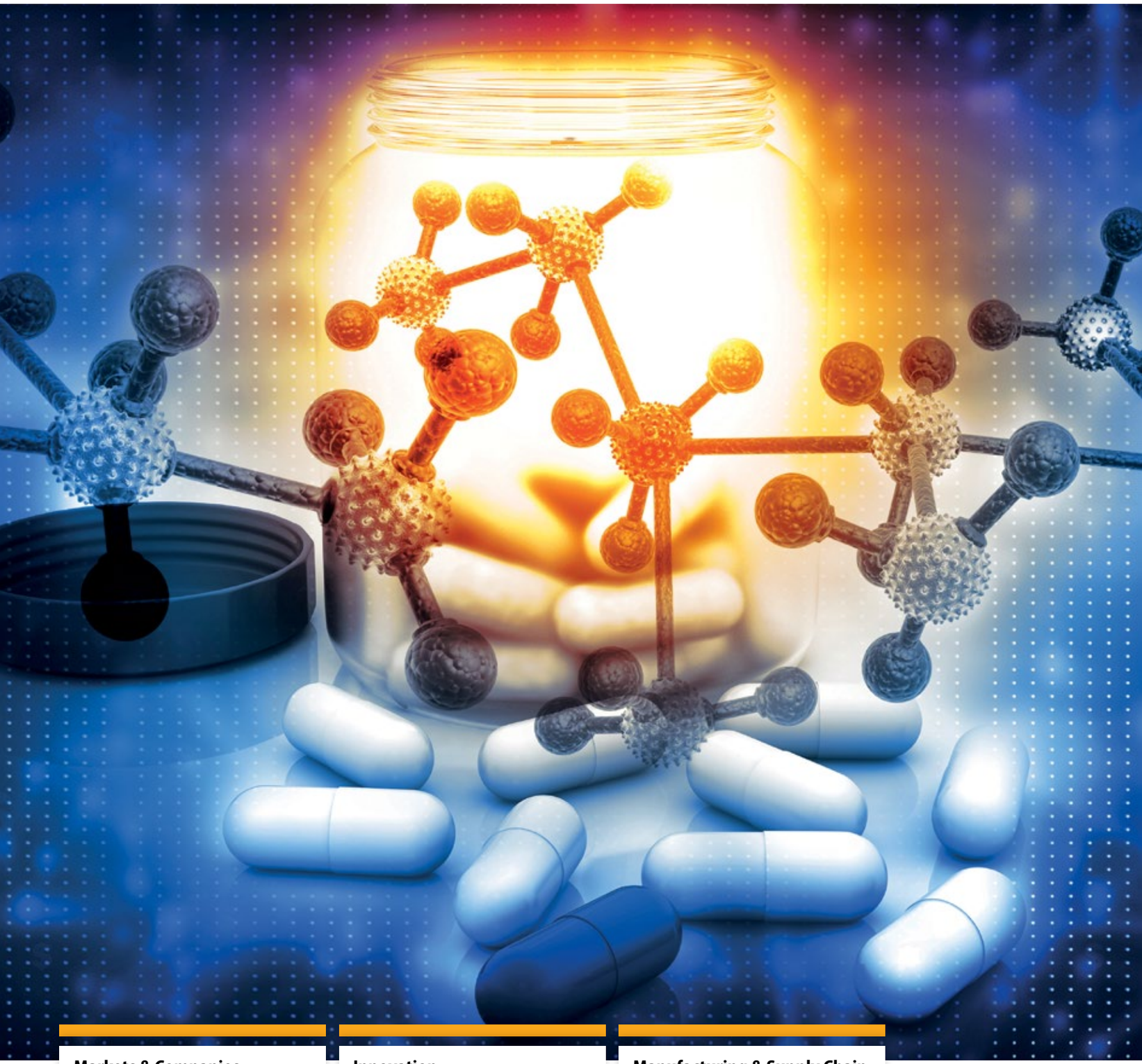
PHARMA & BIOTECH

CHEManager INTERNATIONAL

1/2016



Markets & Companies
Top 10 Brands in the Pharmaceutical Industry, Pharma M&A Update, Market Reports, Expert Opinions, Company News

Innovation
How the Pharma Industry Can Bridge the Innovation Gap, Trends and Success Factors in Chemical and Pharmaceutical Research

Manufacturing & Supply Chain
Developing New Synthetic Routes, High-Potency Manufacturing, Drug Shortage Prevention, Specialized Pharma Logistics

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azelis PHARMA

Creating value, growing together

Diagnosis: Innovation Insufficiency – Treatment: Combination Therapy

Since the beginning of the 21st century, pharma M&A activity has exploded. In addition to mergers and acquisitions, outsourcing of research and manufacturing has become common place.. Whether or not this will translate into a more viable industry, however, has yet to be determined.

Many of the mergers and acquisitions were predicated on increased efficiency in the discovery and development of new drugs and therapies as the lack of new products is a major threat to many pharmaceuticals companies.

The industry has focused on closing the innovation gap for more than two decades. No one solution can bridge the R&D productivity gap. The future of pharma innovation demands a holistic approach that addresses every R&D dimension—strategy, organization, funding, technology and expertise.

Expert Insights

For this first edition of *CHEManager International Pharma & Biotech* we asked R&D experts of chemical & pharmaceutical companies to share their opinions on success factors and challenges in research and the role of IT tools and human ingenuity. More than twenty opinion leaders ranging from CEOs to heads of research and process development have responded to our questions. Their statements deliver first-hand insight into innovation strategies and provide an outlook on the future of pharma research.

The Art of the Alliance

One trend that crystallizes from the expert statements is related to the increasing role of research collaborations. Just two decades ago, many scientists worked isolated in their "silos." Cooperation with companies and institutions was more the exception than the rule. This has changed completely. Alliances between big pharma and academia, hospitals and biotech s are common practice today. Dr. Magid Abou-Gharbia, author of our feature article, is a living example of a scientist who has been an accelerator of collaboration in pharma research.

Staying Ahead In Outsourcing

Outsourcing of research, development and/or manufacturing activities continues to be an important topic for pharmaceutical companies of all sizes as it enhances the overall performance of companies by enabling them to focus their resources on core activities. Accordingly, the contract research, development and manufacturing industry continues to grow, driven by an expanding array of customer requirements presenting new challenges for both, Pharma and contract research/contract manufacturing organizations (CROs/CMOs).

The outsourcing trends also poses new challenges on the pharma supply chain including a strong increase in the complexity of pharma logistics.

Biosimilars and Modular Manufacturing

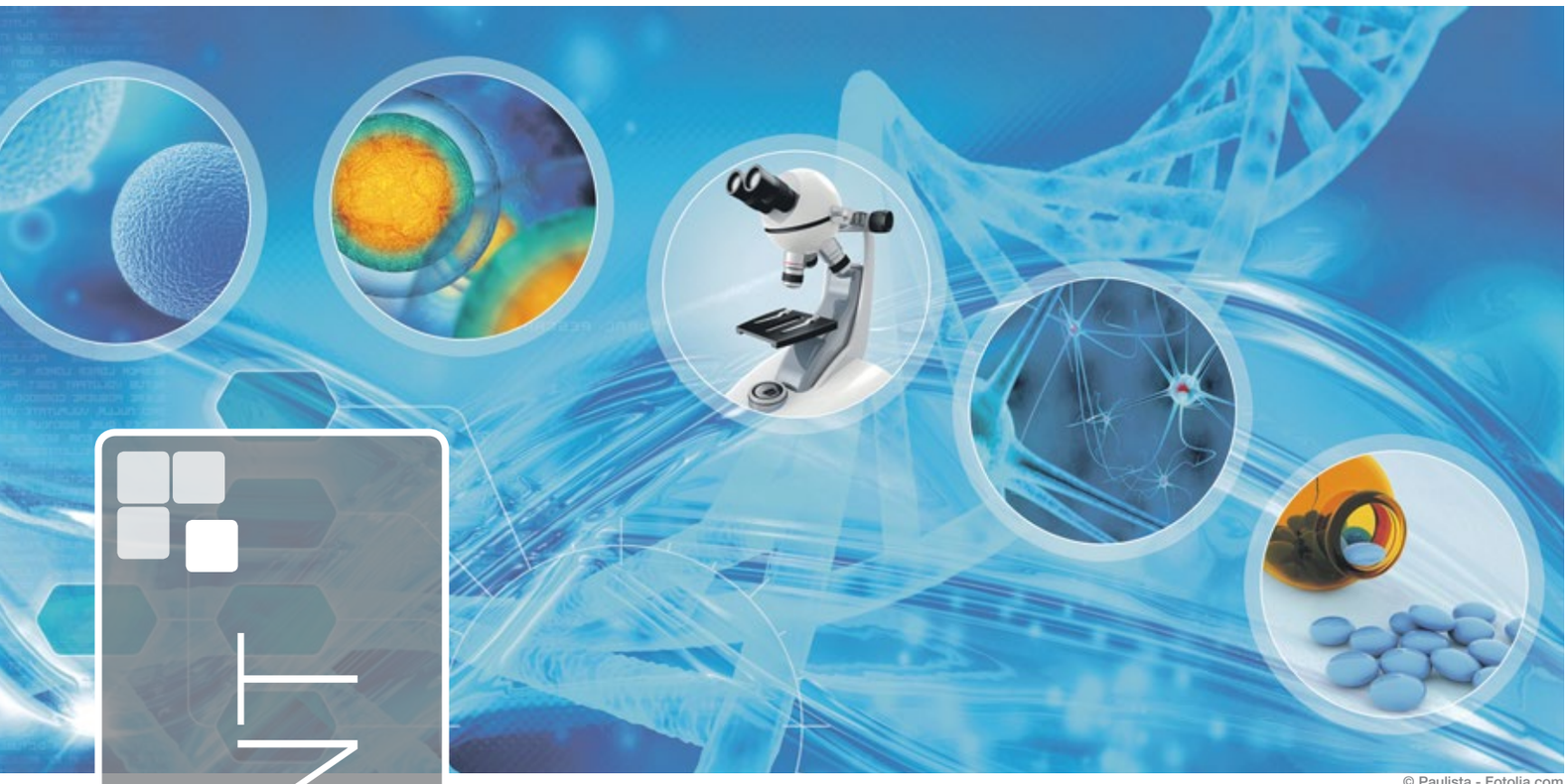
Other trends in Pharma include the upswing of biopharmaceuticals on the products side and the tendency away from big-volume products to small-volume products on the manufacturing side.

The market for biopharma products is expected to boom over the next two decades. Industry estimates that 30% to 40% of all pharmaceutical products in the next 10 to 15 years will be produced with biotechnological processes. With many research-based products in the pipeline, the first batch of biosimilars is approaching registration.

In pharma manufacturing we will see more modular concepts allowing a shorter change over time and a higher agility of a factory. This is of special importance for biopharmaceutical products and underlines the need for excellent engineering. As the importance of high-potency APIs is increasing, CDMOs and CMOs boost investments in dedicated high-potency manufacturing lines.

Please take the time to study this issue, it will be time well invested.

Dr. Michael Reubold and Dr. Ralf Kempf
Editors, CHEManager



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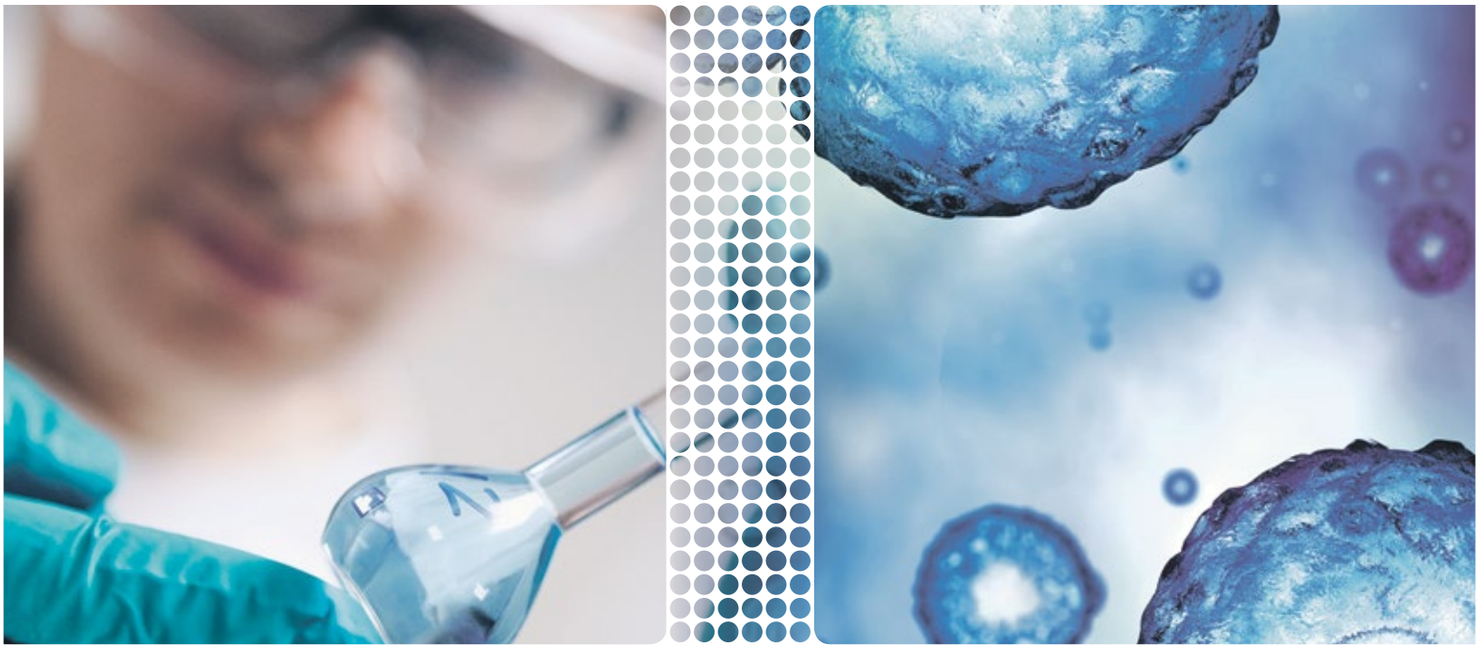
Content

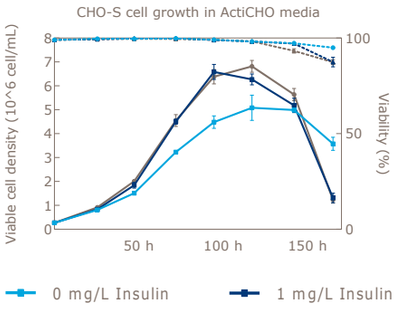
Consistency. Proven

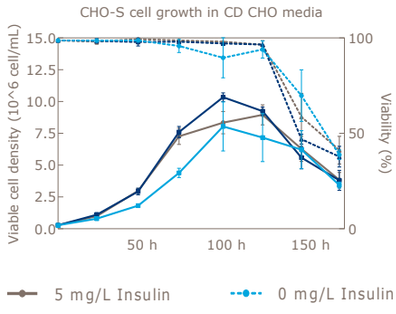


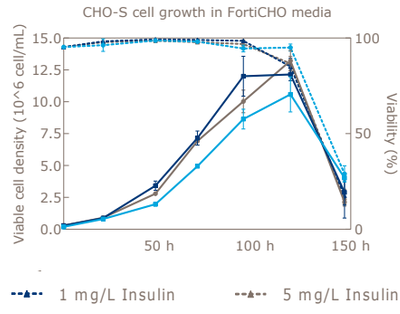
Increase viable CHO cell density by supplementation with recombinant Insulin Human AF

CHO cells are one of the most widely used platforms for the production of biopharmaceuticals. Increased demand for safety and reliability has moved the standard for CHO cell culture media from Serum to Serum free and further on to chemically defined media. UAB in collaboration with Novo Nordisk Pharmatech (world's largest supplier of recombinant insulin) has shown that addition of animal origin free insulin to three leading commercially available off-the-shelf chemically defined media resulted in significant increases in viable cell density. In addition to this benefit insulin has been proven to aid in the expression of difficult to express proteins.

To learn more visit www.novonordiskpharmatech.com







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Best Pharma Brands

Interbrand Health Ranks Pfizer, Roche and Merck on Top

Global brand agency Interbrand has identified the top 10 pharmaceutical brands among the top 25 global pharmaceutical companies. Besides the financial value of the brand, its influence on health-care professionals played an essential role in the selection.

The world's largest pharmaceutical company, Pfizer, is also the company with the best and most valuable brand. This is the result of a global study by Interbrand, a New York specialist in evaluating brands. Interbrand prized the value of the Pfizer brand at about $20 billion and thus sees the US group at the top of the pharmaceutical giants. Next are the big players Roche — with a brand value of $15.5 billion — and Merck & Co. — with nearly $13.9 billion. In places four and five are Johnson & Johnson's pharmaceutical unit Janssen ($13.87 billion) and Novartis with $13.5 billion. In total the top 10 biopharmaceutical companies represent approximately $129 billion in brand value.

The study examines what value means to health-care professionals (HCPs) and illustrates the influence the corporate brand has in conveying that value. It also reveals how leading companies are beginning to deliver on what matters to HCPs.

For its research Interbrand has identified three significant factors: financial analysis, strength or function of trade, and the influence of the brand. They examined the probability that doctors, nurses, pharmacists or health-insurance companies recommend a brand or prescribe its drugs. According to Interbrand Health the value of the company normally increases with the size of the brand value.

Commitment 'Beyond The Pill'

Jane Parker, CEO of Interbrand Health, pointed out that the role of brands in the pharmaceutical industry has changed in recent years. Health-care decision-makers today expect from pharmaceutical manufacturers a commitment to innovative health-care solutions that go "beyond the pill."

As a consequence leading biopharmaceutical companies would change their business models, increase their transparency and conduct more research in areas that do not necessarily belong to the traditional core activities of the pharmaceutical industry, such as digital therapies. In addition, the companies are increasing their socio-political activities. Therefore the industry again would have gained more control over its appearance and would have the opportunity to provide a more convincing picture of what it does for the environment and consumers.

"Biopharma is at a pivotal moment, and the time for change is now," Parker said. The study ranks Amgen, Gilead Sciences, Novo Nordisk, AstraZeneca and GSK in places six to ten.

The investigation "Best Pharma Brands" is based partly on financial and market data of the companies. In addition, the authors took into account the feedback and opinions of decision-makers and leaders in the health-care business.

In Germany, according to the fifth East-West brand study of MDR-Advertising and the IMK Institute for Applied Marketing and Communication Research, the companies Bayer and Ratiopharm rank at the top of pharmaceutical brands. Accordingly, almost every third respondent spontaneously mentioned the Bayer brand when it came to prescription drugs. Around 20% of respondents named Ratiopharm.

The Best Pharma Brands

(Ranking and brand value)

1.	Pfizer:	$19.985 billion
2.	Roche:	$15.479 billion
3.	Merck & Co.:	$13.880 billion
4.	Janssen:	$13.866 billion
5.	Novartis:	$13.496 billion
6.	Amgen:	$13.461 billion
7.	Gilead Sciences:	$13.361 billion
8.	Novo Nordisk:	$10.206 billion
9.	AstraZeneca:	$8.123 billion
10.	GSK:	$6.778 billion

Source: Interbrand, 2016

Controversy Over Brand Valuations

David Haigh, CEO of Brand Finance, which publishes the annual Brand Finance Global 500 report, said that in recent years there has been a growing controversy over the validity of brand valuations in general and brand valuation league tables in particular. The main reasons for differences of opinion about the value of a brand would be, e.g., brand asset definition, the date of the valuation, and the adopted approach or financial forecasts.

But now there is a widely accepted global brand valuation standard called ISO 10668. Based on the results of the latest Brand Finance Global 500, 18% of all quoted company enterprise value is made up of brands, Haigh said. This points to a renewed need to educate and explain how brand valuations are conducted and how critical an understanding of brand value is to marketers, finance teams and CEOs alike.

The 2016 report of Brand Finance Global 500 ranks the US UnitedHealth Group as the health-care company with the highest brand value in the world.

Thorsten Schüller, CHEManager

Envigo Appoints Dr Adrian Hardy as President and CEO

Envigo's Board of Directors has appointed Dr Adrian Hardy as President and CEO, effective July 1, 2016.He also became a member of the Company's Board of Directors. Dr Hardy joined Envigo in 2002 and has held various roles in Sales, Strategic Marketing and Operations, most recently serving as COO.

In related moves, Brian Cass, the previous CEO, became Executive Chairman, and Andrew Baker, the previous Chairman, became Chairman Emeritus and remains a Board Member. These changes also are effective July 1, 2016.

Dr Hardy holds a BSc in Human Biology from King's College London and a PhD in Developmental Biology from University College London.(rk)

Savitzky to Succeed Haag as Lonza CFO

Lonza has appointed Rodolfo Savitzky (54) as new Chief Financial Officer (CFO). In this function he will be succeeding Toralf Haag, who after 11 years at Lonza will become the new CFO of the German Voith Group and member of the Corporate Board of Management. The change will be effective as of Oct. 1, 2016, when Savitzky will also succeed Haag as a member of the Lonza Executive Committee.

Savitzky joined Lonza in March 2015 as Head of Finance & Controlling for the Pharma&Biotech segment. Previously he was CFO for the Animal Health Division of Novartis. Prior to this position, Savitzky held various financial management positions at Novartis and Procter & Gamble. He holds an MBA in Finance/Economics from the University of Chicago. (rk)

Vetter Plans Des Plaines, Illinois, Facility

Pharmaceutical manufacturer Vetter is planning a $320 million production facility in the Chicago suburb of Des Plaines. Vetter, based in Ravensburg, Germany, has signed an economic development agreement with the state of Illinois. Vetter provides manufacturing services to the pharmaceutical industry such as prefilled syringe systems. The family-owned company is not new to the Chicago area. It has a small-scale production facility and sales office in the nearby Village of Skokie. (rk)

Recipharm Lifts Italian Lyo Capacity

Sweden-based drug developer and toll manufacturer Recipharm is investing €3.7 million in expanding its lyophilization capacity at Masate, Italy, near Milan. The company said the expansion forms part of its strategy to become a leading lyophilization provider and at the same time complements its €32 million investment in a capacity increase at Wasserburg, Germany.

Part of the expansion will be the introduction of a new lyophilizer for vials, increasing output capability by about 20%. (dw, rk)

Sartorius Expands Production Site in England

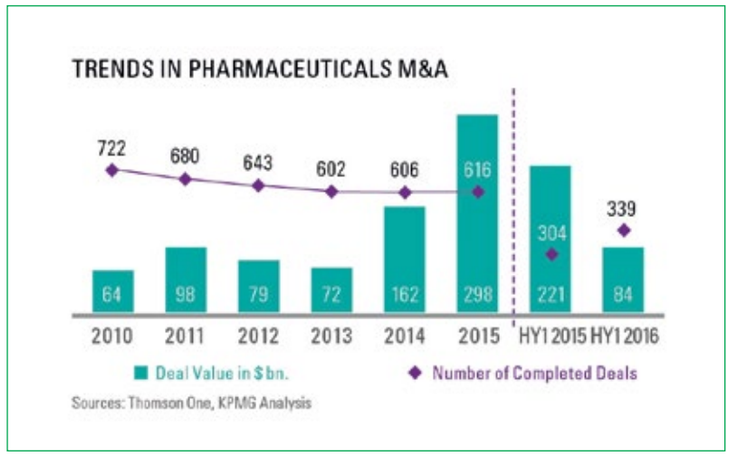
Sartorius opened a new plant at its Stonehouse site in Gloucestershire, doubling its local production capacities. The new building covers approximately 4,800 square meters. Around 110 employees currently work at this facility in production and R&D.

In Stonehouse, Sartorius develops and manufactures a variety of single-use plastic products, such as filtration units and laboratory-scale bioreactors. The new plant, which cost approximately €9 million, additionally serves as a competence center for the group. (rk)

Big Pharma Targets Aspiring Biotechs

Pharmaceutical M&A Activity Remains Buoyant Despite a Decline in Landmark Deals

There were 339 completed pharmaceutical deals in HY1 2016, an 11.5% increase compared to HY1 2015. Big pharma players were especially keen to strengthen their drug pipeline through the acquisition of biotech assets. The focus on smaller targets triggered a decline in the industry's total deal value to $84 billion in HY1 2016 from a record-breaking $221 billion in HY 2015, as evident from a KPMG analysis based on figures released by Thomson Reuters.



The decline in mega deals was due to several reasons. Volatile stock markets at the beginning of the year increased risks and led companies to be more cautious. In addition, new US regulatory tax rules hampered cross-border acquisitions and struck down the $160 billion Pfizer-Allergan merger which was earmarked to become the largest transaction in the industry's history.

Vir Lakshman, KPMG

Shire Leads the Way with Landmark Biotech Acquisition

In light of these developments, Pharma players turned their focus to aspiring biotech companies offering a rich pipeline with blockbuster potential. Almost 30% of pharmaceutical deals in HY1 2016 targeted biotech companies, a 5% increase from HY1 2015.

Amongst the top deals for HY1 2016 was the landmark acquisition of Baxalta by Shire for $32.0 billion, ranked as the second largest deal year to date. Baxalta has placed a strategic priority on its cancer drug business alongside its distinctive portfolio of treatments for rare diseases. After deal completion, cost synergies between both firms are expected to reach $0.7 billion, a 40% increase over previous estimates. Shire, as the world leader in rare diseases, hopes to generate $20 billion in sales by 2020 with its drug pipeline of 40 products.

Prior to the Baxalta acquisition, Shire acquired rare disease specialist, Dyax, for $6.5 billion, securing its hereditary angioedema portfolio. Dyax's lead fast track, breakthrough therapy and orphan drug-designated phase three-ready product, DX-290, is considered to have blockbuster potential.

Biotechs in Oncology Particularly Targeted

The acquisition of oncology-focused biotechs was one of the major deal trends in the first half of the year. The oncology market is projected to more than double in size from $83 billion in global revenues in 2015 to $187 billion by 2022.

AbbVie is expanding its oncology business through the acquisition of Stemcentrx, a Silicon Valley biotech. Its main asset is Rova-T, a late-stage lung cancer drug, submitted to the FDA for breakthrough therapy designation. The deal is worth up to $9.8 billion and is one of the five largest acquisitions ever of a venture capital-backed company.

AbbVie substantially entered into the oncology business through the acquisition of Pharmacyclics for $21 billion, one of last year's blockbuster deals. Through both deals, the US-based company decreases its reliance on Humira, the world's best-selling drug for rheumatoid arthritis which accounted for about 60% of AbbVie's sales in 2015.

After walking away from the Allergan merger, Pfizer plans to bolster its oncology sales by acquiring Medivation, a biotech specialising in cancer medication. The US-giant outbid French rival Sanofi, offering $14 billion, a 55% premium to Sanofi's initial bid. The deal serves Pfizer's current focus on the acquisition of late-stage drugs in order to complement its portfolio consisting of several early-stage assets. Medivation's blockbuster cancer drug Xtandi has already been approved by the FDA. Annual sales of $1.3 billion are expected by 2020.

In Q1 2016, AstraZeneca completed the $4.0 billion acquisition of a 55% stake in Acerta Pharma, a leader in covalent binding technology. The deal enables AstraZeneca to complement its immunotherapy approach by adding acalabrutinib, a Bruton's tyrosine kinase (BTK) inhibitor for blood cancers and multiple solid tumors in late-stage development.

Strong Deal Momentum in Dermatology

In addition to its focus on biotech targets, the pharmaceutical industry also pursued M&A in other therapy areas most notably dermatology, one of the smaller pharma markets with significant upside potential. The dermatology market is expected to double from $12 billion in 2015 to $24 billion by 2022, driven mainly by ageing western societies. Today's market fragmentation and rising product complexity is also driving market consolidation.

Dermatology is a strong focus area for Mylan's expansion strategy this year as it targets complementary portfolios to add to its existing assets. The US-based company acquired the dermatology business of Renaissance Acquisition Holdings for $1.0 billion in Q2 2016. Prior to that in Q1 2016, it announced that it would acquire Meda for $7.2 billion.

After terminating its mega-merger with Allergan, Pfizer is exploring options to bolster its drug pipeline. In Q2 2016, the leading US pharma company acquired Anacor Pharmaceuticals for $5.2 billion. The deal provides access to crisaborole, a topical gel for the treatment of eczema currently under review by the FDA and expected to hit the market in 2017. Analysts predict the gel to become a best seller in the dermatology market, thus earning Pfizer a spot among market leaders.

One of Pfizer's main competitors in the field is Leo Pharma, which ranks among the top 5 dermatology players. Pursuing a strong growth strategy, Leo acquired Astellas Pharma's dermatology business for $0.7 billion in Q2 2016. The acquisition enabled Leo to enter China and Russia increasing sales by more than 20% to around $1 billion.

Consolidation in Generics Continues with Teva Completing Mega Deal

Generics continues to be a major part of the M&A landscape. UK-based Hikma Pharmaceuticals completed the acquisition of the specialty generics business, Roxane Laboratories,

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GLOBAL TOP DEALS COMPLETED IN HY1 2016

BIDDER	TARGET	THERAPY AREA	VALUE[1]	CONTINGENT PAYMENTS[1]	TOTAL VALUE[1]
Shire PLC	Baxalta Inc.	Hematology, immunology, oncology			32.0
AbbVie Inc.	Stemcentrx Inc.	Oncology	5.8	4.0	9.8
Shire PLC	Dyax Corp.	Rare diseases	5.9	0.6	6.5
Pfizer Inc.	Anacor Pharmaceuticals Inc.	Dermatology			5.2
AstraZeneca PLC	Acerta Pharma BV (55%)	Oncology			4.0
ViiV Healthcare Ltd.	Bristol-Myers Squibb – HIV portfolio	HIV	0.4	2.5	2.9
Teva Pharmaceutical Industries Ltd.	Representaciones e Investigaciones Medicas S.A. de C.V. (Rimsa Laboratorios)	Generics (wide range of therapeutic areas), pain, respiratory, gastro-intestinal			2.3
HIKMA Pharmaceuticals PLC	Roxane Laboratories Inc. (part of C.H. Boehringer Sohn AG & Co. KG, 83%)	Specialty generics (e.g. oral solids and liquids, topical solutions and nasal sprays)	2.0	0.1	2.1
Walgreen Co. and Alliance Boots GmbH	AmerisourceBergen Corp. (9%)	Wholesale (wide range of therapeutic areas)			1.2
Xin Jiang Hops Co., Ltd.	Tongjitang Medical Co., Ltd.	Wholesale (wide range of therapeutic areas)			1.2

[1] All numbers are in US$ billion Targets in red are biotech companies

Sources: Thomson One, KPMG Analysis

for $2.8 billion from Boehringer. This boosts Hikma's non-injectable generics business in the US.

Teva Pharmaceutical Industries strives for global leadership in the generics market through strategic acquisitions. Teva bought Rimsa Laboratorios for $2.3 billion in Q1 2016, moving from a small presence to a leading position in Mexico, the second-largest pharma market in Latin America.

At the beginning of Q3 2016, Teva completed the addition of Allergan's generics portfolio for $40.5 billion, a deal it announced at the end of 2015. The acquisition propels Teva into the top three market position in over 40 markets solidifying its global leadership in generics with an overall market share of 20%. Regulators required certain assets to be divested which were picked up by competitors. For instance, Australia's Mayne Pharma Group agreed to buy a basket of drugs for $0.7 billion.

Following Teva's blockbuster deal, the pharmaceutical sector is on track for another year of M&A activity. As the deal momentum remains buoyant, further landmark acquisitions are expected for the remainder of the year.

Vir Lakshman, Partner, Deal Advisory, Head of Chemicals & Pharmaceuticals Germany, KPMG AG Wirtschaftsprüfungsgesellschaft, Düsseldorf

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Bridging the Innovation Gap

Pharmaceutical Research in a Changing Environment

During the last two decades the pharmaceutical industry was forced to undertake significant structural changes to address mounting challenges from strict regulatory policies, lower productivity, patent expiration of major products, innovation gap and fierce price competition from generics. Mergers and acquisitions, layoffs, and outsourcing of research became common place in an industry that had previously been nearly immune to these activities. During the 2000-2010 time period, over 1,345 merger and acquisition (M&A) deals valued at over $690 billion were consummated globally.

Over 300,000 pharmaceutical jobs were eliminated as a result of these activities, and this substantial decrease in internal resources forced the pharmaceutical industry to explore several strategies for improving efficiency and effectiveness of R&D. Many companies began to increase their emphasis on "externally driven" R&D activities. Nowadays, pharmaceutical companies are changing their business model and abandoning their staunchly held position that all R&D efforts should be done internally.

Contract Research

Contract Research Organizations (CROs) and contract manufacturing organizations (CMOs) have become an integral part of the pharmaceutical industry and flourished. They provide quality API and drug candidates addressing and improving pharma productivity. But at the same time a new player entered the drug discovery and development landscape: the academic drug discovery center. The pharmaceutical industry has recognized the potential of the combination of cutting-edge academic research and entrepreneurially minded academic scientists (especially those with previous industrial careers) and has expanded its effort to engage academic drug discovery centers. In some cases, these interactions are in the form of traditional sponsored research programs, but other forms of collaborations have been established.

"Personalized medicine will revolutionize health care."

Pipeline Enrichment

To ensure good return on investment (ROI) and minimize generic competition, pharmaceutical R&D strategies aimed at focusing resources to discover more biologic drug candidates. Big Pharma have expanded their biopharmaceutical efforts and a significant number of new drugs approved in the last 5 years have been therapeutic proteins and antibodies. Many of these biotherapeutics represent "personalized medicine" approaches and hold promise for specifically targeting diseases which will be particularly susceptible.

Dr. Magid Abou-Gharbia, Moulder Center for Drug Discovery

Personalized Medicine

Since the essential completion of the Human Genome Project in the mid-2000s, the pursuit of personalized medicine has grown. The role that a patient's genetic makeup plays in the efficacy (pharmacogenomics) and safety (pharmacogenetics) experienced by that particular patient has become a focus of pharmaceutical companies and regulatory agencies alike. Giving the rise in cost of health care, personalized medicine will revolutionize health care, it will lead to effective diagnostic tools which will give early prediction for diseases and lead effective preventive and therapeutic intervention.

Commitment To Innovation

Despite all of today's challenges, pharmaceutical companies continue with their commitment to innovation and embark on a range of initiatives and projects to address unmet medical needs or identify superior innovative drugs in place of ones with weaknesses, risks or less than desirable efficacy. Some initiatives such as multidimensional optimization and translational research are helping to increase the success rate both at the preclinical and clinical stages.

Skilled researchers in Pharma and academic institutions are engaged in multidimensional lead optimization by embarking on simultaneous optimization of both activity and properties exploring SAR (structure-activity relationship) and SPR (structure-properties relationship). Both are guided by a set of in-vitro assays and utilize several sophisticated enabling technologies which include antibody display technology, high-throughput screening (HTS) technology, drug design technology, pharmacokinetic (PK) technology, and information technology (IT).

Computational Tools

Modern industrial research facilities depend on IT tools to drive productivity, maintain records, interpret data, and to facilitate the coordination of functional teams and work groups. Drug discovery scientists are supported by a wide range of innovative IT systems. Computational tools are now an integral part of drug discovery. The success of any drug discovery project depends to a large extent on the quality of leads that are taken forward into the discovery phase. As a result, in the early stages of a project the goal is to cast as wide of a net as possible or use as "wide of a funnel" as possible to try to identify novel leads for target. Any technology that can aid in this process can have a significant impact on the project.

The Cheminformatics platform, for example, provides a database of chemical structures and associated biological data that can be searched, sorted, and analyzed to facilitate the

discovery of potential new drug candidates. Analysis of thousands, if not millions, of data points provided by biological screening using high throughput systems is made possible through the seamless integration provided by the Cheminformatics IT system.

Medicinal chemists' discovery output could benefit from a recently launched cheminformatics algorithm, ChemPlanner. Based on what it has learned about organic chemistry from literature the web-based tool predicts the shortest, fastest, cheapest route to the target, even through predicted but never-before-reported reactions. ChemPlanner, aimed at boosting creativity and productivity of chemists by reducing literature researching, cuts down on planning time so that chemists can synthesize more molecules and complete more projects in less time.

"Computational tools are now an integral part of drug discovery."

Other enabling tools such as Molecular Modeling and Simulation software provide an excellent platform for visualizing, in silico docking and understanding protein structure and function. This IT platform allows researchers to perform industry standard molecular simulations to facilitate their research.

Industry standard programs for the analysis of pharmacokinetics, pharmacodynamics, and clinical trial data are also available, providing with access the tools necessary to understand how potential new therapeutics behave in an in-vivo setting.

Concluding Remarks

Despite the tremendous challenges the pharmaceutical industry are facing they are continuing with their commitment to innovation and the discovery of innovative drugs to address unmet medical needs for treatment of various diseases. Indeed medicinal chemists are facing a challenge of their own. Trying to survive in a changing environment where Pharma are focusing on biologics drug candidates, this will require chemists to adapt to a new environment and develop approaches to join in these efforts of linking biologics to small molecules through identifying innovative linker technologies for antibody drug conjugates (ADC) and developing bioavailable peptides therapeutics for many diseases.

Pharma will continue partnering with CROs and CMOs to provide quality APIs and drug candidates and improve pharma efficiencies and productivity as well as partnering with academic institutions to have access to innovative early stage drug candidates to address the innovation gap. Many academic drug discovery centers are well-suited for doing the early work around target discovery and target validation and basic research. Pharma-Academia partnerships are expected to continue to grow during the next decade.

Magid Abou-Gharbia, Ph.D., Associate Dean for Research, Laura H. Carnell Professor, Director Moulder Center for Drug Discovery, Temple University School of Pharmacy, Philadelphia, PA, USA

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The Winning Formula

Chemists Who Can Collaborate Will Thrive in Pharmaceutical Research, Experts Predict

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Despite tremendous challenges facing the pharmaceutical industry, it continues with its commitment to innovation and the discovery of novel drugs to address unmet medical needs. Indeed, medicinal chemists face a challenge of their own. Trying to survive in a changing environment where pharma is focusing on biologics drug candidates will require chemists to adapt. CHEManager International asked R&D experts of chemical and pharmaceutical companies to elaborate on their research strategy and share their opinion with our readers. In detail, we interviewed professionals ranging from CEOs to heads of R&D and process development about:

❶ the crucial success factors in chemical and pharmaceutical research,
❷ the role of information technology tools in developing reaction routes and processes, and
❸ challenges and changes affecting the work of R&D chemists in the future.

Read their insightful answers here through page 20.

Statements

"We place great value on providing enough room for free and creative thinking."

❶ What we need is a multifunctional team of experts in medicine, science and economy! It is crucial to harmonize the different skills and expertise. I am convinced that a team can work most efficiently in a cross-functional way — a good collaboration of all team members with their special skills is the key to success.
❸ Furthermore we place great value on providing enough room for free and creative thinking. Researchers have to deal with different challenges, which require the ability to look at problems from different perspectives. In order to provide an efficient working atmosphere there must be room for creative approaches.

Dr. Alexander Biedermann, Vice President Medical, AstraZeneca Germany

"Once you have set up a diverse team of … experts, you need to facili tate an environment of active exchange."

❶ Fostering a broad, deep-diving and continuously growing chemical expertise in diverse and motivated teams is critically important both in medicinal chemistry and process chemistry. Here, you need the right mixture of open-minded senior experts, so-called thoroughbred chemists, with many years of industry experience under their belts, as well as young chemists, freshly educated and highly motivated, who bring in state-of-the-art scientific knowledge and modern ways of working. Offering appropriate career opportunities for chemists within chemical functions also is a crucial factor for success. Once you have set up a diverse team of highly skilled experts, you need to facilitate an environment of active exchange: internally, between the team members, as well as in close collaboration with external stakeholders — be it academic or industrial. And within the teams, you need to be able to professionally challenge each other to come up with the best solution — as a team.

Dr. Timo Flessner, Head of Chemical Development, Pharmaceutical Division, Bayer

❸ Increased complexity is a significant challenge that R&D chemists face today. This is especially true for pharmaceutical R&D and applies to all areas, be it in the identification of innovative drug candidates, dealing with longer-sequenced, more complex synthesis routes or specific regulatory requirements. The diversity of new technologies, e.g., combinations of small molecules — pure chemistry — and biologics such as in antibody-drug-conjugates, adds to the increased complexity. Here, dedicated high-end expertise and resources are required and need to be established, often with the help of external sources. Coping with the further enhanced necessity to collaborate, both internally as well as across the scientific landscape, is another challenge for R&D chemists today. In my eyes, however, this is also an opportunity: close collaboration and interaction will ensure the future need and success of scientific excellence in chemistry.

"Chemists have always been communicative people, and building on this strength we shall continue to fulfill our task."

❸ I believe that communicating effectively in an increasingly complex environment will remain a key challenge for chemists in industrial R&D. Let me give you some examples from our work at Merck, illustrating this point.

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Klaus Urbahns, Head of Global Discovery Technologies, Pharmaceutical R&D, Merck

Example 1: Recently, we generated a clinical candidate destined to modulate the immune system in order to fight cancer. The synthesis was performed in a 17-step linear sequence on a kilogram scale. Managing such an endeavor under time pressure was not only a matter of all hands on deck. The complex logistics required teamwork across three continents, involving sites in the US, China, Italy and our headquarter site in Darmstadt, Germany. Suffice it to say that effective communication was indispensable for delivery of the material in time.

Example 2: In recent years, the industry has established an increasing number of pre-competitive consortia — e.g., the IMI lead factory. They exemplify novel ways of working jointly across companies in difficult areas. Members of such consortia will be at an advantage as they benefit from information shared among participants. Again, effective communication, in this case even beyond corporate boundaries, is an important prerequisite for success.

Example 3: The advent of therapeutic proteins as an injectable treatment modality has been seen by many chemists as a competitive challenge for small molecules. The unparalleled specificity of antibodies has inspired Merck to bring chemists in close proximity to protein engineers by organizing them under the same roof, which we call Discovery Technologies. The new structure enables scientists to learn from each other and share best practice through communication across departments.

Chemistry is often called "the central science," because of its ability to connect different scientific disciplines. Chemists have always been communicative people, and building on this strength we shall continue to fulfill our task in the future.

"The crucial factor … will be people — well-educated and with the right empathy and motivation for research."

Prof. Dr. Jochen Maas, Head R&D FF, Sanofi-Aventis Deutschland

❶ The crucial factor in chemical research will be people — well-educated and with the right empathy and motivation for research. Those people have to be brought together independently of their organizations — academia, industry or biotech. And this requires new and innovative ideas of collaboration, which have already started to be implemented.

❷ The role of software tools to predict and develop reaction routes and processes for given target molecules depends on the research area: a lot of processes already can be predicted quite accurately by in silico approaches — e.g., absorption. Other areas like metabolism will require much more effort to achieve a similar level.

❸ R&D chemists will have to be extremely flexible in the future: at least industry preferences for specific modalities — like small molecules, peptides, proteins, oligonucleotides — will probably change much more rapidly than in the past.

"We envision … new collaborations to intervene and prevent diseases before symptoms even appear."

❶ Collaboration plays a central role in our business today. The one sentence we use most often to describe ourselves is: we collaborate with the world for the health of everyone in it. We've forged hundreds of partnerships with academic institutions, advocacy organizations and companies of all sizes. Through our four Johnson & Johnson innovation centers, we've created new and open innovation models. To find the best science and technology around the world, we're collaborating with entrepreneurs and scientists through 700 deals as part of our efforts to solve the greatest health-care needs of our time.

Stef L.E. Heylen, COO, Janssen R&D

We are also collaborating in the largest public-private partnership in life sciences worldwide, the EU's Innovative Medicines Initiative. In addition, our company was a founding member of TransCelerate BioPharma, a nonprofit organization with a mission to collaborate across the biopharmaceutical industry to identify and implement solutions to drive the efficient, effective and high-quality delivery of new medicines.

Recently we greatly increased our efforts to actively engage patients and seek their input at every stage, from development through commercialization. And, as appropriate, we're working much more closely with regulatory authorities to get new medicines to patients in need. For example, by collaborating with regulatory authorities we were able to greatly accelerate our development of Imbruvica because we and regulatory authorities recognized how urgent the need was for patients.

We are also able to accelerate our development of new medicines through close collaboration of Janssen colleagues and external business partners around the world, enabling us to develop new medicines 24 hours a day.

❸ We expect collaboration will play an even more important role for Janssen in the future. For example, with advances in science and technology, we envision a future where we will be able to forge new collaborations to intervene and prevent diseases before symptoms even appear.

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"Dissemination of data-rich tools across academia and industry will be the ultimate education of future R&D chemists."

Dr. Michael Quirmbach, Vice President, Global Sales & Marketing, Corden-Pharma International

❸ Both the chemical and pharmaceutical industries are rapidly changing in that they both have a need to adapt in order to stay ahead of requirements and competition. I believe it is widely accepted that the traditional way of running and optimizing reactions as a chemist — e.g., simple round-bottom flasks with subsequent TLC, later HPLC, analysis — is not the future for any R&D chemist in a chemical or pharmaceutical research lab. Instead we now discuss the "lab of the future" — but what exactly does it mean? Besides the use of sophisticated automation including online monitoring of reactions using probes, which will all become standard for any R&D lab, it means managing big data.
Integration of all of the available data remains the biggest challenge across the industry and academia. The lab of the future is generally seen as the way to secure sustainability by learning to navigate a large volume of data. The dissemination of data-rich tools across academia and industry will be the ultimate education of future R&D chemists. New skills will be necessary to manage this data-rich environment, which will in turn require intelligent collaboration across departments starting at the university level. The benefits are obvious, i.e., the acceleration of drug development in the scale-up phase for a supply of clinical phase material. Carefully controlled reactions using analytical probes will provide detailed process understanding — important information for faster and more efficient scale-up. Additional topics such as C-H functionalization, that have been historically considered the holy grail of chemistry via functional group conversion, might be solved in the future by a more sophisticated approach. Key elements are the use of experimental design, the parameterization of organic chemistry and the development of sophisticated models that can relate back to a certain reaction mechanism, which may then be used for prediction of effects such as site selectivity.

"The war of talent is on."

Dr. Lukas von Hippel, EO, Pharma Waldhof

❶ Some success factors did not change, and may remain: quality, up-scaling, and safe and stable processes. However, this is only one part of the equation: in a globalized world, intercultural competencies become more relevant. For R&D, project management, a stable supply chain, efficient communication — internal and external, and management of all regulatory aspects are musts. In addition, the borders between chemistry, biotech and biology weaken, not only at high-end molecules but also in the production of feedstock. Interdisciplinary understanding will become more relevant as it was some decades ago.

❷ When design of experiments was introduced, it worked in some cases, in most cases it did not. Today, computerized support of R&D is standard. However, the prediction of reactions remains difficult as long as we are not able to model reactions in total. At the end, every software works by algorithm, and the output can be only as good as the algorithms are. Algorithms are getting better, as AlphaGo showed, amazingly winning Go games. The day software will be able to successfully offer recipes for lab experiments may change our understanding of intellectual property (IP) and proof of evidence.

❸ The war of talent is on: first, Europe has to be attractive for skilled people. Intercultural challenges will come and have to be solved. Second, we will see that work will partly continue to move away from Europe, so the challenge of managing international cooperation, already in R&D status, will increase. Third, interdisciplinary cooperation will become more relevant. The ability to understand others and communicate between disciplines may become even more relevant than it is today.

"Fostering a culture that encourages the sharing of information … is a fundamental requirement."

Dr. Ralph O. Schoenleber, VP Research and Development, Bachem

❶ For a contract manufacturing organization in the competitive environment of the pharma and biotech industry, research and development is extremely important to further enhance customer satisfaction and service quality. Constantly increasing demands on performance combined with growing sustainability requirements, such as those relating to occupational safety as well as waste management, are chief concerns of our markets. There is a continuous trend toward the development of molecules with higher complexity, and at the same time, the patent landscape is more and more crowded. Furthermore, requirements from customers and authorities with regard to documentation in general and data integrity in particular are changing the way people work.

❸ In order to meet the increasing demands of the markets, a company needs the right combination of creative, innovative, but at the same time structured and accurately working scientists on board, and to put a focus on the management of knowledge as a key factor to success. Efforts on knowledge management at Bachem focus on organizational objectives, such as continuous improvement, competitive advantage, innovation, and the sharing of lessons learned. Knowledge management includes expert systems, post-action reviews, cross-project learning, knowledge sharing, best-practice transfer, and collaborative software technologies — e.g., chemistry and technology forums including blogs. Fostering a culture that encourages the sharing of information, based on the concept that knowledge is not irrevocable and should be shared and updated to remain relevant, is a fundamental requirement for successful and future-oriented research and development.

"In the end those will be successful who can combine the right tools with the intuition and experience of a chemist."

Dr. Jürgen Sans, Head of Innovation Management, Alzchem

❶ Efficiency and effectiveness are the key factors for success in chemical research. Success-oriented chemical research is directly linked with chemical production. Lab chemists have to understand not only what is technically possible but also economically feasible. It saves time and money if the design of experiments is focused on those reactions and conditions that could be scaled up easily, safely and — if possible — without an investment. It also has to be noticed that a production process not only depends on the reaction route but also on essential factors like workup conditions, purification, safety, supply chain, waste management, etc. A lab chemist has to consider these points early in

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development. Therefore, a strong technical background and an understanding of the cost of production are required. In some cases it will be more important to be very fast with acceptable costs, in other cases it might be more important to optimize the costs within an acceptable time range. Especially for contract manufacturing projects this needs to be clarified with the customer at the beginning of a project.

For efficiency it is important to have a broad range of technologies available in the lab as well as in the pilot and in the production facilities. The decision for a reaction route has to be based on a series of factors and not only on chemistry. For technologies that are not available in-house, collaborations need to be established as early as possible. It is essential for smooth scale-up that research chemists, engineers and plant managers cooperate closely. For contract manufacturing it is important to offer some unique technologies or to have the ability for the handling of crucial raw materials or to have some special raw materials in-house.

❸ For the future, chemical research will increasingly be impacted by IT tools, both in design and evaluation of experiments. If applied properly, this will certainly enhance the efficiency of lab work. I can think about automated lab reactors, software tools or fast analytical methods. Due to the acceleration of product life cycles, miniplant and continuous reaction technology have to play a bigger role in scale-up of new processes. However, in the end those will be successful who can combine the right tools with the intuition and experience of a chemist.

“The most crucial success factor … is that we do not only talk about innovation but live innovation.”

❶ The most crucial success factor — and this holds true not only for pharma but also for other industries — is that we do not only talk about innovation but live innovation. This means that all units of a company strive for innovation, not just the R&D department, and all consider it as an indispensable factor for the future of the company. It also means that the required resources are provided and people are empowered to make decisions. I am pretty sure that we will see in the future much more interaction — interaction within a company as well as between independent companies whether they are customers, competitors, service

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providers, contract research organizations (CROs) etc. It is great to have our own specialists, but it is impossible to have them in all fields. A high degree of networking between the various specialists will not only solve current problems, but it also offers more opportunities in open innovation. This does not mean that open innovation is restricted to specialists only.

3 On the other hand complexity is also becoming an issue since R&D tasks are getting more and more complex, and in case a company has its own complex structures it generates so many interfaces and obstacles that projects where a lot of units are involved are delayed. Thus companies having explicit organizations and clearly assigned responsibilities are quicker in their internal work and therefore have more resources and capabilities for all kinds of interaction with other parties.

Dr. Karl Kolter, Vice President Global Research & Formulation Nutrition & Health, BASF

Currently, everybody talks about autonomous driving and derived from this the question pops up: Are autonomous developments achievable? Probably not in the near future, but at least digitalization will strongly support R&D work.

"Confidence to try something reasonable in the lab, even if it … does not work, may provide clues on how to succeed."

1 The important skills for individuals within a successful research program are possession of a broad knowledge of chemistry, creativity in problem solving and a willingness to get peer advice. These factors, along with experience in hands-on research, allow chemists to develop and progress.

Not every problem has a straightforward solution, and not every reaction is described in the literature. Having the confidence to try something reasonable in the lab, even if it ultimately does not work, may provide clues on how to succeed. Chemists are not always trying to solve new problems, just similar problems in a different context; so being current on the literature and sharing thoughts with colleagues will help to learn about other people's experiences.

Ingrid Hegbom Ekman, Director R&D, Cambrex

2 Predictive software can provide a complementary tool to literature review and collaborative brainstorming for identifying possible reaction routes. Selecting a route for manufacturing via software may not analyze a number of key points critical to successful and economical process development:

Firstly, software tends to focus on bond making/breaking, and may not capture the costs or difficulties associated with workup, purification, isolation or waste. Additionally, one has to assess the scalability of software proposed routes in the context of the project, and also the available manufacturing facility in which the chemistry will be undertaken, which is often a significant driver for route selection. It is also important that safety evaluation is undertaken when predicting and developing a route, so the use of any modeling software within a wider cross-functional team, where ideas and literature research can be discussed and brainstormed in an open environment, is ideal to successfully transition and optimize a project from development through to manufacturing.

3 Batch and semi-batch processing is still used in chemical manufacturing, which makes classical process development skills, tools and knowledge as important as ever to master. Emerging technologies are being more widely implemented, but it is important to know when and how these new strategies should be integrated into a manufacturing plan to ensure they are utilized efficiently.

Beyond process development for manufacturing, the requirements of laboratory investigations to support regulatory filings are becoming increasingly rigorous. At the same time, newer quality, impurity, safety and environmental policies result in a more restrictive space in which to operate.

A greater number of cross-discipline science degree programs are available in academia, which may be taking time away from developing broader chemistry fundamentals, and there are limited opportunities for chemical process development training ahead of entering the job market. The number of mergers, acquisitions and the closing of research departments promote a perception of uncertainty in the job market, which may be turning potential scientists toward other career pursuits. In the long term, a negative impact on the available trained workforce for the chemical industry may result.

"It will be … important to better integrate and adopt regulatory and environmental require ments into R&D."

1 It will become increasingly important to better integrate and adopt regulatory and environmental requirements into R&D organizations, and more specifically, get the development chemists to consider these factors at an early stage. Automation will also become ever more valuable to improve process understanding and "seeing the process window," as will the adoption of "enhanced development in combination with the traditional way of developing processes," as outlined in ICH Q11. This also includes the use of risk assessments/quantitative risk assessments from an early development stage. High-tech analytical instrumentation and integrated, computerized systems to support data evaluations, as well as storage and tracking of data, will be extremely valuable going forward. Internal and external collaboration in specialist areas is also very important, but takes time to establish and a key is open collaboration with external partners, who may have specialist knowledge and expertise beyond that which is available internally.

Claudio Pozzoli, R&D Director Chemical Division, Cerbios

3 Chemists need to be more aware of all regulations and requirements for a process to be both efficient and sustainable into the future. It is important not to view regulations as being painful but as a natural variable that must be taken into consideration, as very often they are nothing more than common sense.

"A solid background of standard process chemistry … is nowadays not enough."

3 Challenges derive from increasing use of flow chemistry as an alternative production method with respect to the standard one based on batch. This technique, now well-studied and adopted also at the industrial level usually coupled with design of experiment and an online monitoring system, is too far away to be fully understood.

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Dr. Bernhard J. Paul, General Manager, European Pharma Solutions, Johnson Matthey

Chemical complexity of new molecules is increasing; quite often they are not solid, and their purification cannot be done anymore by crystallizations — once considered an art — but by using different types of chromatographic purifications.
Another fascinating challenge derives from the possibility to increase the bioavailability of compounds that are otherwise poorly water soluble, modifying their particle size by using engineering systems of particle-size reduction alternative to the standard one. An interesting way to obtain this effect is by using supercritical fluid, such as carbon dioxide.
The manufacturing of highly potent active pharmaceutical ingredients — HPAPIs — whose market is the fastest growing segment in the pharmaceutical industry, and more specifically of antibody drug conjugates — ADCs — surely an emerging class of compounds attracting a lot of interest and investments from chemical companies, represent great challenges for R&D chemists. The handling of molecules having an occupational exposure limit at or below 10 micrograms per cubic meter of air, their conjugation with monoclonal antibodies — mAb, the necessity to perform these reactions and purifications under glove boxes are all challenges and changes for R&D chemists.
Finally, HPAPIs, ADCs, industrial chromatographic purifications and particle-size engineering are just some of the challenges Cerbios is facing with its R&D department and chemists. This trend is surely true now and I am sure will be much truer in the future. For R&D chemists these challenges mean that a solid background of standard process chemistry, knowledge of good manufacturing practice, HSE, program management, etc., acquired over years of experience and absolutely necessary are nowadays not enough.

“Speed and innovation will be gained from embracing collaboration across different areas of the business.”

Kurt J. Kiewel, Director R&D, Cambrex

1. Having access to a broad range of specialist technologies is becoming increasingly important as researchers develop larger and more complex molecules. For example, being able to use different technologies, such as chemocatalysis and biocatalysis, is particularly valuable for solving complex chemistry problems. Another crucial factor is collaboration. Our customers face complicated problems and we often find a better solution can be provided through collaboration between our different departments. Collaboration is a core principle throughout Johnson Matthey. For example, we have a technology center in Sonning Common in Reading, UK, with capabilities in materials characterization, and this provides an additional resource for our Fine Chemicals Division when dealing with unusual solid form characterization problems.
2. Having more long-term information management for emerging technologies will certainly change the way that we think and work. We use tools today such as statistical design of experiments — DOE — to optimize reactions, and certain technologies, such as continuous processing, that rely heavily on software control for maximal effectiveness. In biocatalysis, our enzyme evolution and optimization capabilities would not be possible without computational tools to design and predict new enzymes. Software tools are vital for much of what we do today and they will play an even bigger role in the future.
3. The biggest challenge affecting the work of R&D chemists relates to the industry’s ongoing need to develop more molecules, more quickly,

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resulting in shorter timelines and greater pressure for R&D teams. The traditional blockbuster drug model no longer works for many molecules, so pharmaceutical companies are looking for different ways to deliver benefits to patients while also delivering profits. R&D scientists will have to be very flexible as well as nimble. Furthermore, today's complex problems do not often fit into a single department, so great advantages for speed and innovation will be gained from embracing collaboration across different areas of the business.

"The future is the coveted ability to harness databases that extend the individual knowledge base to the collective."

Jason Apter, Head of Research Solutions, Life Science Business Sector, Merck

❸ It is not news that chemists are facing significant challenges in their labs today. The current economic pressure on research has made downsizing and materials conservation a new constant. But there is reason to be hopeful. Chemists have been publishing breakthrough methods at an unprecedented rate, enabling innovative methods to be shared widely in order to conserve time and to leverage the expertise of the scientific community. Openly sharing revolutionary approaches has already led to the widespread adoption of high-throughput experimentation — HTE. This rapid, parallel method can be miniaturized and scaled for quick identification of the most promising methods while sparing precious substrates and allowing valuable research time to be devoted to strategic goals. But this is an incremental step forward. The future is the coveted ability to harness databases that extend the individual knowledge base to the collective. On the horizon, the promise of smart chemical tools is coming into focus. Proven successful, they will change the way we do chemistry. They will enable many chemists to uncover new approaches to solve their most difficult problems.

At Merck's life science business, with our celebrated Aldrich tradition of "chemists helping chemists," we are proud to enable chemists to generate faster, more reproducible results. We are proud to support chemists on their unique discovery journey. We strongly believe the best days of chemistry are yet to come.

"Speed and flexibility are of utmost importance when considering the supply of drug substance to clinical development."

❶ For a process development chemist in the pharmaceutical industry, speed and flexibility are of utmost importance when considering the supply of drug substance to clinical development. This not only requires experienced chemists but also the ability to combine chemistry and chemical engineering for manufacturing and scale-up.

Modern laboratory tools are designed to support this challenge with parallel experimentation and fast — preferably online — analytical methods. Seamless collaborations — internally and externally — with plant engineering, quality organizations and health-safety-environment departments are also essential.

Andreas Stolle, Vice President, API Process Development Services, Patheon

❷ Databases for literature, chemical reactions, retro syntheses and properties of chemicals are well-established in the industry. However, for the design of synthetic routes, we strongly believe that a brainstorming exercise of chemists and process engineers remains critical to quickly consider scalability and specific plant features and supply chains.

The usage of design of experiment — DOE — software is vital to simplify and accelerate modern process development, and create more knowledge about critical process parameters.

❸ With approximately 40% of newly developed APIs being classified as complex molecules, manufacturing is no longer a straightforward task. While timelines are expected to be even shorter, APIs now have a larger number of stereo centers, more labile functional groups, longer synthetic pathways and also require unusual reaction conditions.

As a result, conventional pharmaceutical manufacturing equipment may not always cope with this growing synthetic complexity. The task of the chemist goes beyond traditional chemistry and a synthetic route, and an innovative plant concept needs to be co-developed. Only this approach will allow a service provider to deliver high-quality material and a sustainable production concept, which allows for prolonged patent protection by the client.

"Speed, technology and knowledge of complex chemistry are becoming more important as competitive differentiators."

Dr. Jörg Mohr, Head of Process Development & Analytics, Saltigo

❷ It is essential to already identify cost drivers in the bidding process and to envision optimized processes without having developed them in the lab yet. Our process development concept is based on three main pillars. We use design of experiments — DOE — to optimize reaction conditions. Second, our automated mini-plant equipment resembles the plant-scale equipment as closely as possible to shorten development time. Third, we operate a well-equipped process technology lab to closely monitor reaction kinetics and to investigate process safety conditions.

Quality by Design — QbD — and process analytical technology — PAT — play an important role in our compliance system. At-line and online analytics, in particular, are becoming more and more popular, and classical in-process controls are being replaced by PAT. We believe the combination of online/at-line analytics with release procedures is a future trend. QbD, a well-established methodology in the pharmaceuticals industry, is gaining importance in other industries as well.

In addition to established programs, we are carefully observing which new software developments are available to the industry. For example, we tested ChemPlanner and found it to be helpful when the objective is to generate new synthesis ideas. However, that is only a sideline of our activity because Saltigo, whose essential activity is process development, generally has to use manufacturing processes — technical packages — specified by its customers.

❸ We see that the types of compounds being developed are becoming more complex and the total number getting to market is diminishing; therefore

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speed, technology and knowledge of complex chemistry are becoming more important as competitive differentiators.
Our team's know-how makes a major contribution to minimizing scale-up risk, for example. An inherent problem in scaling up a project from the laboratory scale to production is physical in nature. While a mixing process on the laboratory scale frequently takes only a few seconds, the length of time it takes in the reactor is significantly longer and cannot simply be extrapolated to the larger production quantity. The same goes for the effects on process safety. Therefore, we are using a modeling tool for optimizing and predicting the performance of batch process unit operations and a process modeling software for distillation modeling — not least to ensure safe operation.

"It's always highly skilled and committed individuals who at the end make the difference."

Dr. René Imwinkelried, Executive Vice President, Head of Global R&D, Siegfried

❶ Many different factors make an R&D organization successful. Within the contract development and manufacturing organization (CDMO) arena, I think of an organization having broad experience in developing and scaling up chemical and formulation processes, applying state-of-the-art analytical tools to better understand reactions, and also being capable to collect and interpret relevant scientific data to predict the outcome of reactions at scale is important. In addition, a culture of strong collaboration and open communication, both internally and externally with clients and suppliers is essential. Beyond these factors, many more still influence successes.
For me personally, the foundational success factor for an R&D organization is and will remain individuals who have a deep understanding of science, who rigorously apply scientific and engineering principles, and individuals who display a high drive to move things forward.
Yes, of course, we need several of the latest tools and instruments, yes we need strong collaboration and teamwork, and we need efficient business processes. However, I do not know of any successful pharmaceutical product that was invented, developed and commercialized by a business process or a specific top notch tool: It's always highly skilled and committed individuals who at the end make the difference. Individuals who make the difference are those who see the outlier in scientific data that is hidden to others; individuals who challenge assumptions and conclusions based on opinions rather than data; individuals who do not always swim with the flow; individuals who take ownership for a project and push things forward despite the many obstacles along the way; and those individuals who believe in a successful outcome. In my opinion, individuals others want to be around.

"A collaboration ultimately helps us to make the best use of the core competencies of each of our partners."

❶ The most important skills in a successful research group are to know precisely your core competencies — what we do and where we do best — as well as to know what we cannot do and where we can get access to these missing competencies. At Umicore we know our expertise lies in metal coordination chemistry, in excellence in handling highly sensitive or toxic materials, and in chemical process development and scale-up under regulated environments — GMP, ISO, etc. And we know we can rely on a number of close partners bringing related applications and technology expertise.
This leads us to the necessary mindset for success: collaborate. Because a collaboration ultimately helps us to make the best use of the core competencies of each of our partners. Cooperating with customers keeps us focused on understanding them, their strategies and their needs — aiming to deliver faster, better and more cost-efficiently. Collaborations with our technology and development partners bring us out-of-the-box thinking, missing competencies for further organometallic materials development and insights to develop on time the next generation of catalysts, high potency APIs, or even electronic materials.
Strategically aligning these collaborations and leveraging on the tremendous amount of information and knowledge generated, without divulgating any proprietary information, requires efficient tools. Open access to a structured market, technology or customer information is key, combined with quick access to new technical information, as well as shared platforms allowing efficient exchange between the scientists and the specialists of our fields. Because a challenging pharma project may benefit from the successful development of an electronic material!

Dr. Ralf Karch, Head of Research & Development Precious Metals Chemistry, Umicore

❸ The biggest challenge of a chemist today is speed: meaning how to develop a product faster albeit at constant level of quality, with the same level of process safety for a smooth and fast transfer to commercial production

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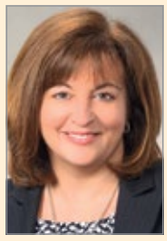
— all this while surrounded by an unrivalled flow of new or even contradictory information.
Does it mean that the research chemist will need to evolve to be more of an analyst, to become an expert in accurately and quickly defining a problem and developing its solution out of the amount of information available? Probably — as well as the "too slow" chemical development may have to be restricted to fundamental research, or to a few strategic development projects.

"The challenges … will require a broad skill set and the ability to collaborate within the company and around the globe."



Linda Hicks, Vice President Global Technology, Vertellus

❶ In today's business climate, it is even more critical to make the business case when it comes to investing in research. Companies must be able to quantify a return on investment for any new research initiative. Accordingly, chemical companies are seeking research chemists who understand chemistry and the practical reality that it takes to create value in the industry. Research budgets simply don't allow companies to retain specialized experts in every specific discipline needed to execute new product development such as reaction kinetics, thermal dynamics and polymerization. Today's chemical companies are looking for individuals with broader, more flexible skill sets that can be applied to different areas of the business and technology platforms as the marketplace evolves. Scientists and engineers are also needed with the skills to establish and maintain collaborative partnerships and consulting relationships to access higher level expertise in needed disciplines.
Interestingly enough, this trend aligns with a demographic shift discussed at a recent US Industrial Research Institute forum for chief technology officers. The millennial generation has a nimble and impatient mindset when it comes to their career paths; companies that can provide opportunities for employees to experience different parts of the business may be more effective at engaging and even retaining young employees.
❸ The nature of our industry today is already creating a shift in how companies approach R&D. Compared with decades earlier, the focus of R&D has moved from pure research discovery toward optimization and application. This shift also applies to the regions of the world where different types of work are conducted. Companies are tending to focus their innovation efforts in the West and outsourcing more routine work offshore. Again, economies are influencing this shift. The challenges our industry faces — both economic and demographic — will require a broad skill set and the ability to collaborate within the company and around the globe.

"It is very important to mix young bright researchers … and experienced people … to find innovative solutions."

Olivier Simon, Head of Technology R&D and Process Development, WeylChem Lamotte

❶ ❷ ❸ The main goal of chemical and process research is to create new pathways: more competitive, cleaner, safer for the users and producers, and respecting the environment. To achieve this goal, the researchers today are strongly supported by extensive access to information, simulation tools and automatized parallel reactors.
Our research focuses on the molecule synthesis or mixture preparation. For this purpose, our R&D teams are trained to develop the best chemical routes and processes. One crucial success factor is the building of a heterogeneous team combining a state-of-the-art knowledge of industrial organic chemistry and a unique know-how gained over the years. Therefore it is very important to mix young bright researchers, trained to the latest technologies, and experienced people, familiar with the existing assets, in order to emulate creativity and to find innovative solutions.
Designing new pathways also means that one is able to test operating parameters out of the standard range: for example, by setting high kinetic rate of reaction using short residence time in continuous reactors like micro reactor systems or microwave heated tubular reactors. Purification of the product or intermediates is not to be overlooked. Nowadays, distillation can be well-simulated when the thermodynamics of the compounds are known. The major problem is that for advanced molecules the thermodynamic is not available or the molecules are too heavy to be distilled. In that case other technologies should be employed. WeylChem develops a number of new ways to provide answers to this challenge. By using continuous liquid-liquid extraction, prototyped in the lab and in mini-plant, or supercritical CO_2 extractions, where we are able to tune the solvent properties by playing with the temperature and pressure, we support our customers with innovative options.
For us the future of R&D is a strong integration of organic chemistry and chemical engineering adapting reactors and purification units for the chemistry and not the chemistry to the vessels. ■

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M&A Process Said to Drive Drug Costs

The wave of mega mergers in the global pharmaceutical industry is driving prices for new "wonder drugs" financed with public funding, a study by the UK's Cambridge University Department of Sociology asserts. Despite putting up the money, the public is the loser, the researchers contend. The successful development of a breakthrough drug, they say, makes the company producing it more attractive as an acquisition target, and the bidding wars compound the price. All of this makes shareholders richer.

What's more, the study says, the high prices lead to a rationing effect, as many public health services only treat the sickest patients with the new drug. When treatment is withheld, infectious diseases spread faster. Cambridge cites several examples of how the process works. After a protracted M&A battle, in which the company walked away with the prize, it says Gilead Sciences more than doubled the price of its treatment for hepatitis C over initial estimates, calculating "how much health systems could bear."

The company, the researchers say, charged public health services in the US up to $68,000 per patient for a three-month course and the National Health Service in England nearly £35,000 then channeled the profits into a share buyback rather than financing additional research.

This is an industry-wide phenomenon, Cambridge notes, adding that large pharmaceutical companies increasingly rely on input from public institutes, universities and venture capital-supported start-ups for their innovations, acquiring the most promising compounds rather than doing the research themselves.

The study's lead and senior authors, Victor Roy and Lawrence King, also cite the example of Sofobuvir, a compound now owned by Gilead, designed to treat hepatitis C. The drug was developed by a start-up, Pharmasset, which eventually also raised private funding. When Pharmasset's Phase 2 trial showed more promising than Gilead's own, Gilead acquired the product for $11 billion in a 2013 bidding war, then priced it at $48,000. By the first quarter of 2016, the $35 billion intake paid for the development costs nearly 40 times, the research alleges. The bulk of the proceeds were funneled into a share buyback.

As another example of how high drug prices are boosting pharmaceutical companies' share price, the Cambridge team said Merck of the US spent $8.4 billion in 2014 to acquire a drug developer specialized in staph infections. It subsequently closed the acquired company's early-stage development facility and scant weeks later announced a fresh share buyback.

In an article for the British Medical Journal, the researchers explore new business models they believe could remedy the situation. These include giving health systems greater bargaining power to negotiate deals for breakthrough treatments and limiting share buybacks. Another proposal focuses on a mix of grants and major milestone prices to "push and pull" promising therapies into wider application while uncoupling drug prices from development costs.

Dede Williams, CHEManager

The Possibilities Of Peptides

Small Proteins Open Window to Better Treatments

Peptides in pharmaceutical development have traveled a rough road. It took a long time for these small proteins to emerge as a basis for new medical products. This has become possible mainly because of a convergence of advanced technologies. Meanwhile many drug projects based on peptides are in the pipeline, and several companies offer customized peptides for different applications. Biotech and pharma companies can choose among them like in a supermarket. Here's a look at the current possibilities and late advances of these little proteins in industry and medicine.

For a long time peptides have remained outside the focus of the pharmaceutical industry. But this has changed. Today peptides are gaining speed as important elements in the research and development of new drugs. The number of new chemical entities based on peptides is rising continuously. While in the 1980s only four to five new chemical entities based on peptides entered clinical studies per year, it was 17 per year from 2010 to 2015. Several factors came together to make this possible. One reason is that scientific, technological and engineering development has improved significantly in recent years. Furthermore the continuous trend to cost efficiency supported the rise of peptides. The small proteins helped bring down the costs of pharmaceutical manufacturing.

It's the structure and their function that make peptides so interesting for pharmaceutical researchers. Peptides are amino acid polymers. They generally represent a small portion of a full protein and don't have sufficient activity on their own. But they may be signaling molecules that function through interaction with specific receptors.

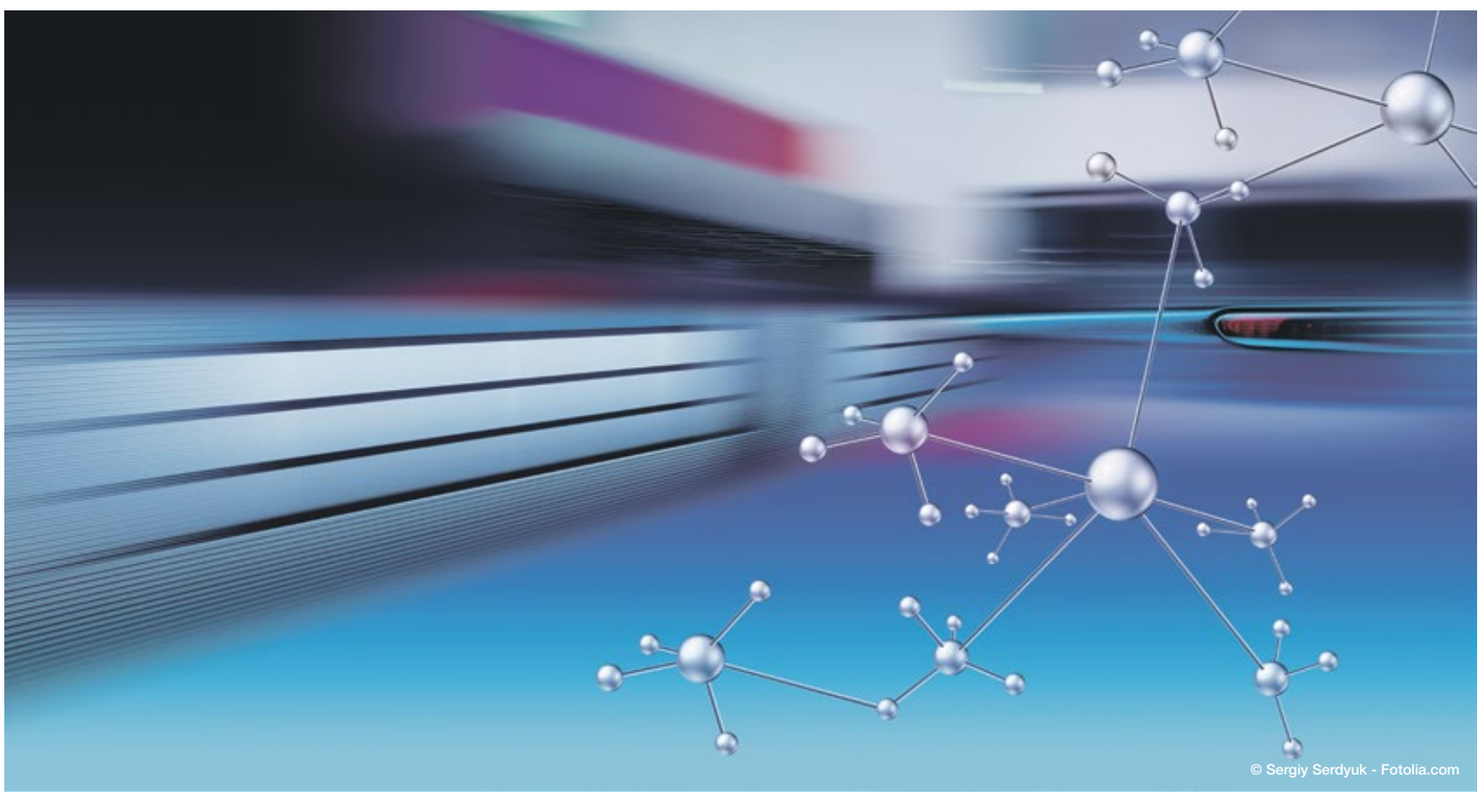
The German company Peptides & Elephants states: "Synthetic peptides are able to influence a wide variety of biochemical, immunological and cellular reactions. They may act as inhibitors of protein-protein interactions, interfere with antibody binding to antigens, and they may be substrates or inhibitors of proteases. Likewise, peptides are suited to mimic protein domains and to simulate protein functions."

Manifold Applications

No wonder peptides today are used in manifold applications, mainly in the areas of oncology, endocrinology, genitourinary medicine, gastroenterology, the central nervous system and immunology. As a result many companies have specialized in developing peptide libraries, firms such as Amyndas, Encycle Therapeutics, Peptidream, Polyphor or the Swiss Bachem. They offer peptides of different size, structure and function in small and huge amounts.

Customers from the pharmaceutical, biotech and also chemical industries can choose individual peptides as if they were buying the ingredients for a cake. In the end they hope to get new lead drug compounds. Experts estimate that the sheer number of companies in the field and the licensing deals they make with large pharmaceutical companies could lead to a further surge of clinical candidates and ultimately of new peptide drugs.

Therefore specialists have a strong look on the latest advances in research findings in which custom synthesized peptides play a key role in advancing science, medicine and technology. The magazine Science Translational Medicine, for example, reports that amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. The magazine Nature Materials describes the synthesis and application of an elastic, wearable crosslinked polymer layer that mimics the properties of normal, youthful skin. It shall be able to improve skin's elasticity and to eliminate wrinkles. And Nature writes that



optogenetics restores the memory in Alzheimer's mouse models. The authors showed that in transgenic mouse models of early Alzheimer's disease, direct optogenetic activation of hippocampal memory engram cells results in memory retrieval.

Improvement Of Properties

Swiss Bachem, which describes itself as a specialist in the process development and the manufacturing of peptides as active pharmaceutical ingredients (APIs), highlights its cooperation with Japanese GlyTech, a company that makes glycans. The partnership is focused on the chemical development and manufacturing of glycosylated peptides. Glycosylation can improve the physicochemical properties of peptides: solubility, stability, half-life and homogeneity. As a result, this can have positive effects on pharmacological properties of a lead candidate such as better binding, modified receptor selectivity, targeting a specific tissue or organ, and better tolerance.

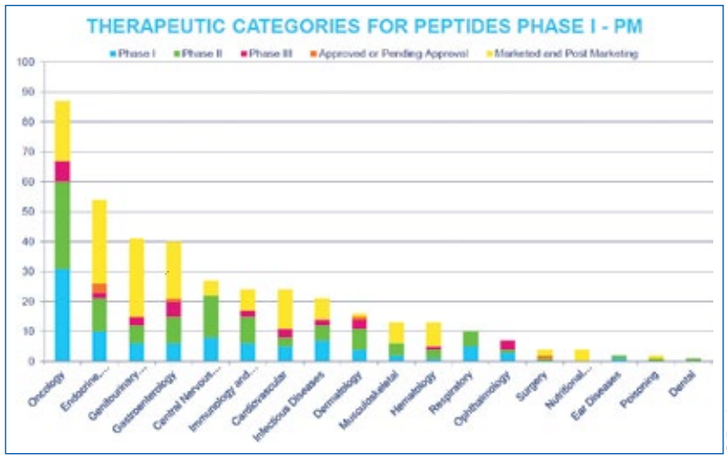
One goal of the Swiss-Japanese partnership is to improve physicochemical properties of peptides through selective glycosylation. Both chemical structure and position of glycosyl moieties can markedly improve the biological activity of a peptide. While Bachem brings into the cooperations its expertise to scale up and manufacture kilogram scale peptides, GlyTech is capable of producing glycans in kilogram amounts by a proprietary technology.

In 2013, both companies announced that they had successfully co-developed a chemical synthesis of Interferon β-1a applicable on an industrial scale. Interferon β-1a is a 166 amino-acid-long glycosylated protein and an approved drug substance to treat multiple sclerosis with a world market of more than $4 billion.

New Ways Of Delivery

Bachem is also working on new ways of delivery of peptide active ingredients into the human body. The basis for this is a robotic pill that would be swallowed by the patient. The tiny robotic device brings the active ingredient directly to the place in the body where it is needed. There a gas pushes needles into the intestinal wall and discharges the peptide active ingredients.

Another question for scientists is how to get peptides through a cell.



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Professor Scott Lokey from the University of California-Santa Cruz approaches this topic inspired by natural products and passive membrane permeability. His laboratory studies membrane permeability in molecules whose structures violate classical predictors of "drug-likeness" based on molecular weight and polarity. Many of these "rule breakers" are natural products such as cyclic peptides. Lokey's mission is to create a drug discovery paradigm that lies at the interface between conventional small molecules and biologics.

A related question concerns professor Roland Brock from Radboud University, Nijmegen Medical Centre. He wants to know how to bring molecules to the cell and detected milk as a blueprint of his peptide-research. Looking at the many ways of uptake of peptides he came to a human lactoferrin-derived peptide as an example. Brock and his team tried to use this method for kidney-specific therapies as there is an urgent need for such treatments.

The Oral Route

The question of oral peptide delivery is in the center of interest for Dr. Leila Hassani-Beniddir, scientist in the Novel Drug Delivery Technologies Group of Ipsen. Mainly because of their poor stability and short plasma half-life, peptides are usually administered by injection, often several times daily. However, the pain and invasiveness of injections, as well as disposal issues associated with used needles and relatively complicated administration protocols mean that alternative routes of delivery are highly desirable for peptides.

Out of all of the available routes of administration, the oral route is the most preferred for its convenience, patient friendliness and cost. However oral peptide delivery faces many hurdles, such as poor absorption, poor permeability and rapid enzymatic or pH-induced degradation in the gastrointestinal tract. The main aim therefore is to improve the absorption. This has been done successfully in mice, Hassani-Beniddir said. She predicted that the oral application of peptides will increase in the next five to 10 years.

There are also researchers focusing on real and practical applications of peptide technology. One is Dr. Don Wellings, CEO of the British company SpheriTech. His company designed several peptides for antimicrobial wound dressing. His aim is to use these products in regenerative medicine for skin repair, stem cell isolation, central nervous system repair, diabetic foot, severe burns or in case of severe accidents.

Looking into the future, peptide experts predict that the evolution of the numerous disciplines involved harbors great promise for peptides. Partnerships and alliances between pioneers in the field of peptides should unleash more productivity increases and catalyze medical progress at affordable rates. Furthermore new peptide drugs and old drugs in new delivery systems are likely to emerge in larger numbers in the decades to come.

Thorsten Schüller, CHEManager

A New Pathway

Novel Metal-Free Nitro Reduction Method Developed by Academia-Industry Collaboration

Reducing nitro groups to amines is a well-known and frequently applied method, which is useful in the synthesis of various classes of compounds of interest in the pharmaceutical and fragrances industries, as well as fine chemicals in general.

A new, patented metal-free invention made by professor Maurizio Benaglia at the University of Milan relates to a completely new production pathway based on the use of trichlorosilane S(a very cost-efficient reducing agent that is widely used in the semiconductor industry) and an organic base. Berlin-based startup DexLeChem has taken over its commercialization. This case serves as a good example of a successful translation of scientific findings into the industry — beyond national borders.

Complex Routes

There is a trend in the production of fine chemicals and active pharmaceutical ingredients (APIs) toward the synthesis of increasingly complex molecule structures that consist of multiple functional groups. A reliable methodology to insert amino groups without harming the remaining molecule structure is of great industrial importance, although technically challenging.

All roads lead to Rome, but which road is the best? When it comes to nitro reductions, state-of-the-art processes involve the hydrogenation of nitro groups with heterogeneous noble metal catalysts such as palladium or platinum on charcoal. As often as not, problems tend to arise during these processes, especially when it comes to complex drugs. Other functional groups of the API can be attacked and alter the needed molecule structure in an undesirable way; metal residues from the catalysts in the product also can cause problems and hinder the drug approval process.

Martin Rahmel, DexLeChem

Furthermore, every organic chemist has probably experienced the problem that compounds lose halogen groups when exposed to hydrogen during a nitro reduction step, resulting in a drop in selectivity and increasing the manufacturing costs significantly.

Chemical reduction methods, on the other hand, have the large drawback that an environmentally safe waste disposal creates prohibitive costs for industrial applications.

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Until now, no solution to most of these problems has been commercially available. In a bilateral approach, involving the University of Milan (UNIMI) and the Berlin-based startup DexLeChem, this shortcoming has been solved.

Academia And Industry Converge

The partnership started at the beginning of 2013, when Benaglia from UNIMI made an important discovery. As a well-known expert in the field of organocatalysis, he had already worked extensively with trichlorosilane to reduce imines, improving the performances of these transformations considerably. Through his research, he then found that trichlorosilane itself could also perform nitro reductions. This revelation was unprecedented by even the foremost experts in his field. It was previously well-known that in the case of the presence of a nitro group in an imine, trichlorosilane reduces only the C=N bond and not the nitro group. However, Benaglia changed the reaction protocol so that he was able to forge a new path in nitro reductions via trichlorosilane.

This new methodology enables a completely new pathway that possesses certain advantages against the former state-of-the-art technologies:

- It does not attack other parts of the compounds (which is described as a high chemoselectivity).
- The work-up is very easy, and enables an environmentally safe waste disposal as the totally nontoxic waste can be discharged into aqueous wastewater.
- There are no risks of product contamination by metals.
- Restrictive patents can be bypassed because of the increasing range of alternative synthesis routes.
- No high-pressure equipment is needed.
- The chirality of drugs, which is of high importance for the pharmacological effect in the human body, is not affected as the new pathway respects the stereochemical integrity of the stereogenic elements of the molecule.

Benaglia recognized the high market potential of his invention immediately and filed an international patent application under the Patent Cooperation Treaty (PCT). He also quickly found his first customer, the Italian pharmaceutical company Zambon and its chemical business, Zambon Chemicals (abbreviated ZaCh System), with which he already had a close relationship.

When Benaglia approached ZaCh, the company was in the middle of a process development for a second-generation synthesis route of Aliskiren. ZaCh directly bought a license to his patent: "The possibility to perform a nitro reduction in the last stage of the production with 100% selectivity and 99% yield solved all of our problems at once: This new method secured us the whole freedom-to-operate of the process and the great performance secured our profitability," said Dr. Massimo Verzini, head of process development.

But after this early success, something happened that happens quite frequently with scientific innovations: the commercialization stopped. Benaglia simply did not have the time to go to fairs or cold call other companies. The end of the PCT application drew closer.

At a scientific symposium in December 2014, Benaglia met Sonja Jost, founder and CEO of Berlin-based chemistry startup DexLeChem. From her own experience, she knew that most scientific findings just do not reach the industry. This was the starting point for DexLeChem.

So Jost asked Benaglia whether he had identified any maturing markets for his scientific findings. Despite his high scientific reputation, no one had ever asked him this question. The nitro reduction method came to his mind, and Jost immediately recognized its potential. A lot of DexLeChem's customers had had problems with nitro reductions. DexLeChem then spent the next January analyzing competitive pathways for nitro reductions.

The company also assigned external specialists to further evaluate Benaglia's discovery. His very mild reaction conditions and the high performance indicators of his process (which were and remain unbeatable for many applications) convinced DexLeChem's team as well as the external specialists. DexLeChem was then able to start the negotiation process about the patent application with UNIMI in February — only one month before the application would have expired. The contract of sale was signed just in time to start with the nationalization.

"Some of our main advantages are the flexibility and short decision-making process that we offer as a startup company," Jost said of the quick closure.

Today, DexLeChem provides the development of the new nitro reduction method as a service to the chemical and pharmaceutical industries. Manufacturers who have internal development departments can also just acquire a license. In addition, ZaCh offers to directly produce compounds in-house with this new method.

"I am very happy that my scientific findings are now much more applied in industry, and I think that startups in general can help to close the gap between academia and the industry, which is still there," Benaglia said.

Martin Rahmel, co-founder and head of business development, DexLeChem GmbH, Berlin, Germany

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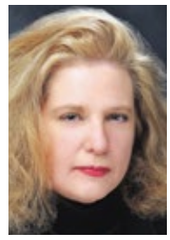
Opportunities in Drug Development and Manufacturing

High-potency Manufacturing Continues to Attract Investment of CDMOs and CMOs

Growth in the global oncology drug market is an important measure of opportunities in drug development and manufacturing, including for contract manufacturers of active pharmaceutical ingredients (APIs) and finished drug products. On the small-molecule side, whether as an API or finished drug product and depending on the product involved, growth in the oncology market is one indicator of potential opportunities in high-potency manufacturing.



Patricia Van Arnum,
DCAT Value Chain Insights

Within the oncology market, a niche segment is antibody drug conjugates (ADCs), which consist of a cytotoxic small molecule linked to a monoclonal antibody (mAb). ADCs, certain oncology drugs, and other high-potency compounds (such as hormones) require high-containment manufacturing, which involves specialized approaches in facility design, equipment selection, and manufacturing processes to achieve the desired levels of containment and minimize operator exposure. Several contract manufacturers have recently invested in high-potency manufacturing. Below is a roundup of activity as announced in 2015 and 2016 to date.

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ADC Biotechnology

In October 2015, UK-based ADC Biotechnology announced a $10-million plan to build a manufacturing facility in St. Asaph, North Wales, UK for advanced anti-cancer drugs. The two-stage expansion program marks the transition of ADC Biotechnology into GMP manufacturing of ADCs. Phase 1 of the project will come on stream in mid-2017, creating a 1,500-square-meter dual-stream facility for process development, manufacturing, and quality testing of ADC drugs. The new facility will be able to produce clinical trial and low-volume commercial quantities. A projected second phase is planned to add another 2,500 square meters of manufacturing space for larger-scale clinical and commercial manufacturing. The company also invested £100,000 ($132,000) for an R&D lab, focused on bio-conjugation and payload-linker chemistry in early 2015.

Aesica Pharmaceuticals

Aesica Pharmaceuticals announced in April 2016 that it had doubled its development capacity at its facility in Queenborough, UK. With the addition of the new capabilities, Aesica can now develop and manufacture a customer product from early formulation development through clinical manufacture and into commercialization. The company's highly potent and controlled drugs service offering was expanded at Queenborough as a result of the new center. The company previously only provided commercial-scale manufacturing capabilities for these drug classifications, but it now offers full formulation and development capabilities. The site handles highly potent drugs for any active up to SafeBridge Category 3, together with controlled drugs, with licenses for both Schedules 2 to 4. The SafeBridge Potent Compound Safety Certification program provides an independent assessment of a company's manufacturing capabilities for safe production of potent active pharmaceutical ingredients and drug products.

Alcami

In August 2016, Alcami announced plans to expand its manufacturing capacity for highly potent APIs at its facility in Germantown, Wisconsin. Alcami plans to invest in 2016 and 2017 toward enhancement of new and existing kilo labs to introduce

the development and manufacturing of high-potency APIs. Two new cGMP-compliant production suites will focus on primary containment technologies with engineering controls designed to meet occupational exposure limits of minimally 0.03 µg/cubic meter (SafeBridge Category 3). The expansion will include a 5,000-square-foot renovation that will be operational by the first quarter of 2017.The newly designed space will include up to 150-liter reactor scale with cryogenic capabilities. These advancements follow operational and technology enhancements across development, clinical, and commercial manufacturing to increase overall production capacity by 50%. The company has global API operations in Germantown, and Weert, The Netherlands.

Cambrex

In July 2016, Cambrex announced that it had completed and validated a $50-million production and warehousing expansion for API manufacturing at its cGMP site in Charles City, Iowa. This facility sits on a 45-acre site and manufactures a wide range of APIs and pharmaceutical intermediates, including highly potent molecules and controlled substances. The new 7,500 square-foot multi-purpose manufacturing facility will initially add a total of 70 cubic meters of glass-lined and Hastelloy reactors ranging in size from 7 cubic meters to 16 cubic meters, along with Hastelloy agitated filter dryers for a multi-purpose configuration that will be capable of handling potent APIs at an occupational exposure limit of down to 1 µg/cubic meter. The facility complements the three existing large-scale manufacturing facilities at the Charles City site.

Carbogen Amcis

In May 2016, Carbogen Amcis announced the extension of its operations in Bubendorf, Switzerland. The company undersigned the acquisition of the land and buildings of GEA Pharma Systems in Bubendorf, close to the company's current headquarters. The space will allow the company to expand its laboratory capacity for highly potent development and small-scale production as well as analytical support. Operations are scheduled to expand into the new building in 2017.

Catalent

In January 2016, Catalent, through its wholly owned subsidiary, Redwood Bioscience, formed a research collaboration with Roche to develop molecules coupling different therapeutic modalities using Catalent's proprietary SMARTag technology, an ADC platform. Under the deal, Roche gains non-exclusive access to the SMARTag platform and will have an option to take commercial licenses to develop molecules directed to a defined number of targets. Roche pays Catalent an up-front fee of $1 million and will provide additional research funding during the initial phase of the collaboration. Catalent has the potential to receive up to $618 million in development and commercial milestones, plus royalties on net sales of products, if Roche pursues commercial licenses and all options are exercised. Catalent acquired an exclusive license to market the SMARTag technology in 2013 and

subsequently collaborated with Redwood for the ongoing development and marketing of the platform. It later acquired Redwood in 2014. The SMARTag technology enables the generation of homogenous bioconjugates and is engineered to improve performance and manufacturing.

On the drug product side, in January 2015 Catalent expanded its potent handling and manufacturing capabilities at its facility in Somerset, New Jersey. The company completed the expansion of facility and engineering controls for its high-potency tableting and OptiMelt Hot Melt Extrusion operations in Somerset to supplement existing potent capabilities in oral solid and its Zydis Fast Dissolve manufacturing. The company invested in additional potent containment for large-scale blending, fluid-bed processing, and high-shear granulation. The expansion created a manufacturing Center of Excellence for potent handling across Catalent's portfolio of oral solid manufacturing solutions, which includes hot-melt extrusion, high-shear and wet-granulation processing, solvent-based capability, extrusion/spheronization, fluid-bed processing, Wurster coating, and compression and encapsulation. The company also invested in high-potency clinical packaging.

Cerbios-Pharma

In early 2016, Cerbios-Pharma opened a new R&D center for high-potency active APIs and mAb development. Cerbios is a privately held company located in Lugano, Switzerland, which specializes in the development and manufacture of both chemical and biological APIs. Exclusive, third-party manufacturing services are offered by the Chemical Division for high-potency APIs and by the Biological Division for mAbs, recombinant proteins, and pharma probiotics.

The construction of the investment was approved in November 2013 and started in April 2014. The new building consists of four floors of 280 square meters each. The second floor houses biological R&D, with three dedicated laboratories for the development of mAbs and/or recombinant proteins based on Chinese hamster ovary (CHO) mammalian cells and a large laboratory to develop pharmaceutical probiotics. The first floor houses a new additional GMP archive and offices for the directors and for the managers of R&D and quality assurance. The ground floor houses chemical R&D, doubling the capacity to develop highly potent APIs for contract manufacturing services, including SafeBridge Category 4 products. Underground floors house two warehouses (one for R&D and one for production) and personnel services.

CMC Biologics and IDT Biologika

CMC Biologics, a contract provider of clinical and commercial manufacturing of mAbs and other therapeutic proteins, and IDT Biologika, a privately held life-science company with expertise in research, development and manufacture of biologics, formed a strategic collaboration in February 2016 for the manufacture of ADCs. Within this collaboration, CMC Biologics will perform process development and manufacture of the bulk mAb, and IDT Biologika will perform services from conjugation of the cytotoxic drug to the antibody substance through to the aseptic fill, finish, and packaging of the ADC final drug product. The joint manufacturing solution is intended to provide speed, reliability, quality ADC manufacturing, and a simplified supply chain, from DNA to finished drug product, for clinical trials through commercial manufacturing.

CordenPharma

In March 2016, CordenPharma announced the completion of expanded development capabilities for mid-scale (up to 20 kg) contained capacity of highly potent and oncology oral dosage forms in its CordenPharma Plankstadt manufacturing facility in Germany. The new and expanded capability provides contained manufacturing of oral dosage forms from grams to 150 kg.

Goodwin Biotechnology

In May 2016, Goodwin Biotechnology, a CDMO based in Plantation, Florida, expanded its bioconjugation capabilities by adding a dedicated suite for developing and manufacturing cytotoxic antibody drug conjugates up to SafeBridge Level 4/5.

Johnson Matthey

In March 2015, Johnson Matthey, a provider of pharmaceutical services, APIs, and catalyst technologies, announced the completion and commissioning of a new high containment facility for potent product manufacture at its Edinburgh, UK site (Macfarlan Smith). The facility has the necessary manufacturing controls and procedures in place to produce compounds with occupational exposure limits of less than 30 ng per cubic meter. Johnson Matthey also manufactures highly potent products through its facilities in West Deptford, New Jersey and Devens, Massachusetts.

Infa

In November 2015, the Milan, Italy-headquartered Infa Group, now part of Olon, reported that Labochem received cGMP certification for its new multipurpose highly potent API plant. The new kilo laboratory has capacity of up to 2.5 kg/batch size and manufacturing capabilities ranging from hundreds of grams to tens of kilograms for advanced intermediates and APIs, classified from Occupational Exposure Band 3 to 5.

MilliporeSigma

In May 2015, SAFC Commercial, Sigma-Aldrich's custom manufacturing services business unit, completed the expansion of its St. Louis, Missouri facility to support commercial-scale ADC manufacturing. In 2015, Merck acquired Sigma-Aldrich for $17 billion and later rebranded its life-sciences business as MilliporeSigma in the US. The expanded capabilities in St. Louis were further enhanced by expanded commercial capacity for highly active manufacturing and storage at the company's facility in Madison, Wisconsin.

Novasep

In June 2015, Novasep announced the addition of a fully integrated ADC facility at its site in Le Mans, France. The new facility will enable Novasep to complement its current ADC offering with full bioconjugation services. The facility was planned to be commissioned in the second quarter of 2016 and will provide contract manufacturing in batch sizes from a few milligrams to 600 g to ADC drug developers during clinical trial and commercial development phases. The expansion is part of Novasep's €10 million ($11 million) investment in clinical and commercial-scale ADC conjugation.

Piramal

In August 2016, Piramal, through its wholly owned subsidiary in the US, agreed to acquire Ash Stevens, a Riverview, Michigan-based CDMO of APIs for $42.95 million plus an earnout consideration capped at $10 million. The transaction was expected to be completed by the end of August 2016. The acquisition provides Piramal with 60,000 square feet of facilities, eight chemical drug development and production laboratories, and six full-scale production areas, which includes highly potent API manufacturing. Ash Stevens' facility in Michigan has engineering and containment controls for the safe handling and cGMP manufacture of small- and large-scale high-potency APIs, with occupational exposure limits ≤0.1 µg/cubic meters.

Also, in November 2015, Piramal Healthcare opened a new £2 million ($2.2 million) ADC manufacturing suite at its facility in Grangemouth, Scotland, according to the Scottish Enterprise, the economic development arm of Scotland.

Regis Technologies

In August 2015, Regis Technologies, a contract provider of custom synthesis and separation services, started up a new potent compound suite (PCS) at its 36,000-square-foot, cGMP facility in Morton Grove, Illinois. The PCS addition provides for small-molecule cGMP manufacturing of potent compounds up to about one kilogram per batch. Regis' new PCS includes isolators, laminar flow hoods, and local exhaust ventilation appropriate for potent compound handling.

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Pharma Facility Awards

ISPE Recognizes Leaders in Drug Shortage Prevention

The International Society for Pharmaceutical Engineering (ISPE) recognized 2016 category winners Baxter BioPharma Solutions and Janssen Vaccines for their exceptional leadership in drug shortage prevention.

At the 12th Annual ISPE Facility of the Year Awards (FOYA) banquet held in June in North Bethesda, Maryland, USA, the society's president and CEO, John Bournas, said: "ISPE is recognizing companies who, by virtue of the accomplishments for which they have won a category or honorable mention, have strengthened their ability to prevent drug shortages or minimize their impact on patients."

Baxter BioPharma's site in Halle, Germany, and Janssen Vaccines' facility in Bern, Switzerland, have been selected based upon excellence in the drug shortage prevention dimensions which form the framework of the ISPE Drug Shortages Prevention Plan and the ISPE Drug Shortage Assessment and Prevention Tool. Those dimensions include: corporate culture, business continuity planning, robust quality systems, metrics, communication with regulatory authorities, and building capability.

FOYA Category Winners

The Facility of the Year Awards (FOYA) are an annual program that recognizes state-of-the-art projects utilizing new, innovative technologies to improve the quality of products, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery.

Baxter BioPharma Solutions is the 2016 FOYA category winner for Operational Excellence. The US company's parenteral manufacturing plant in Germany (cf. photo) undertook a project to add additional capacity to service the CMO market of parenteral oncology and other complex liquid and lyophilized products. Intent was to provide full services "under one roof" that facilitate short startup time and minimize transfer costs.

Janssen Vaccines is the 2016 FOYA Awards category winner for Project Execution category for the "Fast Track Refurbishment for Ebola Vaccine Production". In 2014 Janssen, the pharmaceutical division of Johnson & Johnson, responded to the Ebola outbreak in West Africa and committed to accelerate the development of its candidate Ebola vaccine. While the first volumes were produced in pilot scale, an idle facility was being refurbished for the scaled-up process providing a launch capacity of up to 5 million doses annually.

In addition to the special recognition for their leadership in drug shortage prevention, the following companies were recognized as the FOYA 2016 category award winners:

Ethicon's facility in San Lorenzo, Puerto Rico, was awarded the Sustainability category prize for the site's sustainability efforts that resulted in energy reduction of 26% and water reduction of 9%, while increasing production volume by 11%, compared to 2010 consumption levels.

Genentech won the Process Innovation category for their large scale, Cell Culture Biologics Drug Substance Plant 2 (CCP2) located in Vacaville, California, USA. This project focused upon an upgrade to the original facility, put into an idle but "keep warm" status in 2010, combined with a fast track Return to Service project.

Pfizer's Groton, Connecticut, USA site is the category winner for Equipment Innovation. Pfizer, GEA, and GCON Manufacturing formed a consortium to design and build a portable, autonomous manufacturing environment for continuous oral solid dosage production using GEA's ConsiGma25 system and G-CON's modular system.

Takara Bio's Center for Gene and Cell Processing (CGCP) in Kusatsu city is being recognized for its innovative use of facility integration to house cell products, viral vectors and recombinant proteins within the same facility.

www.ISPE.org

Serialization – The Bigger Picture

Preparing for All Requirements with a Scalable Machine and Software Concept

Potency pills or even life-saving pharmaceuticals such as heparin – the trade with counterfeit medicine is still booming. Accordingly, drug producers and contract packers are shifting their focus to serialization of pharmaceutical packaging. Time is pressing, as numerous laws and guidelines have already or will come into force all over the world in the coming years. Companies concerned are facing the challenge of finding and implementing appropriate technologies, and connecting them with their manufacturing and packaging processes. A scalable machine and software concept undoubtedly is the safest option.

The European Union's Falsified Medicines Directive 2011/62/EU came into effect in February 2016. It stipulates the usage of coded packaging with unique serial numbers for all prescription drugs. Similar to many other countries, the serialization feature is a 2D data matrix code. It contains a randomized serial number, the batch number and expiry date, as well as further data, if required. At the same time, the EU demands a second level of security in form of tamper-evident closures, such as integrity seals or glue, which are recorded in the CEN norm DIN EN 16679:2015-03. They clearly indicate whether a package has been previously opened or tampered with.

Toward Complete Connectivity

On November 27, 2013, the Drug Quality and Security Act (DQSA) was adopted in the U.S. In early 2015, the implementation began on batch level. As of 2017, serialization of primary packaging will be mandatory. The biggest challenge for all parties involved, however, will follow in 2019, when the serial number of each individual pack and outer packaging must be known to pharma wholesalers — either in form of the National Drug Code (NDC) or the Global Trade Identification Number (GTIN). First, all drug producers must comply with this law. In an interval of one year each, repackers, wholesalers and dispensers will follow. Exactly ten years after commencement of DQSA, that is end of November 2023, the complete connection and aggregation is supposed to be implemented. Based on the unique serial number, products can then be electronically traced on all aggregation levels, as well as on batch and single packaging level along the entire supply chain through to the dispensing point — unambiguously and in real time.

In parallel, many other countries are developing and implementing new guidance and laws. In the MENA region (Middle East and Northern Africa), efforts for drug traceability are already underway. Saudi Arabia, for instance, initiated the first phase in March 2015 with obligatory data matrix codes on pharmaceutical packaging. Phase 2 — actual serialization — will come into force in 2017. While phase 1 only requires a machine to print data matrix codes, phase 2 necessitates producers and packers to have machines for serialization as well as an IT infrastructure to generate the serial numbers. Moreover, they must be able to send the numbers to their machines, report the results to manufacturers' databases and record them.

Significant Differences

Now what are the fundamental differences between the different implementation stages? On the one hand, the EU attributes special importance to tamper-evidence. On the other hand, the U.S. wants to implement the first aggregation step at a very early point in time, thus changing the requirements for both local pharma companies and importers. While serialization is currently still often seen as regional responsibility, the different legislations will have a global impact. Many large drug producers operate production facilities in different countries and export their products all over the world. Equipping packaging lines according to only one standard would be very short-sighted.

Take a practical example: a large generic producer from the MENA region sells his products in the local market, as well as in Europe and the U.S. The majority of pharmaceuticals are packaged at the production sites in Jordan and Saudi Arabia. Against this background, all pharmaceutical packaging must conform to different national serialization standards. Accordingly, flexible solutions which are able to fulfill far more than just one national guideline are highly sought-after. The same accounts for contract packers, who must comply with the laws of the respective market, as well as with the requirements of their clients.

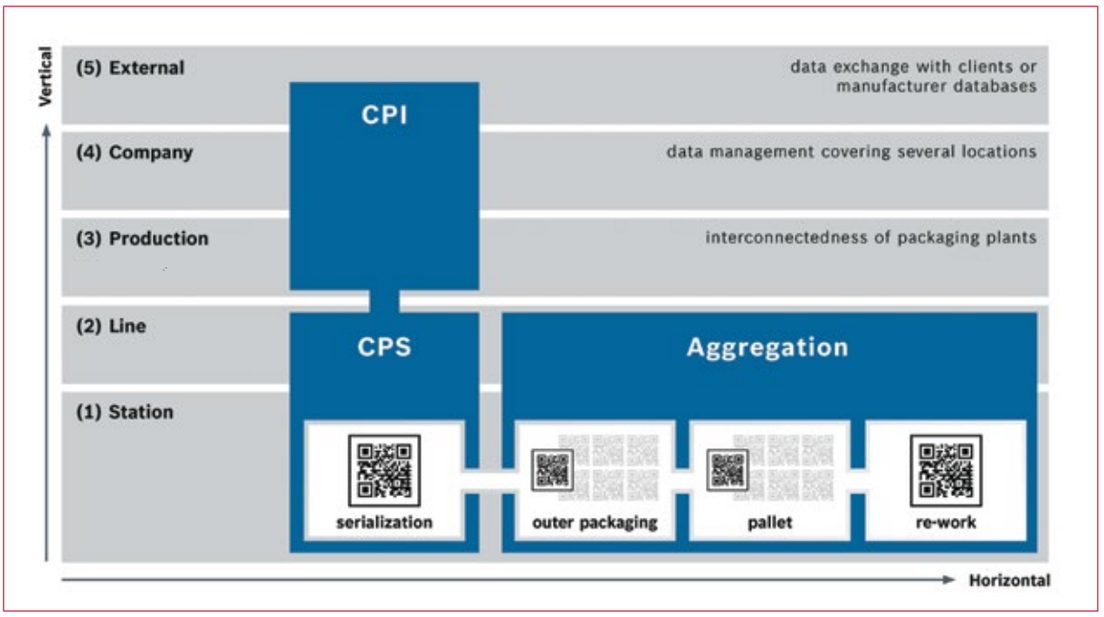
Jörg Willburger
Bosch Packaging Technology

Adapting Established Processes

In general, most producing and packaging companies will not be able to avoid developing and applying a global strategy to consistently assign serial numbers. This requires solutions that are compatible with in-house processes, leading to the adaptation of often highly demanding packaging processes. Furthermore, new processes must be established for both ma-

nagement and storage of serial numbers. The requirements can be subsumed in a single key word: "modular". A comprehensive serialization solution should not only be able to mass-serialize the packed product, verify the codes and apply labels or tamper-evident seals to the packaging. The entire process needs to be controlled, and the data retrieved at any time. Only this way do producers – and later on the dispensing points – have an exact overview of all process steps.

To this end, Bosch Packaging Technology has developed the CPI software for Track & Trace, which can be easily integrated into existing IT infrastructures. The company can rely on the own experience from the automotive sector, where automation and connectivity of machines, processes and IT have been tried and tested for years. Logic and functionalities have been transferred and adapted to the specific pharmaceutical requirements for Track & Trace applications.



From machine to database: Bosch's CPS systems and the CPI software enable the survey of all serialization steps.

From Machine to Database

How can we imagine a holistic serialization process in reality? It starts on the application level (level 1). Here, the modular CPS system from Bosch serializes up to 400 folded cartons per minute. The camera system automatically verifies the printed tracking data. Subsequently, a security seal is applied by the Tamper Evident labeler. The modules can be operated via a central user interface, and the data can be documented (level 2).

To control both operating condition and data at any time, the connection between the physical machine level and the control software must be integrated across many stages of the company's IT (level 3). From this level onwards, the CPI solution for Track & Trace ensures that the entire production environment or several sites are depicted (level 4). Moreover, an interface is also possible for data transfer, for instance to the SecurPharm database or to the customer (level 5).

The Highest Flexibility

Back to the example of the generic producer, who has lately equipped numerous packaging lines with CPS modules and CPI software. The company benefits especially from the new data connection between all lines that are situated at different locations and can now be monitored from the headquarter. Thus all relevant data is available in the entire company network, and all results are recorded in the audit trail. The data sets are bundled with the production results according to aggregation specifications, and sent back to the CPI software. From here, they can be transferred to regulatory or producer-owned databases.

Depending on country and guideline, the serial numbers are either allocated centrally or generated by the company. Contract manufacturers in turn receive the numbers from their clients. This requires very high flexibility within the process cycle. The CPI solution from Bosch is equipped for all three cases. Companies can not only manage serialization from the allocation of the serial number through to the last aggregation step. They can also flexibly connect single components, third party machines, packaging lines, own or third party IT systems and entire factories with each other according to the respective guidelines. Hence it really is worth while looking at the bigger picture — for manufacturers and contract packers, as well as for mechanical engineering companies with a focus on international customers.

Jörg Willburger, Area Sales Manager, Bosch Packaging Technology, Stuttgart

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Pharmaceutical Logistics as a Brand

Specialization in the Logistics Sector: Pharmaserv Establishes a Separate Logistics Segment

In recent years, pharmaceutical logistics has become a highly specialized discipline. This is why Marburg site operator Pharmaserv established a separate segment for the pharmaceutical industry's unique logistical requirements. CHEManager spoke to Thomas Janssen, Managing Director of Pharmaserv and Dr. Martin Egger, Vice President of Pharmaserv Logistics about the background to this step and the new Central Pharma Distribution Center. The interviewer was Dr. Sonja Andres.

Dr. Martin Egger, Vice President, Pharmaserv Logistics

Thomas Janssen, Managing Director, Pharmaserv

CHEManager: At present, special warehouses and logistic centers for pharmaceuticals and biopharmaceuticals are being established in various regions in Germany. In light of your many years of experience in this sector, what do you think is the main reason for this development?

Dr. M. Egger: There are many reasons for this. First, the global demand for medicines has increased continually over the past years, which has resulted in a general and growing increase in market volume. At this point the enormous growth rates of the so-called BRICS countries — about 10% annually — should be emphasized. Due to changing market factors such as expiry of patents, the development of innovative biotechnology products, general cost pressure and a general globalization of processes, manufacturers are being forced to reconsider their supply chains. The issue of outsourcing is becoming increasingly relevant. Professional service providers are looking for opportunities in pharmaceutical logistics.

In addition, the latest changes in regulations — such as the introduction of the GDP Guidelines for drugs in 2013 — have increased requirements on pharmaceutical logistics. This can be seen from the steadily growing demand for temperature-controlled logistics. Although the barriers to entering the market are becoming more challenging, conventional carriers in temperature-controlled transport are moving into the warehousing business. This is because pharmaceutical logistics is seen as an attractive business opportunity in the logistics market. The fact that many companies hope to benefit from this market is clearly reflected in the number of warehouse project developments.

Pharmaserv recently established its logistics segment as a separate brand, Pharmaserv Logistics, at the beginning of 2015. What were the main reasons for this step?

T. Janssen: Over the past years, Pharmaserv has successfully positioned the "Pharmaserv" brand as a competent and innovative partner for technical services and site management. The high level of specialization in the logistics industry and international expansion meant that we needed to differentiate logistics with respect to our other businesses.

A separate market presentation was created, so that we could position our pharmaceutical logistics services more clearly on the market. We found that making this differentiation in a target-oriented manner under the heading "Site Management & Services" was not really feasible. People are not always confident that a local site operator can also be an expert in global pharmaceutical logistics. Because we serve international customers who

want to access global markets with their highly sensitive ready-made drugs, innovative active ingredients or clinical studies, clear differentiation and positioning are important — and this was the right choice.

What are the benefits of this differentiation for your existing pharmaceutical and biotechnology customers — and future ones?

T. Janssen: We examined this question thoroughly prior to the brand differentiation. For example, customer surveys showed that small biotechnology companies do not usually have any in-house logistical expertise. The same also applies for laboratories or hospitals. On the other hand, even medium-sized or large companies with their own logistics structures are increasingly reaching their limits. Their own cold storage has become too small, emerging markets are being opened up, or there is simply too little know-how for efficient supply to international wholesalers. This is precisely where we come in — we aim to support each of our customers in the solution of their individual challenges. Deep-rooted and long-term partnerships often result from these joint, and to some extent innovative projects. This results in genuine added value for both parties.

The "Central Pharma Distribution Center" at the Behringwerke location in Marburg was completed at the beginning of 2016 — a major investment. What do you offer your customers there?

Dr. M. Egger: With the extension of our pharmaceutical warehouse at our headquarters in Marburg, we have increased our pharmaceutical logistics area to 8,000 square-meters and a further 4,000 square-meters space is available, e.g. for packaging material and storage of hazardous substances. The newly constructed "Central Pharma Distribution Center" combines various logistics services. In total we have created space for another 4,000 pallets in the 15-25 °C area as well as for 900 pallets in the 2-8 °C area. For all GxP-relevant products, we profit from our validated Warehouse Management System, which enables deep involvement in our customers' processes.

Are there services going beyond those that you previously offered and if so how are these now being accepted?

Pharmaserv Logistics' central warehouse in the center of Europe can provide efficient distribution concepts for air, sea or road transport.

Dr. M. Egger: Primarily, our investment was intended to adapt our capacities and infrastructures to put us in a position where we can implement our strategic growth path. In parallel with our building infrastructure we have also further developed our partner network for GDP-compliant distribution. Here, we rely on stable relationships, but we also aim for continuous further development. This can be seen in various aspects, such as the validation of additional pharmaceutical freight carriers to increase our performance capacity, introduction of innovative thermal packaging for air freight, the establishment of certified protection systems for loading sea freight, and so on.

What is new, and very important to mention, is the change in our mindset. Previously, we have emphasized our expertise in "Pharma Logistics" or "Cold Chain Solutions" for our customers. We are now increasingly attempting to discover exactly what our customers are concerned about and what gives them sleepless nights. We have recognized that our portfolio is attractive to international customers who wish to expand their business in Europe. This is why we are attempting to address international target customers and communicate to them the advantages of having us as a distribution partner.

How do you rate the German and international market in terms of sensitive and temperature-critical drugs? What are the consequences for logistics?

Dr. M. Egger: Demand within the pharmaceutical and biotechnology sectors for specialized, efficient and temperature-controlled logistics solutions will continue to grow. In addition to the GDP guideline, the cost pressure from the generics sector will force pharmaceutical companies to closely examine their own logistics and look for new and cheaper solutions. We are already seeing a clear trend toward smaller batch sizes, which is shown by a shift in demand from full-truck to less-than-truckload and parcel service solutions. In addition, we also see a trend away from air freight toward cheaper sea freight. No matter what challenges the future presents to our customers, we are here to face them together.

www.pharmaserv-logistics.com

CPhI Worldwide 2016

CPhI Worldwide, to take place October 4–6, 2016, at Fira de Barcelona Gran Via, Barcelona, Spain, is the leading exhibition dedicated to pharmaceutical developments, trends, products and services. Exhibitors include CROs/CMOs, suppliers of APIs, excipients, ingredients, intermediates and finished dosage forms, as well as producers of pharma manufacturing and packaging equipment.
www.cphi.com

DCAT After The Show

DCAT has announced a networking event for member company representatives. The event called „DCAT After the Show" will take place on October 5, 2016 after CPhI Worldwide at Casa Llotja de Mar in Barcelona, Spain. The event offers members an opportunity to establish new business relationships.
www.dcat.org

ISPE Europe Conference on Biotechnology

On October 24 and 25, 2016, ISPE Europe will hold their 2016 Biotechnology Conference in Frankfurt, Germany, under the motto "Reinventing Commercial Biomanufacturing". Attendees will learn about GMP challenges and opportunities for biomanufacturing, see first-hand innovative solutions in process development, and visit Sanofi plants at the Höchst Industrial Park.
www.ispe.org/2016-europe-biotechnology-conference

European REACH Congress 2016

The European REACH Congress, held on November 8–9, 2016, in Düsseldorf, Germany, provides an overview of the current status of REACH, how REACH has influenced non-EU regions and what this means for European industry. The conference, organized by TSGE Forum, encourages shared learning amongst industry, service providers, authorities and policy makers.
www.reachcongress.com

ChemOutsourcing 2017

ChemOutsourcing, the largest USA-Based API show attracting more than 700 chemists, buyers and business development experts from the pharmaceutical, biotech and chemical industries, moves from September to May. The next ChemOutsourcing will take place on May 1–3, 2017, at Long Branch, New Jersey.
www.chemoutsourcing.com

InformEx 2017

InformEx brings together decision makers of the fine and specialty chemicals industry to interact and drive growth in rapidly expanding chemical markets. Adjacent to the next edition of InformEx, on May 16–18 in Philadelphia, Pennsylvania, USA, the first edition of CPhI North America will cover the pharmaceutical value chain, attracting buyers and sellers of pharma ingredients and contract services.
www.informex.com

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