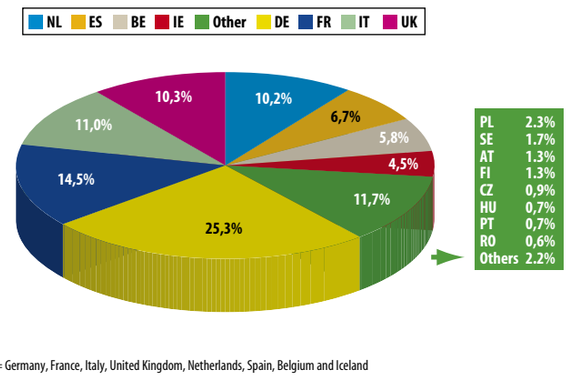
EU chemical industry sales by country Figure 2
Percantage share of European chemical sales



Big 8 = Germany, France, Italy, United Kingdom, Netherlands, Spain, Belgium and Iceland

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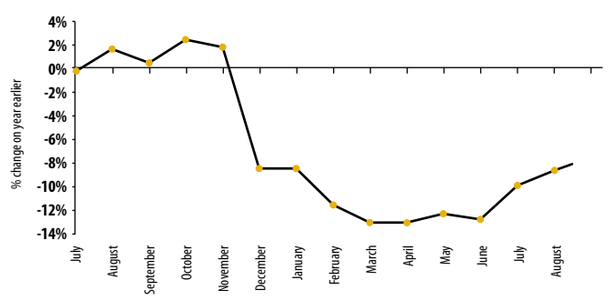
KPMG's recent chemical report, "The Future of the European Chemical Industry" showed that the European chemical industry drives a significant part of the economy across the EU. Over 1.2 million workers are employed in the industry, manufacturing products, supporting research and providing supplies in many regions of the EU. Over the years, the European chemical industry has shown considerable resilience, strength and adaptability. In 2007, 12 of the 30 leading chemical companies in the world were headquartered in Europe, representing 10% of world chemical sales. Recent industry growth has been driven mainly by regional sales. From 1997 to 2007, sales more than doubled among EU partner countries. This growth has been supported by the removal of trade and nontrade barriers among the EU countries and by the size of the internal market – almost 500 million consumers across Europe. In 2008, 23% of European chemical sales were for customers outside of the EU, in particular to markets in North American Free Trade Agreement (Nafta), neighboring countries (especially Turkey and Russia) and Asia.

European chemical industry output, July 2008 – August 2009 Figure 3



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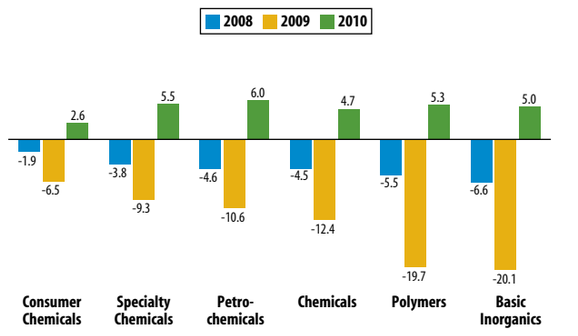
EU chemicals production: sector outlook Figure 4
Production (volume): growth rate (yoy)



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KPMG's report also showed the European chemical industry hit its lowest point in March 2009, where it saw a monthly year-on-year decline of 13.2%, a figure that if annualized would represent an output decline of approximately €56 billion. In Europe, the chemical industry saw massive reductions in demand for plastics, paint and man-made fibers, especially in key markets such as automotive and construction. This fall in demand led to a severe destocking by many companies, with some companies (particularly in the base chemicals, polymers and specialty chemicals sectors) watching their own output decline by 30–60%. Many analysts and industry observers predict a gradual though modest recovery, with demand not returning to 2007 levels until probably 2012 or even later. Cefic expects a 5% increase in output growth in 2010 compared to 2009. Henrik Meinke, writing on behalf of the European Chemical Marketing and Strategy Association (ECMSA), also offers guarded optimism, suggesting that a significant global recovery should not be expected before 2011, although industry conditions have been improving in 2010.

Lanxess plasticizers deemed innocuous
The phthalate-free plasticizer Mesamoll II manufactured by Lanxess has taken its final step toward gaining European approval for use in food contact applications. The European Food Safety Authority (EFSA) published its scientific opinion on the additive concluding that alkyl(C10-C21)sulfonic acid phenyl ester, the chemical component of the plasticizer Mesamoll II, does not pose a risk to humans when used to manufacture toys or in dry and water-based food packaging applications. A positive evaluation from the EFSA is generally the final step before European approval is granted. Lanxess expects to receive official approval from the European Commission this fall.

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Styron Names Richard J. Diemer Jr. as Executive Vice President and Chief Financial Officer

Styron has announced three new members to the company's executive leadership.
Richard J. Diemer Jr. has been named executive vice president and chief financial officer of Styron. Diemer was previously the senior vice president and CFO of Albemarle, a US-$2.5 billion specialty chemical company based in Baton Rouge, LA, U.S. Celso Goncalves, who is currently CFO of Styron, will remain with the company through year-end to ensure a smooth transition.
Diemer brings to Styron a 25-plus year track record in strong financial and strategic leadership. Diemer reports to Pappas, and is a member of the Styron executive leadership team. Diemer's role is effective Sept. 7. He joined Albemarle in August 2005 and was elected senior vice president and chief financial officer (CFO) effective Sept. 1, 2005.

Gerd Löbbert Appointed Borealis Executive Vice President for Polyolefins

Borealis announced the move of Gerd Löbbert from his current position as executive vice president for base chemicals to the position of executive vice president for polyolefins, effective Oct. 1.
Lorenzo Delorenzi, currently executive vice president for polyolefins has decided to leave Borealis by the end of this year and return to Belgium to pursue other career opportunities.
Gerd Löbbert joined Borealis in January as executive vice president for base chemicals. Prior to Borealis, he held various positions at BASF, specifically in the area of pigments, polymers and additives. He was marketing director inks and pigments in the U. S.; vice president, global business unit printing inks and dispersions in Stuttgart, Germany; and group vice president performance chemicals for coatings, plastics and specialities.

Personnel Changes at BASF's Care Chemicals and Intermediates divisions


Walter Dissinger


Gabriel Tanbourgi


Beate Ehle


Sanjeev Gulab Gandhi

In order to prepare for the integration of Cognis, BASF has established a new division. Effective August 1, 2010, BASF's Care Chemicals division has split into two separate divisions: The Nutrition & Health division incorporates the Nutrition Ingredients and Aroma Chemicals businesses, as well as Pharma Ingredients & Services. Walter Dissinger (47) has become President of the newly established division. The Personal Care, Hygiene, Home Care and Industrial Formulators businesses forms the Care Chemicals division that is still headed by Gabriel Tanbourgi (54). Both divisions are part of the Performance Products segment.
Beate Ehle (46), formerly President of BASF's Intermediates division located in Ludwigshafen, Germany, has become President for the regional division Market & Business Development North America located in Florham Park, New Jersey, USA. The former President, Joseph C. Breunig has left the company on August 31, 2010. Sanjeev Gulab Gandhi (43), Senior Vice President, Petrochemicals Asia Pacific, at BASF South East Asia located in Singapore has succeeded Beate Ehle as President of the Intermediates division.

Supplement inside!

This issue contains a supplement from Groupe Novasep.

Novasep presents it's global solutions for the manufacture of synthetic molecules as well as their unique palette of technologies.

www.novasep.com

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