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Pharma & Biotech

Potential of mRNA Technology, Secure Pharma Supply Chains, Flow Chemistry, Continuous Manufacturing, Artificial Intelligence in R&D

Logistics

Outlook for the European Logistics Sector, Special Logistics Requirements for Cell & Gene Therapies, Use of AI in General Cargo Logistics

Innovation

Production of Noncanonical Amino Acids for Drugs with Biocatalysis, Extraction of Cellulose from Biomass with Ultrasonic Fractionation

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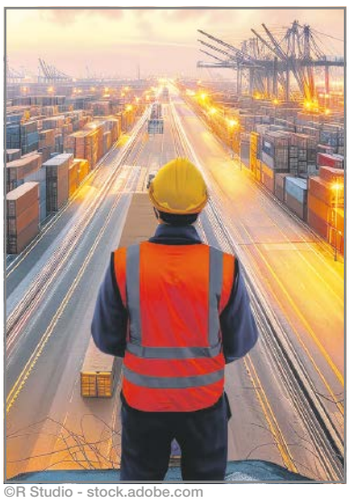
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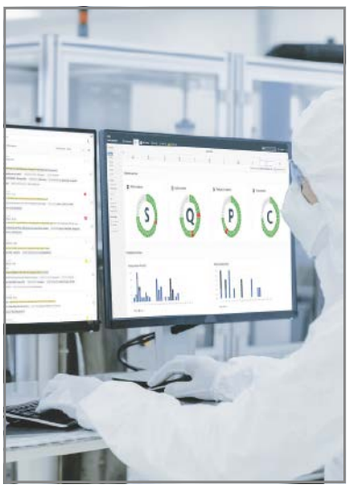

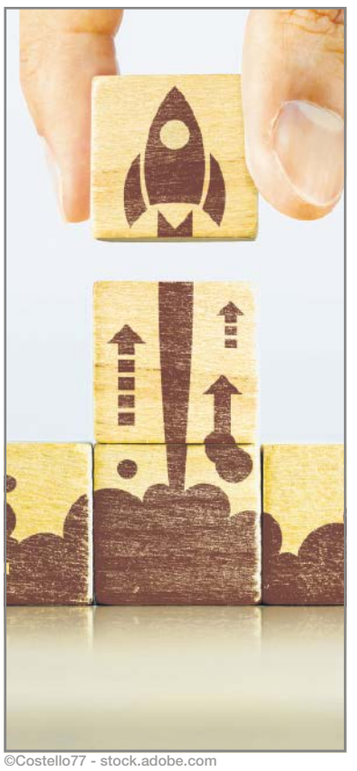
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Pharma & Biotech

Logistics

Digitalization

Innovation

Opportunities to Prosper in an Uncertain World

Breakthrough Supply Chains for the Pharmaceutical Industry Reflect Future Visions

The pharmaceutical industry is a truly global and complex network of ingredients and materials suppliers, manufacturers, distributors for a variety of products ranging from vaccines to antibiotics and to therapeutic drugs for customers/patients. While the top 20 multinational pharma brands are well known, the supply chains were largely unknown prior to the Covid pandemic. Global events and disruptions are motivating executives to reassess their supply chains and look for innovation and change. Breakthrough supply chains reflect future visions and open up opportunities for transformation.

Breakthrough supply chains are defined as composed of holistic end-to-end views of sourcing through to customers, patients, and consumers; and new innovations that meet critical business and societal needs. They involve reimagination, reinvention, and redesign, to meet the uncertainties present in the new era. They require the application of "breakthrough thinking" to navigate the challenges and changes that are associated with national security and intellectual policies, customer needs, risks, the rapid evolution of new technologies, and other critical factors. As such, supply chains today are highly complicated and complex in detail (cf. figure).

The pharma industry has been largely protected from serious disruptions and other occasional challenges by holding substantial inventories and incurring relatively lower-cost supply chain logistics operations. This comfort level was significantly interrupted, however, by the global Covid pandemic when supply chains becoming highly visible and at the top of societal concerns. The vulnerability of pharma supply chains was highlighted, even as pharma companies adapted well to the health security and critical societal needs for medicines (especially as compared to certain other industries and product shortages).

Similar to leaders in other industries, pharma leaders are better understanding their end-to-end supply chains. Strategic questions have begun to enter C-suites and stakeholder meetings, as concerns are being raised about global issues such as sustainability, resilience, risks, and the assurance of supply. These views are facilitating end-to-end views in addition to the functional needs of each of the mega processes: plan — buy — make — move — distribute — sell.

New Visions and Innovative Solutions

The end-to-end views, which include visibility and real-time transparency, require attention and measurement

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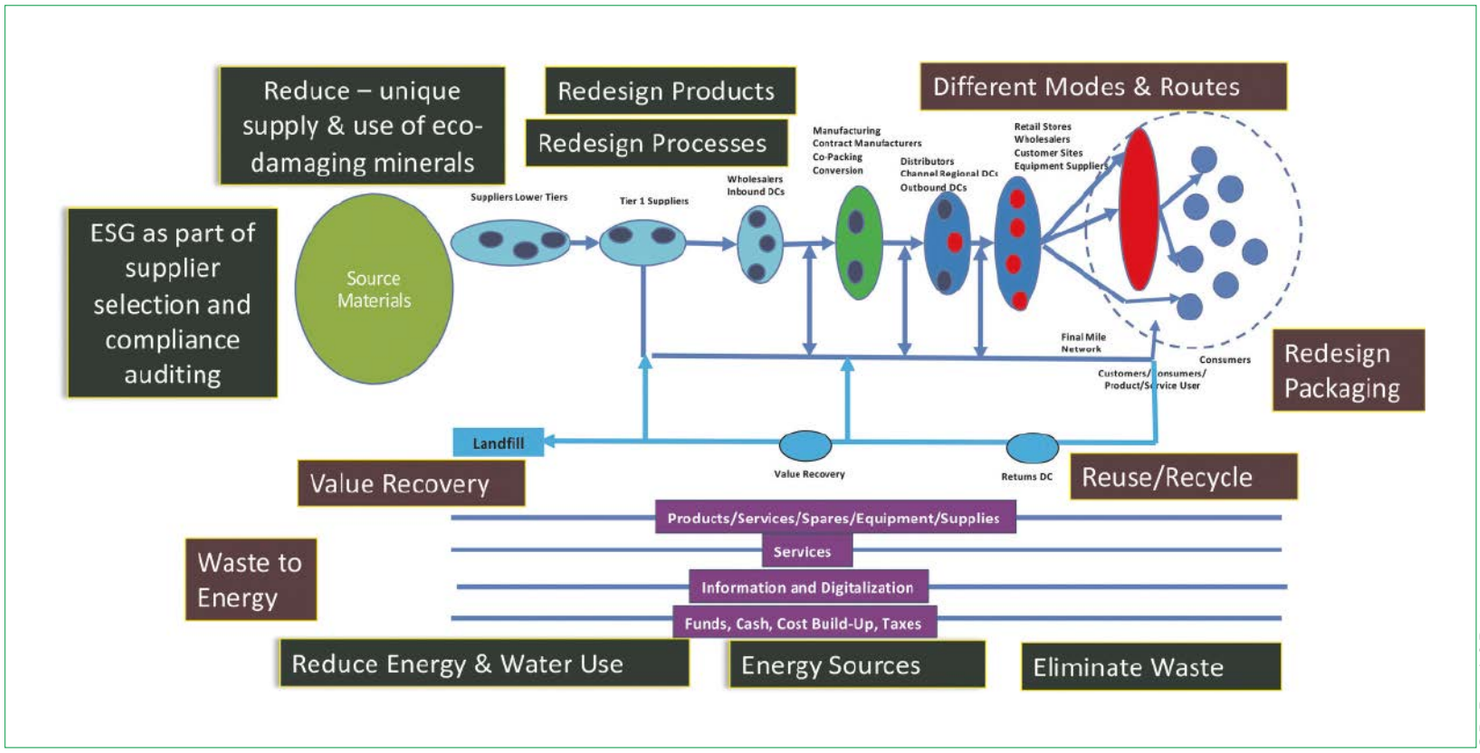

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How to make the end-to-end supply chain more sustainable.

of the integrated nature of the four flows of material/product; information/data; cash; and work/skills. They also require comprehensive global supply chain planning. Total supply chain cost, time, and product availability are all the results of end-to-end supply chain integration. Further, a company's value creation is now more understood to be driven largely by its end-to-end supply chain performance. Operations costs, profitable growth, and capital efficiency are major drivers of value.

Pharma supply chain leaders are also realizing that the often-believed uniqueness of sourcing APIs (active pharmaceutical ingredients) and excipients, formulations, and packaging are really not so different than other complex supply chains. The high-tech and electronics industries, for example, require global sourcing, hundreds of components including essential semiconductors, final assembly, and varieties of packaging that supply chain leaders have been challenged with for decades.

Pharma supply chain leaders are dealing with most global issues that all industries face. These concerns have reached executive agendas, stakeholder questions, and quarterly earnings reports. Geopolitical issues have created disruptions and risks in global supply chains that are unprecedented, and unanticipated constraints are higher than ever. Trade disputes have impacted duties and tariffs in cross-border shipments. Cyberattacks have caused disruptions in business continuity. National industrial policies have changed the business incentives and protections in many countries. There are several more examples of uncertainties that require new visions and innovative solutions.

Advanced Supply Chain Management

The development of new strategies, decision roadmaps, and operating playbooks that yield redesigned global supply chains are demanding that new thinking be applied to the appropriate goals and objectives of each company's supply chain, as well as its processes and structure. We refer to this as 'breakthrough thinking', as it is critical for executives and public policy makers to use in redesigning supply chains.

Breakthrough thinking involves two categories of thoughts, principles, and knowledge. The first is to recognize the myths of supply chains and adapt the lessons learned over the past four decades from the beginning of the creation of the supply chain term and the end-to-end concept:

- Myth 1: Supply chain is synonymous with logistics.
- Myth 2: Supply chains are only about cost and expense control.
- Myth 3: Advanced technologies, including digitalization and artificial intelligence (AI), will replace people as supply chains are automated.

In effect, lessons learned are driving breakthrough thinking from the past optimization of costs and working capital to today's intelligent 'supply-aware and customer-centric' performance.

The second category of thoughts, principles, and knowledge applies breakthrough thinking to deal with the new business and societal requirements and the uncertainties, volatility, and frequency of global market changes. The pharma industry is subjected to these realities especially as drugs come off patent, and customers, patients, and consumers have choices among brands and generics.

"A company's value creation is now more understood to be driven largely by its end-to-end supply chain performance."

In the pharmaceutical sector, customer satisfaction drives advanced supply chains, leading to network designs that prioritize customer needs. Sourcing and manufacturing strategies, influenced by global locations and international requirements, are evolving towards re-shoring, near-shoring, friend-shoring, and regionalization. As pharma becomes a 'strategic sector' in certain nations, increased monitoring and restrictive conditions are anticipated. The sector is also on a path of digitalization, leveraging AI, big data, blockchain, IoT, robotics, and other technologies for improved supply chain performance. Logistics service providers play a key role in this transformation, providing advanced data-driven supply chain capabilities. Amid increasing risks, resilience and comprehensive risk management are crucial, with future supply chain redesigns focusing on flexibility, end-to-end optionality, cybersecurity, and sustainability. Lastly, the focus is not just on making measures visible through dashboards and control towers, but on identifying the most important measures for management.

Pharma Moving Forward in the New Global Era

The trends and challenges driving the changes in advanced supply chain management provide guidance to pharma executives and planners, but specific issues in pharma supply chain transformations require care in their resolution. The lessons learned in the global pandemic about demand and supply, while event-driven, provided motivation to work on improving supply chain strategies and operations.

Demand planning has become more volatile and complex when we move to end-to-end supply chain management. Functional silos must convert to collaborative integrated business planners involving all trading partners and ecosystem stakeholders. Past orders are poor proxies for future demand, as the pandemic clearly proved.

Similarly, supply variability must be solved through tighter trading partner connections and collaboration. APIs, excipients, and packaging must all become assured supply, and safety stocks must be driven by supply, and not demand.

Corporate goals—sustainability, business continuity, ESG, and national supply chain laws/acts—will need to be enabled by supply chains. Thus, supply chain considerations must be built into these public policy goals. Our thoughts earlier in this article provide guidance for progress in meeting goals that are adopted as reasonable.

We see the continued involvement of national governments in the industry, especially to insure supply of essential drugs and protective equipment. Increased collaboration among governments and pharma companies, if executed properly, could benefit common interests. A fundamental common understanding of the complexities of supply chains and needed specialization will be critical.

Resilience is likely to be the most visible in pharma supply chains. The global trends toward near-shoring, re-shoring, and friend-shoring will affect the redesign of pharma supply chains from end-to-end. Sources of ingredients must be available closer to pharma production, no matter where that is located. And, production must be available closer to demand, wherever that is located.

In fact, the pharma companies have a range of viable options for network redesigns. We expect to see changes in diversification of suppliers, producers, and logistics flows that mitigate risks and improve service to the various customers, patients, and consumers. This will change international sourcing, with suppliers relocating closer to producers and the regionalization of product supply.

Last but certainly not least is the continued adoption of advanced technologies that further innovate supply chain management. Artificial Intelligence has amazing potential for not only improving demand planning, but also supply planning, such that synchronization of these mission-critical processes is finally a reality. Supply chain speed, and the speed of recovery, will yield substantial benefits to all stakeholders.

The adoption of new technologies, the redesign of supply and distribution networks, and other supply chain innovations, will require capital investment by the industry. New strategies and visions will guide the priority investments which need to bring returns in talent, processes, and supply chain performance.

To accelerate their digitalization journey, pharma companies should continue to apply means of iterative business and IT innovation (e.g. PDCA cycles, MVP development and SCRUM).

Exciting times are ahead for pharma supply chain leaders and managers. With no shortage of challenges, and the continuing availability of feasible solutions, smart decision-making will be the key to business and societal success.

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This article has been trimmed due to limited space. The complete version is available on CHEManager.com/en

Securing Supply Chains and Strengthening Partnerships

US Pharmaceutical Company Lilly Invests Heavily in European Expansion

In the dynamic landscape of the pharmaceutical industry, Lilly emerges as a catalyst for change. With a commitment to securing supply chains and fostering partnerships, Lilly International embarks on a European expansion that promises a bright future. This expansion encompasses a new location in Alzey, Germany, alongside strategic investments in Sesto, Italy; Fegersheim, France; and Limerick, Ireland. As the pharmaceutical giant navigates uncharted waters, it seeks to forge strong alliances and leverage innovative practices. By bridging visionary science with practical implementation, Lilly aims to revolutionize the pharmaceutical industry landscape. In an interview for CHEManager International, Christene Smith sits down with Edgardo Hernandez, President of Lilly Manufacturing, to delve into the intricacies of this bold endeavor.

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Edgardo Hernandez, President Manufacturing, Lilly

CHEManager: How do you plan to enhance manufacturing capabilities within Europe to strengthen supply chains and ensure timely delivery of medications?

Edgardo Hernandez: Our purpose is to improve the lives of people worldwide. We research and develop innovative medicines in indications such as diabetes, obesity, oncology and Alzheimer's disease. Our most important goal is to provide a safe and reliable supply of our medicines to the people who rely on them. Germany's role in this is growing and from 2027, our new facility will further expand Lilly's global parenteral—injectable—product and device manufacturing network, helping meet increased demand for Lilly's medicines, including our diabetes and obesity portfolio. The new plant at Alzey will produce medicines for the German market, for Europe and worldwide.

Can you elaborate on the strategic significance of the new German location for Lilly in Europe?

E. Hernandez: Every investment in manufacturing capacity around the world renews our commitment to patients today—and to those who may need our medicines tomorrow. Germany is strategically important for Lilly and the planned plant in Alzey brings us to a total of six major production sites in Europe, including sites in France, Italy and Ireland. This new facility in Alzey, alongside our site in Fegersheim, near Strasbourg in France, will create a cluster of manufacturing sites, providing operational synergies, strengthening links to academia and government, and diversifying our growing Lilly presence in the area.

Did you compare different countries for this investment? What led to the decision to build up a new greenfield site in Germany?

E. Hernandez: We look at multiple factors when considering where to locate new manufacturing sites; these are long-term decisions and major investments; and we've announced €10.2 billion—$11 billion—of investments in the last three years. First, the right infrastructure—roads, services, and the

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Preliminary design of Lilly's high-tech production facility in Alzey, Germany.

ability to build the facility itself. We look at the political and fiscal context; we value stability, a workable planning framework and support and incentives for innovation. And of course, we need access to a skilled workforce, which we know Germany can offer.

What specific improvements have been made to the facilities in Italy and France as part of the expansion efforts?

E. Hernandez: Lilly recently announced a capital investment of €150 million in Sesto, Italy, and an investment of nearly €160 million in Fegersheim, France to expand production of innovative medicines in Europe.

Could you share insights into the job creation initiatives resulting from this expansion, particularly in terms of local employment opportunities?

E. Hernandez: The site in Alzey will employ up to 1,000 highly skilled workers such as engineers, operators and scientists, who will leverage state-of-the-art technology, including automation and high-speed manufacturing lines, to produce life-changing medicines. In addition, an estimated 1,900 jobs will be created during construction, which is scheduled to begin in Q2/Q3 2024. We are already recruiting future Lilly employees.

What collaborative efforts are being fostered between Lilly and European research centers to drive innovation and advance medical breakthroughs?

E. Hernandez: In November, we announced an investment of up to €92.2 million—$100 million—to dramatically increase our footprint in Germany's early-stage biotech ecosystem. These investments will focus on biotech and the life sciences venture capital funds—expanding Lilly's incubator and accelerator engagements and strengthening Lilly's ties and activities with world-renowned academic and innovation partners.

Our search and evaluation teams are focused on discovering and building partnerships that will drive our future pipeline of medicines, augmenting our external innovation efforts through Lilly's different partnership models. Specifically, our enhanced external innovation in Germany will include capital and/or equity investments to support funds or companies; support to establish world-class lab space; and leveraging the best R&D capabilities and expertise (including internal Lilly resources) to help accelerate innovative medicines.

We are invested in advancing science, and we want our industry leading capabilities to drive additional impact for patients by supporting assets beyond our immediate pipeline and partnerships.

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Given the competitive landscape, how does Lilly differentiate itself in the European pharmaceutical market?

E. Hernandez: We are committed to working with stakeholders and governments across Europe to build a more prosperous environment for R&D and find sustainable solutions for challenges within the healthcare systems.

An average Lilly product, from procurement of raw materials through production, may use about 800 different ingredients, components, and materials which are procured globally across about 150 vendors. Because our supply chain is global, we can be flexible and adapt resources and supplies to ensure our medicine is available at the right time for each patient. Our global monitoring and risk mitigation systems allow us to determine the supply of medicines to meet our obligation to patients.

What role does sustainability play in your expansion strategy, especially concerning environmental impact and resource utilization?

E. Hernandez: Making medicines requires the use of valuable resources including energy, water, and raw materials. Sustainability is a key consideration in the design of our new manufacturing facilities. Our new Alzey site will use the very latest manufacturing technology to support advancements in science, productivity and sustainability which will help achieve our goal of continually reducing our environmental footprint.

How do you envision the long-term impact of these expansions on patient access to Lilly's medications across Europe?

E. Hernandez: This investment will increase our capacity to support increased demand for our existing medicines, including our diabetes and obesity treatments, and well as playing a critical role in bringing Lilly's future pipeline to patients around the world.

Expanding EU advanced manufacturing capabilities, while maintaining a diverse and secure global supply chain helps deliver flexibility in supply chains that protects against shortages. Geographic diversity is key, enabling us to access the resources we need and adjust avoid production disruptions and mitigate the impact of natural disasters or other public health emergencies.

Are there any specific challenges or regulatory considerations unique to each country—Italy, France, and Germany—that you've encountered during this expansion process?

E. Hernandez: The European Union's pharmaceutical legislation must ensure patients across the EU have timely and equitable access to safe, effective, and affordable medicines while also providing a collaborative environment for innovation, R&D, and production of medicines.

However, we have fundamental concerns about some components of the proposed changes to this legislation, in particular the reduction and modulation of intellectual property. This risks accelerating the decline in Europe's competitiveness to attract investments in innovation, while failing to deliver on the goal of accelerating patient access to medicines.

We are committed to working with the German government to build a more prosperous environment for R&D and find sustainable solutions for challenges within the German healthcare system. ■ www.lilly.com

The Future of mRNA Technology

Beyond Covid-19: The Versatility of mRNA in Health and Innovation

Vaccines against the coronavirus based on mRNA have become firmly established in medicine since the pandemic. Nevertheless, the technology is still at the beginning of its potential. Hundreds of clinical trials with corresponding active ingredients are now underway worldwide. Experts see a wide range of potential applications for this relatively new technology, particularly in infectious diseases and cancer.

Until the beginning of 2020, only experts were familiar with the term mRNA. But with the coronavirus pandemic and the feverish search for a vaccine, the term became part of the daily news within a few months. There was great hope that messenger RNA could be used to find a cure for the increasingly widespread pandemic. A hope that ultimately proved to be true: several biotech and pharmaceutical companies developed mRNA vaccines against Covid-19 in a comparatively short time and under high pressure of expectation.

Today, around four years later, the term mRNA has fallen somewhat out of the public eye, but scientists and developers are working hard to exploit the full potential of this technology. At the center of interest is the question: For which indications and against which diseases can mRNA-based therapies or vaccines be developed in the foreseeable future?

More than 700 Clinical Studies Worldwide

A look at the international database clinicaltrials.gov shows just how intensive research is in the world of mRNA. According to this digital library, which keeps records of clinical trials worldwide, the number of tests with mRNA agents has almost doubled in the past two years. In total, the document currently lists over 700 studies with mRNA agents worldwide. In addition, there are more than 1,200 completed studies.

Nobel Prize Winner Karikó Sees Wide Range of Applications

Katalin Karikó, Nobel Prize winner and one of the key pioneers of mRNA-based vaccines, also sees considerable potential in the technology. According to the researcher, in addition to coronavirus vaccines, it could potentially soon be used against a number of other diseases such as influenza, HIV or the herpes simplex virus (HSV). The biochemist, who works as an external consultant for the Mainz, Germany-based pharmaceutical company BioNTech, also sees good potential applications for the technology in cancer therapy.

John Cooke, Medical Director of the Center for RNA Therapy at Houston Methodist Hospital in the US, is also confident that in ten years' time there will be numerous mRNA drugs and vaccines on the market for diseases for which there are currently no effective therapies.

According to Carsten Watzl, Head of the Immunology Research Unit and Scientific Director of the Leibniz Institute for Occupational Research at TU Dortmund University, Germany and Secretary General of the German Society for Immunology, mRNA technology has two major advantages: Firstly, it ensures robust T-cell immunity to Covid-19 more than conventional inactivated vaccines. Secondly, mRNA can be used to specifically deliver various blueprints for the production of proteins into the cells. These proteins cause the creation of antibodies that help to fight the virus in the event of subsequent contact with it.

More Effective Cancer Therapy with mRNA

Scientists are making use of this property in mRNA cancer therapies, among other things. The aim is to teach the immune system to recognize and destroy its own tumour before it spreads by using an individually adapted mRNA.

Niels Halama, Head of the Translational Immunotherapy Department and Senior Physician and Head of the Adaptive Immunotherapy Research Group at the National Center for Tumor Diseases in Heidelberg, Germany, points out that precursors of cancer cells are created every day in every person, e.g., through mutations that occur during cell division. Normally, the immune system recognizes the altered cells as "foreign" and destroys them. However, some cancer cells manage to camouflage themselves or thwart the immune system's attack. The vaccination is intended to teach the immune system again that the tumor cells are "foreign" and must be fought.

Klaus Cichutek, who was President of the German Paul Ehrlich Institute (PEI) from 2009 to 2023, also points out in a podcast with Ärzte Zeitung that developments in cancer therapy are moving towards variable and individually tailored tumor vaccines. The corresponding RNAs would be mixed individually for patients and would

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enable a completely new approach to cancer therapy if clinical data confirms this. Cichutek: "This type of therapy is exactly what we need: as individual as the body is, we also need individually tailored active substances."

The now retired scientist even believes it is possible that mRNA could one day be produced in special printers, virtually at the patient's bedside.

However, the Heidelberg scientist Halamba points out that the development of active substances is still "in its infancy". Initial results would indicate that a vaccination against cancer could be effective. "We are therefore very confident," says Halamba. Ultimately, however, large clinical trials would have to show which patients would benefit from the vaccination — and which would not.

According to a report in the Deutsches Ärzteblatt, Nobel Prize winner Karikó sees another approach to fighting cancer in the intratumoral injection of mRNA. This principle has been successfully tested in animal models and studies with humans are currently underway.

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Vaccines Against Infectious Diseases

There is also a lot going on in the field of mRNA therapies against infectious diseases. Karikó points out that phase 3 studies are currently underway on the use of mRNA-based vaccines against respiratory syncytial virus (RSV) infections, for example. In addition, mRNA vaccines against influenza, HIV, HSV, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are being researched. Scientists are also working on a vaccine against the Nipah virus, which is particularly prevalent in Southeast Asia.

But viruses are not the only focus of mRNA vaccine research. Investigations into vaccines against tuberculosis and malaria have also begun. Furthermore, vaccines against borrelia are being evaluated in preclinical studies. According to Karikó, another interesting aspect is multivalent vaccines against tick bites.

The Companies' mRNA Projects

Long before the coronavirus pandemic, German company BioNTech was already researching a vaccine against cancer. The development pipeline currently has 21 cancer product candidates in clinical trials, eight of which are based on mRNA technology. BioNTech states: "Our cancer vaccine platforms Fixvac and Inest are set to revolutionize cancer treatment as we know it. They are designed to offer cancer patients a customized treatment approach that is specifically tailored to a particular tumor indication or even to their individual tumor."

In addition, the company's pipeline includes several mRNA projects in the field of infectious diseases, including influenza, tuberculosis, and malaria.

The pipeline of the US biotech company Moderna includes more than 40 mRNA projects that are in various clinical stages or close to market launch. These include vaccine candidates against influenza, Covid and RSV, as well as against HIV, norovirus and zika virus. Moderna is also working on cancer vaccines and therapeutics for various rare diseases. "We believe that our mRNA platform can tackle the world's biggest health challenges — from diseases that affect millions of people, to highly rare diseases that affect a few, to medicines that can be personalized to patients," Moderna quotes its CEO Stéphane Bancel on its website.

The product candidates of the Munich, Germany-based biotech company Ethris are at a comparatively early, preclinical stage. Development is focused on the treatment of respiratory viral infections and rare pulmonary diseases, as well as next-generation prophylactic vaccines that are mucosal, multivalent and mutation-agnostic.

The French pharmaceutical company Sanofi is also working on mRNA programs. These include product candidates for the treatment of RSV and influenza. The Tübingen, Germany-based biotech company CureVac, a self-proclaimed mRNA pioneer and one-time hopeful for a Covid-19 vaccine, is continuing to work on mRNA vaccines against influenza and Covid after its flop with the product candidate. The projects have not yet progressed beyond clinical phase 2, the former management has been almost completely replaced and the share price has plummeted. Although the company has been in existence for around 24 years, it has not managed to develop a drug to market maturity in this time.

In the fall of 2023, Darmstadt, Germany-based science and technology company Merck announced that it was the first provider to offer an integrated service for contract development, manufacturing and testing (CTDMO) of mRNA and related products. To this end, the company opened two new manufacturing facilities for mRNA active ingredients in Darmstadt and Hamburg.

Mode of Action of mRNA

Messenger RNAs (mRNA) are essential molecules in our cells that serve as the link between our DNA and all biological activities in our bodies. mRNA consists of four different building blocks, the nucleotides. An mRNA molecule is made up of many nucleotides that are strung together in a unique way. This is how the information for the production of the respective protein is transmitted in the cells. In therapy, mRNA can therefore be used as an information carrier.

The mRNA Knowledge of the Population

The acceptance of future mRNA vaccines and therapeutics depends not only on the quality of the products but also on the knowledge of the population. With this in mind, Moderna Germany conducted a survey by the market research institute Civey. According to the survey, 42% of respondents believe that mRNA technology will have a decisive influence on future medicine, and 8% even believe that it will revolutionize medicine. 68% see cancer treatment as a promising area of application for mRNA technology, followed by infectious diseases, autoimmune diseases, and rare diseases.

According to immunologist Watzl, who analyzes the results for Moderna, the continuous media coverage of mRNA technology during the coronavirus pandemic has borne fruit. Generation Z, born between 1995 and 2020, has the most mRNA technology know-how compared to older people. Overall, however, a lot of educational work is still needed to dispel misinformation.

Thorsten Schüller, CHEManager

More Than a Traditional CDMO

Sterling Pursues a New Standard of Collaboration for the Pharmaceutical Industry

Headquartered in Cramlington, UK, Sterling Pharma Solutions is a contract development and manufacturing organization (CDMO) that provides a range of services to the global biopharmaceutical industry, including active pharmaceutical ingredient (API) development, scale-up and cGMP manufacturing, as well as antibody drug conjugate (ADC) R&D and clinical-scale GMP manufacturing. The company has a strong pharmaceutical and engineering heritage dating back to the founding of its first facility in Cramlington, in 1969. Since then, Sterling has grown significantly, both organically and through a global strategy of acquisitions. Today, it has six facilities across Europe and the US and over 1,350 employees. CHEManager asked Kevin Cook, CEO at Sterling, to analyze current market trends and present his strategy to further develop and grow the company's business.

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Kevin Cook,
CEO, Sterling Pharma Solutions

CHEManager: Which areas of the pharmaceutical value chain can Sterling cover, and how is the company positioned in these segments in terms of portfolio range and core competences?

Kevin Cook: Sterling's main focus is in supporting the development of small molecule APIs, and we work with customers around the world, across the drug development continuum, from preclinical through to commercial supply. Predicting which molecules will be successful is impossible, so our strategy is to follow a molecule for as far as we can through development, adding value by applying expertise at each step, and assisting clients to navigate the technical and regulatory challenges towards commercialization.

Sterling also supports ADC developers, from the design and synthesis of chemical linkers and highly potent warheads, through to final GMP ADC conjugation at our sites in Deeside, UK, and Wisconsin and North Carolina, US.

In October last year, Sterling acquired UK-based contract research organization NewChem Technologies. What was the intention behind this takeover?

K. Cook: Having worked with NewChem over a number of years, we understood its expertise in high-level scientific and technical problem solving. Its close proximity to our manufacturing site in Cramlington provides additional non-GMP development capabilities, which are vital to increase the support and number of early-phase clients in our customer pipeline that need agile and flexible services to overcome initial development challenges.

Do you have other investment plans you can share with us, either in existing facilities and capabilities or in new ones?

K. Cook: Sterling has an ongoing process of organic growth, and we have investment plans in place to increase capacity to meet market needs. Key areas include chemical and analytical development, highly potent API manufac-

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turing, commercial flow chemistry capabilities, as well as additional GMP manufacturing for ADCs.

What do you perceive as the most pressing needs and requirements of your customers?

K. Cook: Increasingly, customers are looking beyond technical expertise and facilities as differentiators between partners as they are taken as a given, and the focus is more on how a partner's culture aligns with its needs. The highest level of customer service is crucial, as well as speed of response, delivery, and the intimacy between partners, as many clients wish to be deeply involved in the process beyond a pure transactional relationship.

Overall, what do you think are the predominant trends in API/drug development?

K. Cook: One of the most important changes that the industry has seen is in volume requirements: the end market for APIs is reduced, as drugs are being developed for more niche applications with lower patient populations. However, this drop in volume demand comes with increased molecular complexity, a greater number of processing steps and the likelihood of complex, and often hazardous, chemical transformations. This means there is a need for greater variation of manufacturing assets to handle the necessary reagents and reaction conditions, as well as a broad range of vessel capacity to efficiently process potential swings in volumetric needs.

In chemical development, Sterling's goal is not only to provide customers with the most efficient process for each stage of a molecule's development but also one that is future-proofed in terms of scale-up and sustainability. This is achieved by carefully selecting reagents and solvents and optimizing their use to be both efficient and have minimal environmental impact.

As small molecule complexity continues to rise, pharmaceutical and biotechnology organizations continue to seek innovative solutions to complex chemistry challenges. How can Sterling help its customers to tackle these challenges?

K. Cook: The decades of experience that Sterling has in manufacturing provides us with a deep level of knowledge and expertise that we can leverage to meet modern day challenges.

We also provide our customers with access to specialized expertise in new methodologies through our Technology and Innovation Program, which sees us work with academic institutions. Sterling has links with numerous international universities and has forged partnerships and sponsored post-graduate research in areas such as flow chemistry and enzyme-catalyzed reactions, to further understand how these can be applied to industrial processes.

Sterling does not define itself as a traditional CDMO, but as a PDMO, or partnership development and manufacturing organization. What does that mean?

K. Cook: As previously alluded to, working with customers now goes beyond a transactional relationship, and for projects to succeed many people across a number of teams within both the manufacturer and the customer come together to share ideas and act as a partnership. Sterling originated, and indeed, trademarked the acronym PDMO for Partnership Development and Manufacturing Organization to recognize this shift in approach, and to build the aspiration of success through close collaboration and the highest quality of customer service.

Driven by the three core characteristics of service, passion, and science, Sterling prioritizes true scientific partnership with all of its customers, is responsive to their needs, committed to their products, and is capable of adding a deep level of scientific value.

What kind of collaborations do you have in place?

K. Cook: Alongside the academic partnerships we have in technologies, Sterling has also joined a number of industrial collaborations such as the Supply Chain Initiative and Science-Based Target Initiative so that as a company, we can work with our peers to drive change and promote innovation for the benefit of all in the industry.

Sterling is part of a consortium of industrial innovators from across the chemical industry supply chain that aims to accelerate the adoption of continuous manufacturing across a range of industries, with a focus on digitalization. In your opinion, what are the key advantages and main areas of application of this technology, also known as flow chemistry?

K. Cook: The consortium to accelerate the use of continuous manufacturing that Sterling joined in 2023 is led by Imperial College London and BASF.

Flow chemistry allows greater control over chemical reactions, and by tuning conditions, the formation of impurities can be reduced, simultaneously increasing both efficiency and yield. Toxic and hazardous materials can be handled safely as the active volumes being reacted or created are much smaller. Additionally, the capital commitment to commercial-scale production is reduced with a flow reactor, as the physical space needed to run a process is significantly less than in batch.

Not every reaction process will be suitable for transfer to flow chemistry, however, if the conditions are optimized and appropriate, these three factors can combine to support an overall lower cost of goods.

The topic of sustainability is increasingly making its way into the pharmaceutical value chain. What role do the various sustainability aspects play for Sterling?

K. Cook: It is my firm belief as CEO that doing the right things leads to getting the right results, and this drives Sterling's commitment to protecting its people and our planet. Our entire team takes sustainability seriously, and we are continually working to reduce our environmental impact, with an initial goal to reduce emissions by 50% by 2025 as the first step towards becoming carbon neutral.

Our Cramlington facility leads the way in finding solutions and creating a roadmap for sustainability. It is almost self-sufficient in electricity, and also has an on-site anaerobic digestion plant that converts complex waste streams into energy to supply back into the national grid, reducing emissions by up to 65%. Trials of a new, ultra-low charge ammonia chilling technology at the site have demonstrated a quantifiable energy cost saving of more than 60%, and we are now looking to roll this out across our global network.

These forward-looking initiatives also demonstrate that sustainability improvements can have economic benefits. In recognition of our ESG policies, actions and results Sterling was awarded a gold medal by EcoVadis, placing it in the top 4% of all companies assessed globally, and in the top 1% of pharmaceutical companies.

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A Long and Winding Road

Sustainability in Production is Key—What Does Flow Chemistry Bring to the Table?

Numerous articles have been published within the last years in chemical science and business media (including this one) on the advantages of continuous reactions, aka flow chemistry. While the innovative technology has long since outgrown its infancy, it is still struggling to find widespread use outside of laboratories and technical centers. Now, with sustainability being named everywhere as the new guiding light for the industry, a paradigm shift from batch to flow reactions is likely to happen. Or isn't it?

Undoubtedly, flow chemistry, also known as microreaction or millireaction technology, does have several advantages for chemical and pharmaceutical production, and all of them have a sustainability component, be it safety, resource and energy efficiency, product quality, selectivity or flexibility.

Pros and Cons

The advantages of flow chemistry are fast and good mixing and excellent heat transfer, enabling higher selectivity and yields while lowering raw material requirements. Besides, the number of by-products and the energy demand for their separation (downstream processing) is reduced—about 70% of energy costs correspond to the separation of by-products. Regarding safety, fast, explosive, and highly exothermic reactions involving toxic substances can be run in much smaller reactor volumes than batch reactors.

Thus, the contribution of flow chemistry for designing chemical processes with a lower environmental footprint compared to batch production stimulates justified hope for society's need of a greener, more sustainable and safer chemical industry. Various aspects of flow chemistry also support the design of novel strategies for the transformation from an exclusively fossil-based to a biobased industry, or at least to a more sustainable chemical industry, with applications ranging from commodity to specialty chemicals to fine chemicals, including agrochemical and pharmaceutical intermediates and active ingredients.

However, on the flip side, there are challenges and limitations that hamper a broader application of flow reactors in industry that may explain why flow chemistry is still not as common in chemical and pharmaceutical production as it should be, given its benefits.

During a recent roundtable discussion on the topic of sustainability in chemical and pharmaceutical production organized by CHEManager, participants from several manufacturers as well as service and technology providers shared their views on flow chemistry. One key finding from this discussion may not come as a surprise: Safety, and not sustainability considerations are still the most important, if not—as for many manufacturers—the only criteria when deciding to run a reaction in a flow reactor.

Microreaction technology can improve the safety profile of a reaction, as hazardous and reactive reagents can be handled more safely and highly exothermic chemistry can be better controlled in a microreactor (or millireactor, depending on the tube diameter) due to smaller volumes and to higher heat and mass transfer.

Peter Markus, Senior Director Marketing & Sales / Key Account Management at Midas Pharma and a chemist with 30-years industry experience, explains: "The motivation was always safety. Flow processes have been used for hazard-driven chemistry, because the reaction mixture could be reduced to small volumes at the moment of flow, hence less risk of damage in case of an event."

Annegret Vester, Chief Sustainability Officer of German chemical company CHT, and a chemist whose vision is a sustainable future for the chemical industry, regards safety as one significant aspect of sustainability. "We have established microreaction technology in Germany for many years for the production of H-siloxanes, i.e. organosiloxanes with Si-bonded hydrogen atoms, and it works excellently. For siloxanes, the introduction of microreaction technology had a clear focus on occupational safety. We thought that we could do a lot more with flow chemistry, but we had to recognize that our large and diverse portfolio of products and technologies is more suitable for batch processes because for flow processes you need a certain throughput. If you have a large-volume product, flow chemistry is unbeatable, it's actually more sustainable than batch production. With 5,000 products in our portfolio, you can imagine that they do not all run on a large scale, but there are a lot of product changes every day."

Sustainability in general is not necessarily seen as top priority for choosing a chemical manufacturing process, but any improvement of occupational safety or process efficiency automatically enhances the sustainability performance of a process.

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Indeed, most large-volume processes use continuous reactions due to the efficiency benefits. At a smaller scale—maybe even at a scale of about 10,000 t/a—batch reactors dominate as establishing a continuous process is expensive and requires a substantial upfront investment that can only be justified when the production scale is large.

Vester's statement is congruent with others. For instance, Daniel Wagner, Head of CMC Synthetics Early Development Germany at Sanofi, said: "When it comes to flow chemistry, sustainability is not the only important aspect for us, key is also the advantage to accelerate the scale-up from smaller to larger batch sizes."

And Ulrich Mayerhoeffer, Head Technical Evaluation and Development at Swiss Contract Development and Manufacturing Organization (CDMO) Arxada, told CHEManager in a previous survey: "We are strong believers in the benefits of flow chemistry." But he admits that technology selection is mainly driven by process safety, quality, sustainability, and overall economic considerations, with safety as the strongest driver towards a flow process. The CDMO space in pharmaceuticals and fine chemicals is still dominated by batch and semi-batch processes performed in multipurpose plants.

But why are benefits like product quality, control of side product formation or preservation of stereo-information not enough reason to switch from batch to flow? Especially in the pharma or agrochemical sector, where many products require multistep syntheses, that could be performed in sequence or in parallel by connecting different flow reactors?

Hurdles to Overcome

The reasons for the hesitancy of many manufacturers to adopt microreaction technology can be manifold, including, as mentioned above, the high initial investment for the flow equipment and infrastructure, but also the lack of standardization and compatibility among different flow systems and components, or the lack of expertise and training among chemists and engineers. This applies in particular to new processes for which there is no comparison with batch processes, and, in addition, it usually takes several years for new technologies to find their way into standard educational literature.

Another aspect that is particularly significant in the pharmaceutical sector is the high level of regulation. The development and approval of a synthesis process for pharmaceutical chemicals by the regulatory authorities is a lengthy and costly process. Many companies are therefore reluctant to replace an established and audited process with a new one.

According to Kai Rossen, Chief Scientific Officer at EuroAPI, the former CDMO business of Sanofi, the regulatory context with its strong impact on the quality of the products as well as the responsible control of waste streams is important. Rossen said: "The last 20 years have shown a re-discovery of flow chemistry. The application of flow chemistry enables reactions that could not be performed in a simple batch process and are thus a critical tool in finding the optimum for the synthesis of a compound, such as an API."

In addition, batch processes in dedicated or in multipurpose reactors have been optimized in many areas to such an extent that they no longer have any significant disadvantages in terms of efficiency and sustainability compared to flow processes. Ulrich Scholz, Head of Chemical Development at Boehringer Ingelheim Pharma, described one such experience: "We tried to show that flow chemistry is superior. We had several examples, but in the end realized that although the flow process works well, the batch process is not much worse or even got better with a catalytic upgrade."

But the adoption of continuous flow technologies for pharmaceutical applications is now strongly advocated by regulatory authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). This may lead to faster regulatory approval which could lead to quicker adoption of flow processes for the manufacture of pharmaceutical chemicals.

One reason for the hesitancy to implement flow technology may simply be the resistance to change. Thomas Riermeier, Senior Vice President & General Manager, Health Care at Evonik, said: "We invested in flow chemistry years ago and built a modular pilot plant. As a CDMO company, Evonik had evaluated the technology for customer projects, and we've seen an increasing customer interest in more sustainable solutions. But as of now, a real breakthrough is yet to occur." According to Riermeier, the decisive factor was that customers preferred the established process at that time.

For Riermeier, it is not a black and white decision, but the crucial success factor is: "How can we expand our chemistry toolbox making processes as efficient as possible? I believe, we have to face it with an open-minded setup towards technologies—if continuous flow, or classic batch—and by doing so favor those with the most positive sustainable impact."

A risk-averse mindset may predominate particularly among seasoned chemists who have not been educated or trained in this technology. Although flow chemistry is not a novel technique and many of the top commodity chemicals by volume are produced in continuous plants, fine chemicals and pharmaceuticals production are still almost exclusively dominated by batch manufacturing.

So, as the lack of know-how in the field and the late adoption of the technology are perceived as major hurdles, general education and proper training in flow chemistry in the early chemistry curricula would contribute to a more widespread technology transfer and faster adoption. An indicator of the technology's maturity status is recent job offers from the pharmaceutical industry, where skills in flow chemistry are often required. However, these challenges and limitations are being addressed by ongoing research and development

Silver Linings

Flow chemistry can be considered a green technology because flow reactions can be performed in a sustainable way, with advantages for safety, efficiency, waste reduction, the avoidance of hazardous chemicals, continuous product formation, and easy recovery and reuse of the catalyst. It, therefore, could be a powerful ally in achieving the 12 Principles of Green Chemistry.

Significant efforts have been made globally to develop the manufacturing flexibility and robustness of processes used to produce chemicals in a continuous way. Andreas Foerster, managing director of Dechema—the German Society for Chemical Engineering and Biotechnology—explains: "Since the early research in microreaction engineering the field has evolved and diversified. Millimeter instead of micrometer structures are more often used in continuous production equipment today. Such channels sufficiently provide the advantages of microreactors while being more robust for example in the handling of solids, which remains challenging in microstructures." Förster adds: "In this sense, microreactors are used in production processes in the form of modular continuous production units or flow chemistry set-ups containing such structured devices."

Yet, despite these developments, a major challenge for the fine chemical and pharmaceutical industry is the established application of flow technology to commercially relevant examples. The identification of opportunities to apply micro or millireactors to current processes is critical to the success of this technology for pharmaceutical and fine chemical companies.

There are, however, examples that may indicate that flow chemistry is really a technology on the upswing and may proceed faster than expected. For instance, in the spring of 2023, Italian CDMO Flamma Group announced to invest $200 million over the next three years to expand its capabilities and add innovative technologies which will include expanding its existing flow chemistry capabilities in Italy. And in summer of 2023, Axplora, a pharmaceutical CDMO established previously by the merger of German CDMO PharmaZell and French CDMO Novasep, said that it has completed the installation of a new cGMP flow chemistry pilot unit at its German site in Leverkusen, costing more than €1 million. Ester Masllorens, Chief Technology Officer of Axplora, explains: "Continuous processing is a key enabling technology for the future of pharmaceutical manufacturing, strongly supported by regulatory bodies such as the FDA. This technology has high potential to enhance sustainability, improve control and quality as well as reduce costs and time to market."

Conclusion

The decision for or against it falls within a narrow range of criteria and parameters that have to be fulfilled in order to make technical and economic sense for manufacturers of chemicals and pharmaceuticals. Flow chemistry is not a one-size-fits-all technology, but it is an innovative, yet matured technology that offers numerous advantages and benefits to transform chemical production in a sustainable way. Hence, flow chemistry in pharmaceuticals and fine chemicals manufacturing is gaining momentum, however, it will not prevail rapidly but rather in a step-by-step kind of marathon walk with twists and turns along its way. As a new generation of chemists and managers is eager to embrace green and sustainable chemistry—especially in new processes—the long-term prospects are clear: Flow chemistry is here to stay.

Michael Reubold, CHEManager

Advertorial

Sustainability and Energy Efficiency at a Turning Point

Flow Chemistry: A Groundbreaking Approach for Chemical Production

Flow chemistry was named as one of the ten technologies that have the potential to make our planet more sustainable in 2019 by the IUPAC. But what does more sustainable actually mean? And how can flow chemistry contribute to this?

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Anne Lakmanaarachchi, Ehrfeld Mikrotechnik

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Rafael Kuwertz, Ehrfeld Process Technology

Flow chemistry, and particularly microreaction technology, is a technology platform that consists of carrying out chemical reactions in a continuous flow rather than in traditional batch reactors. It offers major advantages over conventional methods in various aspects, such as optimum heat and mass transfer, safety, scalability, selectivity and productivity. In addition, flow chemistry can also contribute to sustainability and energy efficiency goals by reducing the environmental impact and carbon footprint of chemical production.

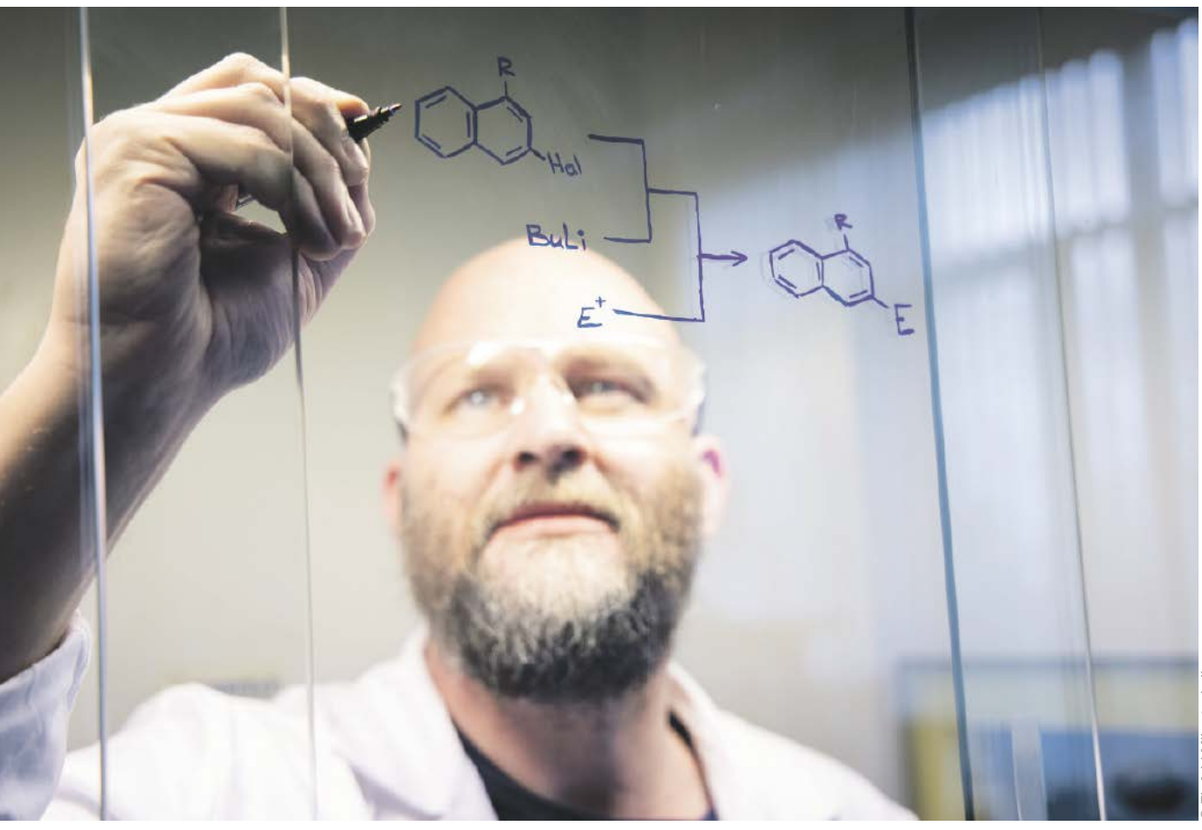
The need to reduce global CO_2 emissions has become increasingly important in recent years as climate change has become one of the greatest challenges of our time. The chemical industry plays a crucial role in the transition to more sustainable practices. Reducing the carbon footprint requires innovative approaches to minimize energy consumption and implementation of alternative, more sustainable production methods.

One of the basic strategies for reducing CO_2 emissions is to increase energy efficiency in chemical production plants. This includes the optimization of processes, the use of energy-efficient technologies and implementation of heat recovery systems to minimize overall energy consumption. Compared to conventional batch processes, flow chemistry enables more accurate control of reaction conditions. Continuous mixing and temperature management minimize unwanted side reactions, resulting in increased energy efficiency and thus in reduction of CO_2 emissions.

In chemical industries, energy costs for downstream processing amount to approx. 40–80% of the total costs. Up to 56% of the material used in active pharmaceutical ingredient production are solvents which are responsible for approximately 50% of greenhouse gas emissions in active pharmaceutical ingredient production. Precise control of process conditions minimizes the formation of side products, therefore reducing the required downstream effort. In addition, solvent waste is avoided. These aspects not only support ecological goals, but also offer economic advantages through more efficient use of resources.

Flow chemistry enables fast reaction times as mixing and heat transfer are greatly enhanced. This leads to increased productivity and enables the production of chemicals in less time, which in turn reduces energy consumption and lowers the CO_2 footprint.

A visible example in the US is Sanofi's continuous manufacturing plant in Framingham, Massachusetts, which is producing 80% less carbon dioxide emissions compared to the company's first-generation facility and reduces water and chemical usage by 91% and 94%, respectively, according to details released by the company.



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„Compared to conventional batch processes, flow chemistry enables more accurate control of reaction conditions."

Another, increasingly important benefit is that flow chemistry can improve supply chain integration and optimization by enabling modular, flexible and distributed production. It reduces the need for large-scale facilities, storage sites and transportation networks, which lowers capital and operating costs as well as environmental impact. It also facilitates the adaptation of production to


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demand and resource availability by using smart sensors, data analytics and digital platforms. Shorter reaction times compared to traditional batch processes help to reduce overall production time, which in turn shortens delivery times. Accelerating production cycles increases flexibility in the supply chain and allows companies to respond more quickly to market changes. If a production process needs to be adjusted due to increasing demand or changing market conditions, the technology enables a faster and more flexible changeover. This in turn helps to minimize bottlenecks in the supply chain and ensure a more efficient use of resources.

"Flow chemistry enables fast reaction times as mixing and heat transfer are greatly enhanced."

Here too, the precise control of reaction conditions in flow chemistry systems ensures more efficient use of raw materials. Lower material usage and fewer waste products often also mean lower costs in the supply chain. Continuous production reduces the need for high stock levels. Storage costs are minimized while ensuring that products are fresh and available on demand. Companies integrating this technology can better adapt to dynamic market requirements and at the same time fulfill their ecological responsibility. This promotes customized solutions and supports the supply chain in responding flexibly to the diverse needs of customers. The evolution of supply chains in the chemical industry is in full swing, and flow chemistry is playing a key role in this transformation process.

Summarizing all the advantages of flow chemistry or microreaction technology at a glance:

- Efficient use of resources
- Lower energy consumption
- Reduction of waste quantities
- Time and space savings
- Increased safety by avoiding hazardous reaction conditions
- More flexibility and simplified scalability

Ehrfeld Mikrotechnik has the perfect, industrially applied example in China with a production throuput of 30 kt/y. As just summarized, this example perfectly illustrates all the advantages of flow chemistry and microreaction technology.

Due to the use of our flow reactor technology, the yield was increased by 41% from 70% to 99%, leading to nearly no waste quantities in comparison to the former batch process. Additionally, no further energy intensive downstream process is needed. The obtained product solution is directly used in the following process step without any purification step. This efficient use of resources is essential for sustainable development, ensuring to meet present needs. Furthermore, the use of the continuous process eliminates the need for heating and cooling phases of the batches. A cooling machine provides the necessary cooling capacity and therefore no further steam (former amount of 8000 t/y) as heating/cooling media is needed. Electricity as utility media is used exclusively. The overall power consumption was reduced by a factor of nearly 80 to 3.6 kWh/t. The safety risk of the used highly hazardous chemicals is reduced by a factor of 1,000 in terms of reactor volume of only 150 L and a factor of 130 in terms of footprint (only 75 m² production area is necessary) providing a production capacity of 30 kt/y.

"The evolution of supply chains in the chemical industry is in full swing, and flow chemistry is playing a key role in this transformation process."

Looking ahead: Continuous research and innovation in flow chemistry play a key role in advancing sustainable practices. New materials, advanced control technologies and improved reactor designs can increase efficiency while minimizing environmental impact. This is exactly where Ehrfeld Mikrotechnik comes in. It is not only the continuous further development of our high-performance reactors, but above all the overall package of comprehensive service and equipment that makes the big difference. We support our customers worldwide with a holistic solution concept from the laboratory to the production of several cubic meters per hour in continuous flow.


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References to this article can be requested from the authors.

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Integrated Continuous Manufacturing in Pharmaceuticals

A Completely Modernized Model for Cost-Competitive End-to-End Drug Production

As Covid emerged, scourged, and finally receded into a manageable disease, we were all alerted to the fragility of our pharmaceutical supply chain. It was sobering to learn, for the first time for many, that we did not have access to all of the drugs we consume, even those that are lifesaving.

Unfortunately, this problem predates the Covid era, and is the consequence of an outdated production system and a disproportionate reliance on foreign manufacturers, particularly countries where quality standards are often lacking. In the United States, it is not uncommon for over a hundred drugs to be on shortage at any given time. The majority of these cases are a result of manufacturing issues, such as quality infractions.

The current standard of pharmaceutical manufacturing, batch, is an antiquated system characterized by many stops-and-starts. For example, after a reaction step, the intermediate product is isolated, tested, and then transported to the next step, or unit operation, if it meets the required specifications. This requires human intervention, exposing the process material to potential quality infractions. Additionally, much time is spent on these "offline" activities, increasing lead times and inventories needed to provide adequate service levels. Typically, this mode of production is performed in campaigns, where large quantities are produced during discrete time periods, requiring sizeable equipment. Thus, the major manufacturing parameters, which include time, personnel, and equipment size, are all amplified.

To evolve this paradigm, Novartis and MIT collaborated through the Novartis-MIT Center for Continuous Manufacturing. A highlight of this project was a pilot plant that could produce tablets from raw material with a lead time of two days, a process that would require two hundred days in batch. The innovative manufacturing platform that enabled this revolutionary improvement is called integrated continuous manufacturing (ICM), and was spun out of MIT by Continuus Pharmaceuticals.

ICM represents a completely modernized model for drug manufacturing. Process material flows seamlessly from one unit operation to the next, without the need for isolation and offline testing. Rather, advanced analytical systems, such as process analytical technologies (PATs), are used to carefully monitor the process on a second-by-second basis. Variations from targeted parameters (e.g., optimal reaction temperature) are recognized immediately, and corrective actions taken through automated control loops directed by a sophisticated control system. These capabilities require a deep process understanding and identification of the critical process parameters (CPPs) that impact the drug's critical quality attributes (CQAs). In addition, new process technologies, such as Continuus' proprietary continuous filtration and drying systems, enable continuous processing and improve performance.

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Bayan Takizawa, Continuus Pharmaceuticals

Consequently, ICM can provide many advantages. Personnel requirements will be greatly diminished because the entire system runs fully automated, without the typical labor-intensive stops-and-starts. Corrective steps that are often used in batch can be eliminated through a system-wide approach, rather than local optimization. This is possible because all manufacturing is integrated in a single line, and not spread across multiple disconnected unit operations located in different facilities. Additionally, a robust plant-wide quality-by-design (QbD) strategy is possible, whereby CPPs throughout the process can be closely monitored and controlled, ensuring the final products meet their specifications. The

"Integrated continuous manufacturing (ICM) represents a completely modernized model for drug manufacturing."

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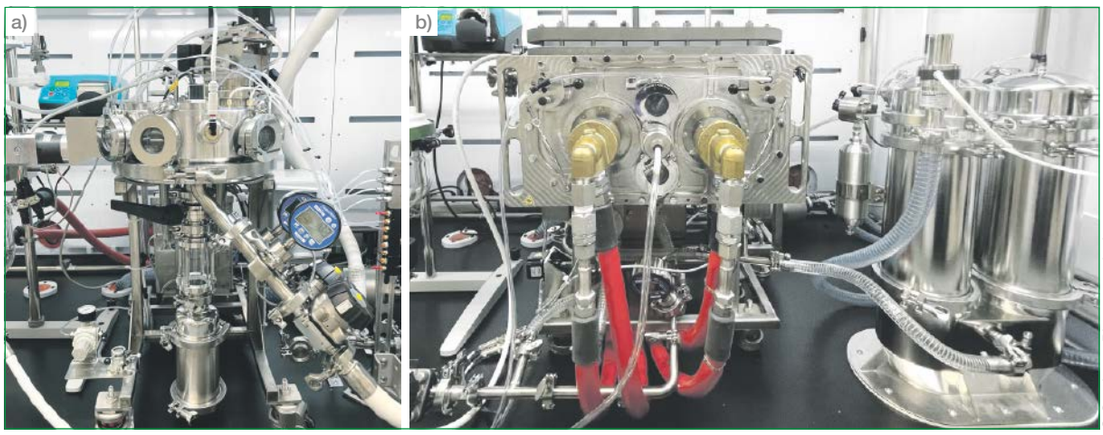

Fig. 1. Proprietary Continuus unit operations: a) continuous rotary filter, and b) continuous drum dryer (both with CIP capability and able to process high-potency compounds).

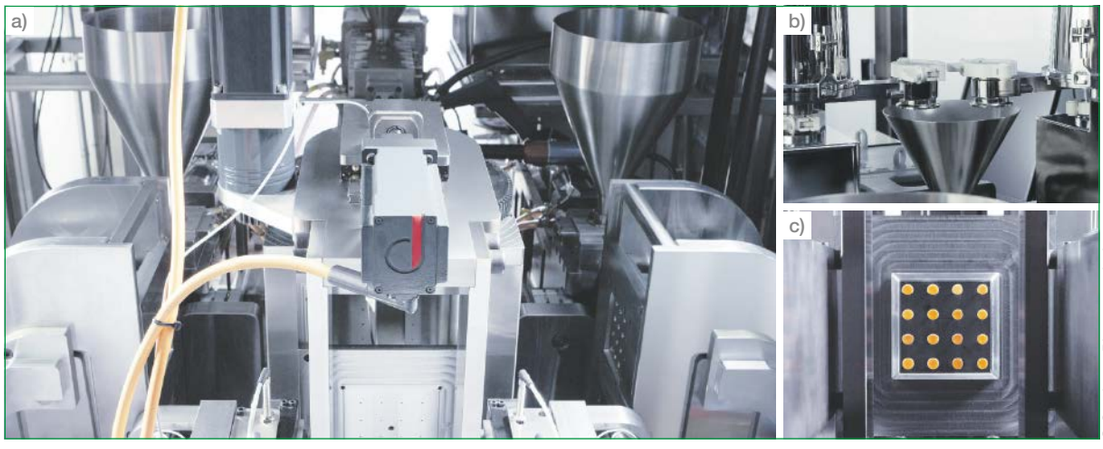

Fig. 2. Proprietary Continuus extrusion molding unit operation: a) main view, b) gravimetric feeders, and c) tablets in the mold.

adoption of QbD has been supported by regulatory agencies. Utilities consumption will be reduced. For example, instead of heating and cooling a vessel, both of which require energy, reactors are maintained at their targeted values. Facilities will be much smaller, as much smaller equipment are needed to process material at any given time. This is because manufacturing is performed on a continuous (i.e., 24 hr/d) basis. These advantages and others, such as the greatly reduced lead time, also contribute to significant cost savings.

ICM's unique operational advantages will allow for cost-competitive end-to-end manufacturing facilities to be built in countries such as the United States. This option will enable a more robust and responsive supply chain for critical drugs. In particular, the manufacturing of low-value active pharmaceutical ingredients (APIs), largely allocated to low-cost countries in the current system, will be able to be reshored, increasing their availability. Consequently, patients will have better access to the drugs they need, and when they need them. The eco-friendly nature of these ICM facilities, compared to that of a batch facility, will also be a critical factor.

There may still exist a dependence on the API starting materials, as many are made in the same countries that manufacture the bulk of our APIs today. However, shifting the dependence upstream will enable drug manufacturers to better control the production and quality of their APIs. While it is important to ascertain the quality of these ingredients that are used to produce APIs, it is more important to ensure the quality of API production, as there is limited ability to modify/refine the API once it has been produced and sent for final formulation. Furthermore, impurities introduced in the starting materials can be removed during production of the API.

"The outlook for continuous manufacturing in the pharmaceutical industry is greater than ever."

Beyond the operational and environmental benefits, there are other important considerations. For example, early utilization of ICM during drug development could allow access to process space not appropriate for batch processes. For instance, specific parameters, such as surface area-to-volume ratios, could be dramatically improved, enabling certain chemistries. Thus, drug development can be improved. Regulatory review times can be decreased through early engagement with specific teams (e.g., FDA Emerging Technology Team) and existing incentives to adopt advanced manufacturing technologies, potentially saving companies millions of dollars through faster approvals. Decreased lead times for clinical trial material as well as reduced tech-transfer times between clinical and commercial manufacturing could further accelerate this process.

To advance the state of drug manufacturing, Continuus has engaged with multiple pharmaceutical companies, as well as government agencies (e.g., US FDA, NSF, DoD, HHS) to demonstrate how continuous processes can provide advantages compared to batch. Work has ranged from targeted solutions (e.g., application of a single continuous unit operation) to end-to-end solutions (e.g., application of a continuous process that integrates drug substance and drug product manufacturing). Through these projects, the company has been able to unequivocally show the value of ICM. For example, with one of these commercial products the projected lead time for production was reduced from ~1.5 years to less than three days with ICM. Through all this work, there were important lessons learned to guide future efforts:

- ICM should be considered for pipeline strategies, as ICM lines are flexible to be multi-product and the economics are more favorable when CapEx is spread over multiple products.
- Improved environmental/social/governance scores with ICM will become a more compelling factor for adoption.
- Government funding is essential for efforts to produce shortage drugs, as most are low-value and do not justify private investment. Similarly, government offtake contracts will be critical.
- There are key regulatory incentives that need to be considered, such as the Advanced Medical Technology designation, which apply to continuous technologies.

The outlook for continuous manufacturing in the pharmaceutical industry is greater than ever. Enabling technologies, such as innovative PATs and new continuous unit operations, as well as timely regulatory guidelines have reduced barriers to implementation and mitigated the risks of abandoning entrenched systems. Additionally, recent drug access challenges, such as the shortages associated with the Covid-19 pandemic, have highlighted the need for robust manufacturing and a dependable supply chain. ICM will continue to play a central part of the ongoing solution.

References can be requested from the author.

Acknowledgement: I would like to thank Stephen Born for his critical input into this paper.

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Navigating the Logistics Impact

Unique Requirements of Cell & Gene Therapies

Cell and gene therapies (CGTs) present a revolutionary approach to the pharmaceutical industry. CGT is addressing various diseases with personalized and targeted treatments tailored for individuals with various rare diseases that were previously incurable. However, with such innovation, several complexities do arise on a logistical spectrum that diverge from those of traditional pharmaceuticals.

CGTs, particularly autologous therapies, require specific handling procedures throughout the transportation journey. This involves the transportation of the apheresis sample from the clinic to the manufacturing site and, ultimately, from the manufacturing site back to the clinic as the final product. In some therapies, multiple shipments are conducted for the apheresis sample, which further complicates the logistics requirements and intensifies the overall operations. It is crucial to note that such therapies, whether the apheresis or drug product, are time-sensitive and have unique handling and packaging requirements. Complexities further intensify when clinics and manufacturing sites are across regions with limited connectivity and still have to abide by the zero margin for error.

Pharmaceutical companies encounter diverse challenges in managing their CGTs, with variations arising from factors such as their existing capabilities (both internally and through partnerships), handling and packaging specifications, proximity and connectivity between manufacturing sites and clinics, among other considerations.

However, some of the most prominent challenges are outlined below, each requiring strategic considerations for effective resolution.

- 1. X-ray exemption requirements: Securing X-ray exemptions or optimizing procedures for CGTs is crucial to minimizing disruptions in the supply chain. Delays in inspections or non-compliance with regulations can adversely affect product quality and, ultimately, patient outcomes. Implementing streamlined procedures and maintaining a robust regulatory compliance framework is essential to navigate this challenge successfully.
- 2. Limited logistics service providers with required expertise: The current landscape witnesses a scarcity of logistics providers well-versed in the significance, procedures, regulations, and ecosystem of CGTs. Adapting operations to include the management of the cold chain, real-time tracking, and specialized packaging becomes imperative for logistics providers aiming to support the unique requirements of these therapies. Pharmaceutical companies must proactively seek partnerships with logistics specialists to enhance their supply chain capabilities.
- 3. Limited visibility, especially with local agents: Disparities in reporting systems, language barriers, regulatory variations, and a lack of standardized processes contribute to limited visibility in the logistics chain. This information gap poses operational risks, making real-time monitoring difficult and potentially resulting in delays and challenges in addressing unforeseen issues promptly. Establishing standardized processes, leveraging technology for data integration, and fostering communication can mitigate these challenges.
- 4. Scalability via exploring various transportation modes: The prevalent use of the on-board courier method for transporting apheresis samples may present scalability challenges due to the intricate nature of the process and associated documentation requirements. Exploring and adopting alternative transportation modes that align with the evolving needs of CGTs is crucial for long-term scalability and efficiency.
- 5. Setting contingencies on a single shipping route: Relying on a singular shipping route for transporting CGT components introduces potential challenges in terms of flexibility, adaptability, and responsiveness to unforeseen disruptions. Proactively establishing contingencies for shipping routes and diversifying transportation methods can enhance resilience in the face of evolving logistical landscapes.

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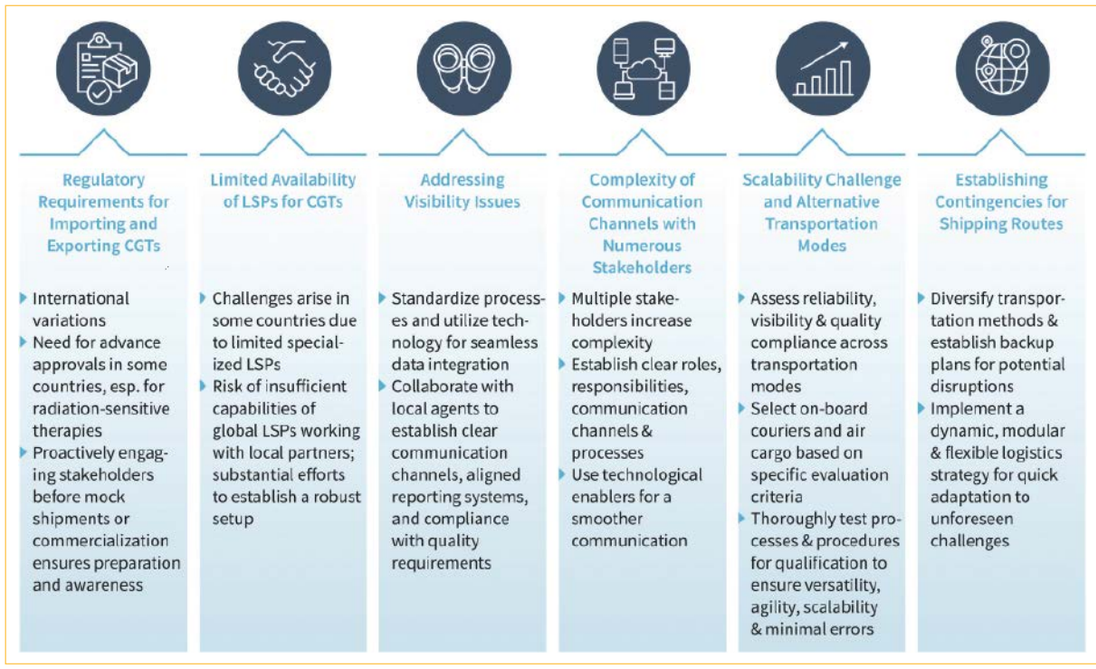
Tackling the Challenges

To overcome these hurdles, strategic adjustments in logistics operations are paramount. This involves a multifaceted approach encompassing regu-

latory compliance, technological integration, partnerships with logistics providers, and consideration of varied transportation methods. Stakeholder awareness along the value chain is essential for fostering a collective understanding of the intricacies of processes, documentation, and logistics requirements, ultimately ensuring the successful delivery of the final product to the patient.



Challenges in CGT logistics. (source: Camelot Management Consultants)

Engaging with stakeholders

The regulatory requirements for importing and exporting cell and gene therapies vary significantly from one country to another. Some countries demand specific approvals in advance, involving coordination among numerous internal and external stakeholders, particularly for therapies sensitive to radiation that require X-ray exemptions. Consequently, pharmaceutical companies must engage proactively with relevant stakeholders before conducting mock shipments or commercializing therapies. These proactive engagements ensure thorough preparation for all shipment requirements and enhance stakeholder awareness of their responsibilities, thereby ensuring successful and timely shipments.

Collaborating with multiple LSP

The limited availability of logistics services providers (LSPs) specializing in CGTs can pose challenges in certain countries due to the restricted footprint of specialized LSPs. Despite LSPs with global pharmaceutical contracts typically establishing local partnerships as an initial solution, the capabilities often fall short of requirements, demanding significant efforts such as training and due diligence to ensure a robust setup.

"CGTs, particularly autologous therapies, require specific handling procedures throughout the transportation journey."

In such cases, it is advisable to engage multiple partners to mitigate the risk of courier underperformance or failure to meet set requirements. To enhance the likelihood of success, it is essential to ensure cross-functional collaboration and involve all key stakeholders, checking their current operational capabilities in relation to the specific requirements, such as handling, to further streamline the logistics process for CGTs. This collaborative and comprehensive approach is crucial for meeting the unique and demanding needs of CGTs.

Establishing data analytics and communication processes

Addressing limited visibility issues, especially with local agents, involves implementing standardized processes and leveraging technology for data integration. Pharmaceutical companies can collaborate with local agents to establish clear communication channels, align reporting systems, and ensure compliance with quality requirements. Investing in technologies such as real-time tracking and data analytics enhances visibility throughout the supply chain, enabling proactive decision-making and reducing the risk of operational disruptions.

The involvement of numerous stakeholders, particularly when additional local players such as local agents and distributors are present, elevates the complexity of communication channels and introduces a higher risk of operational issues. To mitigate these challenges, it is crucial to establish clear roles and responsibilities across all stakeholders and ensure the implementation of appropriate communication channels, processes, and procedures. Additionally, leveraging technological enablers is essential to enhance visibility throughout the supply chain, promoting smoother communication and reducing the potential for operational disruptions.

Diversifying transportation modes

Addressing the scalability challenge associated with different transportation modes necessitates pharmaceutical companies to evaluate factors such as reliability, visibility, and quality compliance. Currently, on-board couriers and air cargo stand as the two primary transportation modes adopted by pharmaceutical companies, selected based on meeting specific evaluation criteria. However, when opting for the on-board courier, it is imperative for pharmaceutical companies to assess its long-term implications on scalability. To ensure versatility, both transportation modes should be viable options, requiring the establishment of clear processes and procedures that are thoroughly tested for qualification. This strategic approach allows for enhanced agility and scalability and minimizes errors. Decision criteria should prioritize flexibility and adaptability to facilitate future scalability.

"Implementing a dynamic, modular, and flexible logistics strategy allows for quick adaptations to unforeseen challenges."

Establishing contingencies for shipping routes involves diversifying transportation methods and creating backup plans for potential disruptions. Implementing a dynamic, modular, and flexible logistics strategy allows for quick adaptations to unforeseen challenges, ensuring the continuous and timely delivery of CGT components. This proactive approach enhances flexibility and minimizes the impact of unexpected events, contributing to the supply chain's reliability for CGTs.

The key in addressing the logistics impact of CGTs lies in the proactive planning of pharmaceutical companies, where effective cross-functional collaboration and learning from trial and error during mock shipments lead to a smooth and successful delivery of CGTs. It is important to highlight the proactive measures taken, including ensuring regulatory compliance, establishing partnerships with logistics specialists, incorporating technology, and maintaining flexibility in transportation methods, to enable scalable therapy in the future.

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High Dynamics in the Supply Chain

Several Trends and Expectations Will Shape the Market for the Logistics Sector in 2024

The European Logistics Association (ELA) is a federation of national logistics associations, covering almost every country in Europe and even some non-European countries. The members of these national logistics associations are professionals working in a logistics function, mainly in the industry but also in different service sectors. Throughout this network, ELA reaches 57,000 professionals. CHEManager asked Markus Mau, President of the ELA, about developments in the logistics sector, the particular challenges in chemical and pharmaceutical logistics and the role of the ELA. The questions were asked by Birgit Megges.

© Markus Mau

Markus Mau, President, European Logistics Association (ELA)

CHEManager: Mr. Mau, which developments, both among your customers and the logistics specialists themselves, do you see as challenges for the sector—and which as opportunities?

Markus Mau: In the pharmaceutical sector, several developments pose challenges and opportunities for both customers and logistics specialists which are indeed similar to several other industries.

The challenges are numerous—but fortunately so are the opportunities that arise from them. To name just a selection, in addition to the basic requirements for regulatory compliance, which are complex and cost-intensive in themselves and require trained personnel and adequate infrastructure, temperature-controlled transportation and counterfeiting and security, for example, are cost-driving requirements. Ensuring product security and authenticity throughout the supply chain is an ongoing significant challenge. Ensuring end-to-end visibility in the supply chain is challenging, especially with the involvement of multiple stakeholders and hand-off points. Lack of visibility can lead to delays, losses, and compromised product integrity. Ultimately, 100% transparency of the logistics processes also ensures temperature control. And as if all this wasn't enough of a burden, it has to be done in an environment with strong external cost pressure.

On the opportunity side, however, the high value of the products in the pharmaceuticals sector in particular means that opportunities arise through innovations such as robotics, predictive analytics blockchain, IoT—Internet of Things—, and AI—Artificial Intelligence—to improve supply chain visibility, efficiency, and traceability, leading to better management of pharmaceutical logistics.

How do you expect the market for the logistics sector to develop in 2024?

M. Mau: Predicting the precise developments in the logistics sector for 2024 is challenging due to various factors such as economic conditions, technological advancements, geopolitical events, and regulatory changes. However, several trends and expectations

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will shape the market for the logistics sector in 2024.

Achieving the EU's self-imposed environmental targets is a long way off, so unless there is a course correction, there must be even greater emphasis on sustainability in logistics operations. The speed with which the charging infrastructure for electric trucks is being set up will drive the fleet conversions forward. Despite all the lip service, rail is not in a position to offer additional capacity before 2030—which would then still have to meet the aforementioned requirements.

> "Resilience and risk management is a fundamental logistics topic that everyone has been aware of since Covid-19."

Of course, the Green Deal requirements also include energy-efficient warehouses, packaging materials to reduce their carbon footprint etc. All in all, a broad spectrum of investment measures—even without using the options provided by the aforementioned advancements in technology.

Resilience and risk management is a fundamental logistics topic that everyone has been aware of since Covid-19. Logistics companies invest in strategies and technologies to enhance supply chain agility, mitigate risks, and ensure business continuity in the face of future disruptions. The current geopolitical situation illustrates this very well with regard to supply security.

What is the situation in logistics with the use of digital solutions? Where do you see the greatest progress, where is the greatest need?

M. Mau: I've just come from California and have been catching up on the latest developments. It is not just there that really big changes are on the horizon that will have an impact on many areas of logistics. Digital solutions such as IoT sensors, RFID—Radio Frequency Identification—write tags in combination with GPS tracking enable real-time visibility into the movement of goods throughout the supply chain—as a starting point for logistical optimizations. By leveraging big data and predictive analytics, logistics companies can forecast demand, optimize inventory levels, and anticipate potential bottlenecks or disruptions in the supply chain. This proactive approach helps in minimizing costs and improving overall efficiency. Automation technologies such as autonomous vehicles, drones for stock control, inventory and security at site boundaries and robotic process automation (RPA) are transforming logistics operations, streamlining processes, and reducing reliance on manual labor. Robotic solutions in warehouses and driverless solutions in logistics centers are increasingly being used—and this is also where there is still the greatest need to compensate for the decreasing availability of employees.

Depending on the product group, blockchain applications meet the exact requirements for enhanced security, transparency, and traceability in logistics operations. It enables secure and tamper-proof record-keeping, particularly in areas such as supply chain provenance, customs documentation, and payment settlements.

As an association that works on behalf of its members, how is the ELA adapting to the changing market environment with its economic and geopolitical challenges?

M. Mau: With its 57,000 members, the ELA is active throughout Europe as an umbrella organization for national logistics associations. ELA addresses economic and geopolitical challenges through various strategies.

ELA is engaging in advocacy efforts to support policymakers and government authorities on issues affecting the logistics sector. This includes advocating for policies that promote infrastructure development, and regulatory harmonization as well as emphasize the importance of fundamental logistical efficiency for a strong Europe.

We offer events and exchange for all the topics mentioned as ELA or via our members such as industry events, conferences, and workshops where members can exchange insights, best practices, and learn about strategies—because we all have very similar challenges to overcome. ELA also works closely with partner organizations, for example in America.

With ELA Certification, we have been ensuring for many years that logisticians worldwide have uniform practical knowledge—at every level. Over 10,000 logisticians have been certified to ELA standards in recent years!

The logistics sector is also increasingly confronted with a shortage of skilled workers. Does the ELA have any initiatives to support its member companies in finding qualified employees?

M. Mau: We are orchestrating the Day of Logistics in Europe throughout Europe—and every company and institution is invited to celebrate and it with us on April 18, 2024. The Day of Logistics is an annual event aimed at promoting awareness of the importance of logistics and supply chain management. The ELA members organize various activities and initiatives on the Day of Logistics, including seminars, workshops, networking events, and educational programs, to highlight the vital role of logistics in supporting businesses, industries, and societies. This is a great help in drawing the attention of potential applicants and career changers to logistics.

> "Ultimately, every unrealized optimization is wasted money that multiplies with every single item in the supply chain."

In addition to attracting employees, retaining them plays an important role. ELA Certification is very helpful here and can also be used to recruit foreign specialists. I have been to a number of events in Europe where graduates have enthusiastically received their ELA Certificate and friends and family have congratulated them on site and on social media. That's fantastic for the graduate, the company and logistics as a whole. The trusted ELA standards that are the foundation for this benefit us all.

How do you see the future of logistics? How can companies play to their strengths even better in the future in order to further expand their role as an important partner to the chemical and pharmaceutical industry?

M. Mau: The more a pharmaceutical or chemical company is directly affected by the developments outlined above or wants to take advantage of technological developments to gain a competitive edge, the greater the importance of logistics in the company will become.

Ultimately, every unrealized optimization is wasted money that multiplies with every single item in the supply chain—you have to keep that in mind. In addition, the cost effect of logistical errors is really severe—not to mention the lawsuits and penalties that can result.

There is a lot of supply chain dynamics evolving. Continuous innovation and adaptation is key and to embrace a culture of learning about—logistics—innovation and adaptation to stay ahead of emerging trends and disruptions in the logistics landscape.

By leveraging strengths in state-of-the-art technology solutions, sustainability, compliance, visibility, collaboration, and innovation, logistics service providers will be indispensable partners to the chemical and pharmaceutical industry, driving value creation, reliability, and excellence in supply chain management.

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Programming the Future

Judging How to Harness the Potential of AI for the Logistics Sector

In this increasingly complex world, providing the chemical industry with first-class groupage logistics means continuously enhancing the services on offer. Artificial intelligence (AI) applications play a major role in this perpetual and lasting transformation. But what exactly is AI's potential for the logistics sector and how is it helping companies active in this industry to overcome current challenges?

Dachser made digitalization a priority early on, and by introducing the SSCC barcode and highly integrated core systems, the company helped shape the digital course logistics has taken. Today, the top items on the company's digitalization agenda are machine learning and AI.

The logistics industry now urgently needs digital transformation to ensure quality and to tackle challenges such as the shortage of drivers and other skilled workers. Moreover, the industry is being called upon to further pick up the pace when it comes to adopting new technologies and to incorporate societal megatrends such as digitalization, urbanization, e-mobility, and connectivity—which are changing the way we live—into its development activities. This calls for a strategic mindset and a firm grip on the controls, because it all comes down to actively shaping the future by anticipating what will be required. Dachser is exploring three key use cases for AI applications that will also benefit its customers in the chemical industry: groupage handling itself, planning processes, and reducing emissions.

The Digital Transformation of Groupage Logistics

Groupage logistics is a fundamental factor in the competitiveness of industrial economies and thus also of the chemical industry. Here, too, the volumes of goods loaded onto pallets and into big bags are decreasing, meaning it makes sense to share cargo space with other consignors. This is the only way to deliver goods quickly and cost-effectively while keeping CO_2 emissions to a minimum. However, broken supply chains plus the sharp upswing in deliveries to end customers are putting pressure on even the most efficient groupage networks. This is where intelligent data management, algorithms, and AI come in: these can generate the best possible solutions with the help of mathematical models that are able to "learn" the patterns and structures present within their training data.

It all starts with logistics practices, which are built first and foremost on human expertise and the physical assets required to provide services, such as network and terminal structures. Efficiency is largely determined by what happens at the network hubs, where long-distance and short-distance transports connect. Success hinges on the logistics operatives, especially the loaders and unloaders, who have the experience required to optimize the load capacity of trailers and swap bodies, similar to playing a game of Tetris. The difference in load capacity utilization between an experienced loader versus an inexperienced loader can be as much as 15%. In light of demographic change, the associated lack of qualified personnel and the space shortages, it is essential to adopt increasingly intelligent and efficient ways of dealing with the resources available to us. To overcome these challenges, Dachser has teamed up with the Fraunhofer Institute for Material Flow and Logistics (Fraunhofer-IML) to develop @ILO at, a technological innovation that comprehensively digitalizes general cargo logistics processes. The project was awarded the German Logistics Award by the German Logistics Association (BVL) at the end of 2023.

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@ILO Digital Twin as Quantum Leap

The @ILO digital twin is nothing less than a quantum leap in groupage logistics. @ILO, which stands for advanced indoor localization and operations, can provide a comprehensive digital map of a transit terminal in real time. As identifiers, @ILO uses two-dimensional data matrix codes—similar to QR codes—affixed to the top of each pallet. These codes are registered by the several hundred optical scanning units on the terminal's ceiling. In a matter of seconds and with the help of AI-based algorithms, this technology produces a digital twin—a real-time representation of all processes in the terminal, including volume measurements and item location to within one meter. Accessing this information on displays and mobile devices, forklift drivers and warehouse workers know exactly where each pallet is and where it needs to go next. This can shave anywhere from 15% to 35% off individual process times. The same applies for dangerous goods, which must naturally still carry regulation labeling. What's changed here is that the new

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The information provided by Dachser's digital twin @ILO on displays and mobile devices can save forklift drivers and warehouse workers 15% to 35% off individual process times.

system provides this information much more clearly and efficiently than previous solutions.

@ILO is the result of more than six years of joint research carried out by Dachser and Fraunhofer IML. Dachser has already implemented the technology at four of its European locations and will roll it out at its larger branches in Europe over the next few years.

Transit terminals aren't the only places AI can help provide sensible solutions. Take automation in the warehouse: automated guided vehicles (AGVs) equipped with sensor systems like cameras, lidar, and radar find their way around with the help of AI. These self-driving transporters work autonomously, performing simple repetitive tasks such as moving pallets from the warehouse to the transit terminal.

AI for Intelligent Planning

Another crucial factor for achieving efficiency and quality in logistics is plannability. Here, too, AI can really make a difference, as demonstrated by Dachser's first machine learning project: PAnDA One. This is an acronym of predictive (P) analytics (An) Dachser (DA), where "One" denotes that it is the company's first machine learning project. The PAnDA One model was specially designed to forecast inbound volumes at our European logistics branches, providing decision-making support for capacity planning. That makes it possible to obtain suitable load capacity on the market at an early stage, or to plan resources in the transit terminal. To that end, the forecasting model provides the relevant inbound volumes up to 25 weeks in advance. PAnDA One thus gives branches another valuable tool—one that provides data to underpin the "gut feelings" of experienced operations managers and to validate the insights gleaned from discussions with customers. The technology helps people make sound decisions.

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Reducing Transport Emissions

Sustainable practices—with their ecological, social, and economic dimensions—pave the way to a secure and economically stable future. Dachser aims to achieve net zero CO_2 emissions for its own facilities and vehicles as soon as possible. For this reason, the company established special e-mobility locations in Freiburg, Hamburg, and Malsch near Karlsruhe. These German locations focus on researching and testing zero-emission battery-electric trucks and their charging infrastructure, the use and self-production of renewable electricity, and intelligent power and load management. It might not seem obvious at first, but collecting data and using it intelligently plays a key role here as well: developing reliable models and application scenarios for rolling out zero-emission short- and long-distance transports calls for data gathering on a grand scale. This is an exciting use case for Dachser's future application of AI.

Wanted: Critical Thinkers

What Dachser has learned from using AI applications is that machine learning often involves taking a trial-and-error approach. It's about testing training data for as long as it takes to arrive at the desired degree of precision and a level of quality sufficient for the use case. In contrast to conventional coding, this calls for one thing above all else: patience. AI can also come with its share of downsides, such as loss of control, liability risks, and other challenges. That's why it's important to scrutinize each process critically and using human common sense. But on the whole, digital transformation offers outstanding opportunities for sustainable, future-proof development. Rather than replacing people, a sensible dose of AI and machine learning will help them make more informed and thus better decisions. Logistics is made by people, for people—and that's not going to change. In other words, each company has what it takes to shape its own digital future.

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Generative AI in Chromatographic Analysis

The Speed of Development of AI Applications Has Increased Exponentially Across all Areas of Research

Generative AI refers to the subset of artificial intelligence focused on creating new content and analyzing existing content, whether that be text, images, or in the case of chromatography, generating hypothetical data sets, methods, and models. Generative AI can impact the field of chromatography in various innovative ways, however, great care needs to be taken to carefully validate any use of this emerging technology from a technical, quality and regulatory perspective.

It is important to draw proper distinctions with the field of artificial intelligence and this article will concentrate on deep learning generative machine and large language models which, when trained with a suitable amount of raw data, can produce statistically probably outputs.

Existing machine learning models develop artificial intelligence through learning gathered from input data, developing and refining this learning from the patterns which emerge without human intervention. Perhaps the turning point in the exploration and interest in more generative models, was the development and introduction of variational autoencoders (VAE's) which added a critical ability to produce variations on the training data, are easier to scale and can handle volumes of data which were previously unmanageable (in human terms). In the prevailing years, a huge number and variety of artificial intelligence models have been introduced, including the generative adversarial networks (GANs), which produce original data based on transformer tools, working with unlabeled data in a parallel fashion, significantly speeding up the training process.

Innovation in Chromatographic Method Development

Chromatography relies heavily on the optimization of numerous variables to achieve the desired separation. There have been a growing number of studies which cite the use of generative AI in predicting chromatographic retention times, optimizing separations and helping to discover previously unresolved analytes.

DeepLC, a deep learning peptide retention time predictor using peptide encoding based on atomic composition has been used to predict the retention time of (previously unseen) modified peptides. Several other studies are cited in this area and include the use of deep learning for retention time prediction in reversed-phase liquid chromatography and predictive retention index modelling of organic compounds in one and two-dimensional gas chromatography.

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In his 2021 paper 'Perspective on the Future Approaches to Predict Retention in Liquid Chromatography', Fabrice Gritti postulates that in order to add further rigor to the simulated method development process, account needs to be taken of the fundamental solid-liquid adsorption process which, when using Monte Carlo or Molecular Dynamics simulations, can explain the complexi-

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ties of retention data in reversed phase HPLC systems which are beyond empirical or statistical models.

AI in Data Analysis

Perhaps the most active area of development for generative AI is the prediction, deconvolution and interpretation of mass spectral data. Whilst statistical tools for these operations have been in use for several years, generative AI approaches are gathering pace in the literature.

IDSL_MINT is a customizable deep-learning framework to train and utilize new models to predict molecular fingerprints from spectra for the compound annotation workflows in LC-MS/MS of untargeted metabolomics and exposomics datasets.

General adversarial models have been used to generate predictions for the rose oil characteristics of the Taif Rose, based on a training set of GC-MS spectra. This could lead to a reduction in laboratory testing and higher throughput screening to select genotypes for cultivation which retain a controlled profile of volatiles.

"The most active area of development for generative AI is the prediction, deconvolution and interpretation of mass spectral data."

Deep learning models have been used to interpret the LC-MS spectra of novel psychoactive substances and transformer models have been used to elucidate the structures of small molecules within the metabolomics sphere, with the aim of maximum coverage of biologically feasible small molecules in this space.

Generative AI for the People

For those in the laboratory who wait for the VAE and GAN based models to be successfully commercialized, what is possible using the popular text (and now image) based AI engines such as ChatGPT (GPT4) or Perplexity AI.

We have recently used GPT4 to undertake image recognition of problematic chromatograms or the mass spectra of compounds which are not contained in popular or in-house libraries.

For troubleshooting chromatographic data, we have been very pleasantly surprised by the LLMs ability to discern problematic features and offer suggestions to overcome the issues. Generally, some fundamental understanding of chromatography theory and experience are necessary for positive identification of issues, but as a diagnostic aide, LLMs offer a useful contribution.

We have also successfully used ChemCrow as an API for GPT4 to provide more domain expertise. This model contains enables the generation of molecular structures from SMILES strings and vice versa, can cite patents including the structure and deliver physicochemical information such as Tanimoto similarity indices, pKa and LogP(D) data etc. The inclusion of this domain expertise within a generative context can be very useful.

Future Perspectives

Instrument vendors are currently exploring the use of the huge amounts of instrument telemetry data which are gathered from each chromatographic analysis to build models which could be used to predict failure rates and modes and to monitor equipment and columns to assess the likelihood for a system being fit for purpose for a particular analysis (will the column last for these 100 injections!).

We also believe that the production of synthetic data sets from limited training data represents an exciting possibility for future development of generative tools.

Conclusions

Following the introduction of VAE and GAN generative models, the speed of development of AI applications has increased exponentially across all areas of research. The speed, efficiency and data handing capabilities of these models lend themselves well to further development of tools to assist the chromatographer. However, the data produced needs to be carefully validated and we need to consider the use of these generative tools in line with regulatory and ethical frameworks.

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References can be requested from the author.

AI-Powered Knowledge Transfer in Manufacturing

Harnessing AI to Access Valuable Organizational Knowledge with Smart Search

As experienced staff in the process industry approaches retirement, manufacturers are facing a significant knowledge and skill gap for incoming employees. Artificial intelligence (AI) can help them capture, retain and access valuable historical expertise and ease the transition for new colleagues in the plant. Bayer CropScience solved the challenging knowledge transfer with the AI-powered module Smart Search. The module is part of the Plant Process Management (PPM) solution Shiftconnector by the global software provider Eschbach.

"Knowledge transfer is a big issue in shift operations," explains Matthias Heskamp, former Head of Site Operations and Excellence at Bayer CropScience in Muttenz, Switzerland. "In a 24/7 plant operation, data is generated around the clock. That's 168 hours per week. Day operations teams, responsible for coordinating problem solving, only work 40 hours per week, but need to access information that is generated 24/7."

The responsibility of keeping all manufacturing processes up and running depends on the collaboration of many stakeholders in various departments, including engineering, board and field operations, research and development, maintenance, and plant management. Several years ago, Bayer CropScience implemented Shiftconnector as a PPM solution to improve communication and information transfer across shifts, departments, and different levels of hierarchies.

The PPM solution gathers data generated by users, such as shift notes, logs, and observations, as well as automated data retrieved from sensors. In doing so, machine data receives relevant context, which serves as crucial background information, shows the full picture of specific plant operations, and is important for decision-making when process upsets occur. Bayer CropScience is further optimizing its production with a new AI-based module.

Andreas Eschbach, Eschbach

Process-Relevant Information Meets AI

Important best practices and experiences that go beyond the knowledge documented in writing, i.e. explicitly in training documents or standard operating procedures (SOPs), often remain hidden in the minds of employees. As soon as those workers leave the company, relevant knowledge might be lost. Day operations teams need exactly this implicit know-how to evaluate the production processes and make the right decisions in cases of events and process upsets.

With Shiftconnector, manufacturing teams generate vast volumes of

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AI-infused Smart Search enables to tap the valuable implicit knowledge of experienced manufacturing teams.

information in every single shift, and all these inputs have become a huge repository of historical knowledge. Mining this big and valuable source of expertise can help shift teams discover opportunities for continuous improvement, learn from prior mistakes, and find solutions for recurring problems (see figure).

That's where AI comes in. AI-driven applications can quickly browse through large volumes of data to identify patterns and surface insights that would be difficult or impossible for humans to discern within a reasonable timeframe. National language processing (NLP), a specific area of AI, enables the system to process queries and instructions provided in plain language, derive meaningful information from text-based sources, and return results that humans can understand.

"AI helps our employees work as efficiently as possible."

Matthias Heskamp, former Head of Site Operations and Excellence, Bayer Crop-Science

Custom-Oriented Design

Process-relevant information that is processed with a smart application offers an opportunity for greater efficiency and safety in manufacturing. AI also makes it possible to collect implicit knowledge to make employees' experiences available for future generations.

Capturing and managing knowledge is domain-specific, which is why Smart Search is designed with customers in mind. The software provider worked closely with Bayer CropScience and the University of Göttingen to develop the AI-driven module. "In the field of NLP, applications such as chatbots already work very well for common conversations, but specialized domains, such as the chemical and pharmaceutical process industries, need solutions tailored to their exact needs," explains Bela Gipp, professor at the University of Göttingen. "Key to the success of this project was the close collaboration with the customer from the very beginning to understand their specific use cases, jargon and pain points."

Using NLP, Smart Search can comprehend the meaning and context of a query to surface the most relevant results. In addition to filtering stored information, the module can process communications by cataloging and indexing topics, keywords, phrases and more. This far surpasses what we know from internet search engines. The tool provides exclusive plant insights, and, in the event of disruptions, delivers solutions that have already been proven to work.

From Ideation to Implementation

Smart Search at Bayer CropScience was taken from ideation to implementation within only two years, and long before AI consumer apps like ChatGPT went viral. It was built using industry- and plant-specific terminology, data formats and information provided by process engineers, board operators and shift leaders during workshops and onsite investigations. The result is an AI-infused system that is highly customized to the client's workflows, language, and requirements.

"Sifting through huge amounts of data to find the information needed can be a very time-consuming and cumbersome job for shift teams."

Matthias Heskamp, former Head of Site Operations and Excellence, Bayer Crop-Science

Workers can now quickly uncover the information they need to perform their jobs more effectively. For example, if a problem develops at a particular point in a process, they can simply submit a query such as 'Dark color of product?' to easily identify any previous instances of the problem and what was done to resolve it. "Smart Search has reduced the amount of time our employees spend searching for relevant information, often from several hours to mere minutes," Heskamp adds. "AI helps our employees to work as efficiently as possible." This enables faster troubleshooting, facilitates problem resolution, and improves plant performance.

Smart Search has transformed Bayer's Shiftconnector installation from an information repository and standard shift communication system to a future-proof, intelligent knowledge hub. Workers at Bayer can quickly scan a decade of information to find what they need at any moment. This means that the wisdom and lessons of the past are stored and readily available for workers today and tomorrow. It can be integrated into any Shiftconnector installation based on Eschbach's cloud and adapted to the precise needs on-site.

Next-Generation Knowledge Management Platform

Looking forward, knowledge management will be essential to helping process manufacturers adapt to new workforce realities. In 2021, the German Institute for Employment Research (Institut für Arbeitsmarkt- und Berufsforschung) predicted that, statistically speaking, around 15% of people in employment will disappear from the German labor market by 2030.

A knowledge management platform with AI can help companies retain valuable tacit knowledge from experienced operators, technicians and engineers and make it accessible for the coming generation. Over the next few years, Shiftconnector will provide increasingly diversified AI-based applications, including features that may help users understand search results faster by providing a meaningful classification of results and offering complete text-based instructions for troubleshooting.

Maximizing the effectiveness of younger, less experienced shift teams using Smart Search will help companies address the skill gap and get more done with a smaller workforce. Eschbach's aim is to increase efficiency in the process industry, boost productivity, and ultimately ensure a seamless transfer of knowledge.

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Noncanonical Amino Acids Made by Enzymes

Biocatalysis Reduces Cost, Time and Risk to Make Diverse Amino Acids at Scale

Aralez Bio, a San Francisco-based start-up, has engineered a platform of enzymes that creates 100 times more compound diversity using processes that are also 50 times greener than conventional methods. Chiral noncanonical amino acids (ncAAs) of high quality are needed both to innovate in established therapeutic modalities and to create new drugs that target "undruggable" disease mechanisms. Co-founders, Christina Boville, CEO, and David Romney, CTO, explain their technology and outline plans for the company's future development.

Christina Boville, Aralez Bio

David Romney, Aralez Bio

CHEManager: How did Aralez Bio start?

Christina Boville: David and I met at Caltech in the lab of Frances Arnold, who was awarded the 2018 Nobel Prize in Chemistry. Her work focuses on directed evolution, which is a way to engineer and improve desired protein characteristics. Years ago, she began working with tryptophan synthase, the enzyme that makes the amino acid tryptophan. We engineered it to take in different substrates and produce a wide range of tryptophan analogs in high yields. We incorporated in 2019 to commercialize this process and since then have built out a large selection of noncanonical amino acids that give chemists access to new chemical space.

What are noncanonical amino acids?

David Romney: First the significance: 12% of the top-selling drugs contain at least one noncanonical amino acid (ncAA) and newsworthy drugs like GLP-1 agonists, macrocycles, and antibody drug conjugates contain ncAAs. Many new peptide drugs are composed of greater than 50% ncAAs. Noncanonical amino acids are any amino acids beyond the twenty proteinogenic amino acids. Proteinogenic amino acids are used by all living things to make peptides and proteins. Many ncAAs are natural, while others have been dreamed up by chemists to serve a particular function. We focus on ncAAs that are at the intersection of hard-to-make and therapeutically interesting. For example, ncAAs containing aromatic side chains can be prohibitively expensive to make but are needed and critically important in actuating binding to a drug target.

What have been some of your biggest challenges in bringing these to market?

C. Boville: Access to high quality ncAAs is a long-standing issue in drug development. Many ncAAs are impractical to make even at research scale. Other ncAAs require contending with high costs, long lead times, and supply chain risks when scaled to commercial quantities. Since ncAAs have been effectively unavailable at the scope and scale needed by the industry, many opportunities to deploy ncAAs have gone untapped. Despite the compelling need for our products, as a new product area we have to take the time to understand our customer's timelines and requirements, then match our development to their needs.

Why are amino acids the key to solving the new drug development puzzle?

D. Romney: There have been basically three classes of traditional drugs—small molecules, medium-sized peptides, and large biologics. These are loosely based on the "lock-and-key model" in which a drug binds very tightly to a specific site of a protein. Noncanonical amino acids are useful across these established modalities. However, for many complex diseases, such as cancer, that interaction is just the start of a complex cascade of signaling that is dominated by protein-protein interactions (PPIs). Next-generation drugs disrupt these PPIs by targeting multiple, weaker binding spots spread across larger areas. Small molecule drugs cannot span the sites while large molecules are usually too big to access the locale. Peptides—small to medium sized drugs that are composed of amino acids—can be made the right size with the right properties to access and then disrupt PPIs.

How is biocatalysis green manufacturing?

C. Boville: Biocatalysis means using nature to improve chemical manufacturing. Enzymes adhere to many of the principles of green chemistry: they work in water, which reduces the need for harsh solvents, and they often accomplish in a single step what would take multiple steps in a traditional process.

What are other advantages of using enzymes?

D. Romney: It's about producing highly pure, chiral compounds. Enzymes are also very versatile tools for making large libraries of related products. Early studies showed that our flagship enzyme could make diverse tryptophan analogs from slightly modified starting materials. Since then, we have engineered our enzymes to produce an even broader scope of products. We now have variants that accept over 500 ncAA side chains, and 75% of products are unique to our platform.

Personal Profiles

Christina Boville is co-founder and CEO of Aralez Bio. She received her Ph.D. in biochemistry from the University of Colorado and then conducted her postdoctoral research at Caltech as a Resnick Prize Postdoctoral Fellow, where she co-developed the enzyme platform used by Aralez Bio. She founded Aralez Bio in 2019 with David Romney and Caltech professor and Nobel laureate Frances Arnold.

David Romney is co-founder and CTO of Aralez Bio. He received his Ph.D. in chemistry from Yale University, where he worked on amino acid and peptide synthesis and was recognized in 2015 with the Richard Wolfgang Prize in Chemistry. He then joined Caltech professor and Nobel laureate Frances Arnold's lab as a NIH Postdoctoral Scholar, where he co-developed the enzyme platform used by Aralez Bio.

Business Idea

Key Building Blocks for New Drugs

Supplying diverse, high quality starting materials is a decades-old supply-chain challenge for drug development. Aralez Bio supplies unique noncanonical amino acids (ncAAs) made using enzymes for the next generation of therapeutics. Enzymes make pure, chiral products with fewer and more sustainable synthesis steps, meaning ncAAs can be made at commercial scales without cost overruns or project delays. Aralez Bio uses Nobel Prize-winning technology to produce an ever-expanding platform of engineered enzymes, which in turn make thousands of unique, high purity ncAAs, many of which have never been available before.

The twenty proteinogenic amino acids are the building blocks of the protein "machinery" controlling virtually all functions of the body. Chemically related to these vital amino acids, ncAAs share similar biocompatibility, and are used across bio-based industries such as biopharma, cosmeceuticals, and agricultural biotechnology. Aralez Bio offers these compounds end-to-end from R&D through clinical trials to commercial production. Aralez Bio works with companies of all sizes to do catalog sales or structured partnerships.

Aralez Bio's biocatalytic platform is built on three solid biotech foundations which together allow for both chemical diversity and large-scale production of highly pure ncAAs:

- Step 1: Protein engineering techniques—perfected over the past two decades—create enzyme diversity. Enzymes are evolved by making small changes in their DNA code and selecting for their ability to synthesize specific amino acids at high yields and high purity. More enzyme diversity equals more amino acid diversity.
- Step 2: Enzymes are then produced at any scale using industrial fermentation techniques which have been around for several decades. Larger reactors produce larger batches of enzymes.
- Step 3: These enzyme batches are then used in simple chemical reactors to allow large-scale manufacturing of ncAAs.

- Aralez Bio, San Leandro, CA, USA
- www.aralezbio.com
- https://www.linkedin.com/company/aralez-bio/

ARALEZ BIO

Elevator Pitch

Biocatalytic Platform for Noncanonical Amino Acids

Aralez Bio was spun out in 2019 from the lab of Nobel laureate and Caltech professor Frances Arnold. The San Leandro-based start-up uses enzymes to make thousands of novel noncanonical amino acids (ncAAs) readily accessible for the first time at both lab and commercial scales via efficient, sustainable biomanufacturing. Aralez Bio's biocatalytic platform produces high-quality, chiral building blocks that enable drug developers to create the next generation of therapeutics to treat diseases previously considered undruggable. Diverse ncAAs are useful across all stages of drug development from hit identification, to lead optimization, and to clinical/commercial scale-up. Noncanonical amino acids are found in blockbuster peptide drugs such as Semaglutide as well as in the latest generation of drug modalities such as macrocycles and antibody drug conjugates (ADCs). Aralez Bio makes unique, never-seen-before ncAAs and creates isomeric series of ncAAs that allow for fine-tuning of chemical properties.

Milestones

2019
- Incorporation of Aralez Bio
- Move to San Francisco and incubation at Lawrence Berkeley National Lab
- Pre-seed funding round raised
- First 1 g quantities sold
- Production process for flagship product line: tryptophan analogs established

2020
- Independent lab space established
- First 100 g quantity sold
- 1 kg made in production
- Launch of β-branched amino acid analogs

2021
- Enzyme production scaled to 100 L
- N-methylated amino acid production process established

2022
- ISO 9001:2015 certification
- Development of tyrosine analog process

2023
- Scale-up of amino acid production to 10 kg
- Launch of phenylalanine, naphthylalanine, D-amino acid analogs
- Introduction of structure-activity relationship kits

Roadmap

2024
- Market launch of α-methyl-α-amino acids and proline analogs
- Production scale up to 100 kg

PROCESS COMPARISON

PROTECTED AMINO ACID

PROCESS PARAMETER	ARALEZ BIO	OTHER METHOD
STEPS	2	7
PROCESS HOURS	20	134.5
SAFETY HAZARDS	ELEVATED TEMPERATURE (65 C.) FLAMMABLES (ORGANIC SOLVENTS)	CORROSIVES (NaOH, LDA) PYROPHORICS (LDA, LITHIUM) FLAMMABLES (ORGANIC SOLVENTS) MUTAGENICS (METHYL SULFATE) TOXIC FUMES (AMMONIA, ORGANIC SOLVENTS) CRYOGENIC TEMPERATURE (-78 C)
OVERALL PROCESS YIELD	85%	18%
REACTOR NEEDED TO MAKE 1 KG OF FINAL PRODUCT	10 LITERS	300 LITERS

ASSUMPTIONS: YIELD FOR OUR PROCESS IS BASED ON AN ACTUAL RUN-THROUGH (UNOPTIMIZED); YIELD FOR COMPETING PROCESS IS BASED ON PUBLISHED RESULTS AND CUSTOMER DATA.

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A comparison of Aralez Bio's platform to the conventional production process of noncanonical amino acids.

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Microbial fermentation produces Aralez Bio's enzymes which in turn make noncanonical amino acids.

Revolutionizing Green Chemical Production with Ultrasound

Converting Low-Value Woody Biomass into High-Value Green Chemicals

Plastics have been used in car manufacturing for many decades, becoming the main constituent of everything from dashboards, bodywork and seating to battery packs, fixings and thermal management systems in the latest electric vehicles. In fact, plastic can account for up to 50% of a car's total volume. Unfortunately, the majority of this plastic content is not recovered from end-of-life vehicles, and instead enters landfill or is incinerated, meaning that the global transport sector generates over 350 million t of plastic waste every year. This environmental issue is now forcing manufacturers to explore alternative methods of plastic production that will enable them to become more sustainable and progress towards net zero.

Biorefining offers an answer for vehicle manufacturers, allowing low-carbon feedstocks—such as lignocellulosic biomass—to be processed into intermediate chemicals that can be made into renewable plastics. This approach has the potential to replace fossil-derived chemicals and lower carbon emissions during automotive production. However, existing biorefining technologies are often inefficient, wasteful and unprofitable, using energy-intensive processes that consume large volumes of toxic petrochemical-derived acids and aldehydes. Ironically, these methods generate significant greenhouse gas emissions that make them environmentally unsustainable.

Exploring the Potential of Ultrasonics for Sustainability

Sonichem Technologies is a small UK company founded with the aim of converting woody biomass into green platform chemicals using ultrasound. The company's breakthrough biorefinery technique uses ultrasonic energy alongside mild organic acids to fractionate UK-sourced softwood sawdust into its three main constituents: hemicellulose sugars, microcrystalline cellulose and high-quality lignin. This sawdust is a by-product of sustainable forestry operations, and would otherwise simply be burned or left to rot, releasing all the stored carbon back into the environment. Conversely, all the biomass that enters the Sonichem process is upcycled into pure platform chemicals with virtually no waste. The ultrasonic technique also requires significantly less energy than conventional fractionation methods, resulting in green chemicals with a low carbon footprint.

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Andy West, Sonichem

The renewable hemicelluloses, microcrystalline cellulose and lignin generated by this innovative process can be used as additives or low-carbon feedstocks for green platform chemicals to manufacture renewable plastics for a wide range of applications. For example, the hemicelluloses—sugars that provide flexibility and integrity to plant cell walls—can be dehydrated into furfural, a compound that confers properties such as corrosion resistance, thermosetting and physical strength to furan resins. They can also be used as a polyfurfuryl alcohol (PFA) precursor to help multiple sectors, such as the construction industry, become more sustainable. Hemicellulose sugars can even be converted to other high-value building blocks—including xylitol and sorbitol for pharmaceutical, dental care, and food and beverage applications—and show promise as feedstocks for production of bio-based surfactants, films, natural dyes and renewable jet fuel.

> *"Plastic can account for up to 50% of a car's total volume."*

Microcrystalline cellulose has strong binding properties, making it a reliable filler and excipient in phar-

maceutical formulations, personal care products, performance composites, and foods and beverages. Cellulose is also routinely modified at a huge scale in the chemicals industry to create building blocks for the production of packaging films, adhesives, sealants and even explosives. It can even be broken down further into glucose for use in fermentation, flavor and fragrance, and fuel applications.

© Sonichem

Sonichem's patented breakthrough approach converts sawdust, the biomass by-product from forestry operations, into high-quality lignin which can then serve as the basis for bio-based platform chemicals.

The Limitless Potential of Lignin

Arguably the greatest value of this unique ultrasonic fractionation process lies in the production of high-quality, sustainable lignin. Lignin is the world's second most abundant renewable biopolymer, and is also the only known aromatic polymer found in nature, making it a plentiful and low-toxicity alternative to the finite feedstocks made from petrochemicals. Lignin is extremely versatile, possessing innate hydrophobic, flame-retardant, antimicrobial and UV-resistant properties, and can be added to industrial composites to confer these benefits and improve flow. The material is also known as nature's binder, and can be used instead of certain fossil fuel-derived chemicals—such as the toxic petrochemical phenol—to produce resins for composites, including those required to build wind turbines. Demand for bio-based platform chemicals for this application in particular will only continue to grow in the coming years, as more countries seek to transition to renewable energy sources.

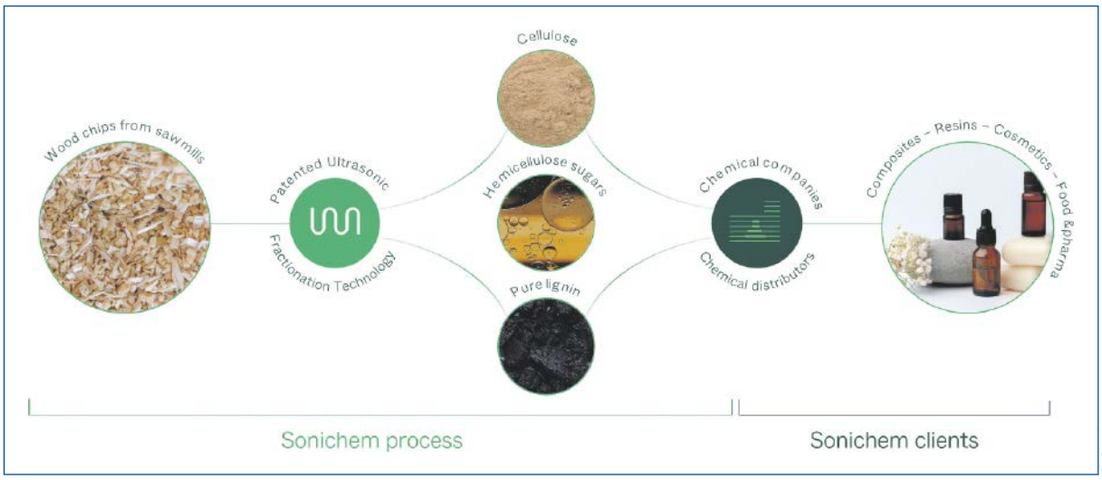
"Trailblazing ultrasonic technology has the potential to enable large-scale green chemical production."

Sonichem lignin is different from the lignin obtained using the conventional Kraft process. Kraft lignin contains sulfur, which corrodes metals—such as processing equipment and steel reinforcement bars embedded in cement—raising safety concerns as well as environmental issues. It is also very high in molecular weight, giving it low solubility. Consequently, Kraft lignin is challenging, time consuming and expensive to process into useful products, with goods produced using Kraft lignin often demonstrating inferior mechanical properties. Sonichem lignin, on the other hand, has a very low molecular weight—one of the lowest in the world—is of high purity, and does not contain any sulfur. These features give it high reactivity and solubility in a host of common solvents—such as ethanol and acetone—and polymers, for instance in the production of bioderived carbon fibers.

Driving Change in Automotive Manufacturing

Sonichem has recently launched an international project in collaboration with industry leaders CPI, the National Composites Centre, Scott Bader, SHD Composites and Polestar. The project, entitled 'Carbon-neutral agroforestry-derived resins to materials for automotive applications (CARMA)', will apply Sonichem's patented technology to the development and commercialization of bio-based feedstocks made from the company's high-quality lignin. These feedstocks can be used in the production of sustainable, cost-effective replacements for the platform petrochemicals that are currently used to produce plastics, resins and composites for automotive manufacturing. CARMA will extend Sonichem's pioneering ultrasound approach to the transport industry, driving the sector toward net zero, enhancing the UK's bioeconomy, and helping to establish a resilient national lignin supply chain. Producing home-grown green plastics also aligns with the UK Government's focus on resource-efficient, sustainable industrial materials, as it could significantly reduce the UK's reliance on imported composite materials, which currently amounts to approximately £250-260 million per year.

Trailblazing ultrasonic technology has the potential to enable large-scale green chemical production across the UK, supporting bio-based plastic manufacture for use in multiple applications. The high-quality, bioderived chemicals generated through Sonichem's revolutionary technique could help to decarbonize numerous industries, reducing the nation's reliance on polluting, finite petrochemicals.



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Sonichem's biorefinery technique uses ultrasonic energy alongside mild organic acids to fractionate softwood sawdust into hemicellulose sugars, microcrystalline cellulose and high-quality lignin.

Adrian Black, CEO, and Andy West, Chief Chemist, Sonichem Technologies Ltd., Southampton, UK

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Interphex 2024

The International Pharmaceutical Expo (Interphex), dedicated to pharma and biotech innovation from development to marketing, is scheduled to take place on April 16–18, 2024, in New York, NY, USA. The annual trade show and technical conference brings over 10,000 global industry professionals and 625+ leading suppliers together. The event provides a combination of no cost technical conference, exhibits, demonstrations, and networking events.

■ www.interphex.com

Achema 2024

Achema, to take place on June 10–14, 2024, in Frankfurt, Germany, is home to the full scope of technology and services for the process industry. Manufacturers, service providers and forward thinkers meet at the event, overcoming the boundaries between different specialist fields and industries. Core topics at Achema are next generation pharma manufacturing, hyperscaling hydrogen, artificial intelligence and autonomous systems, fossil-free production, and a fully resource-efficient chemical.

■ www.achema.de/en

Chemspec Europe 2024

Chemspec Europe is to take place on June 19–20, 2024, in Duesseldorf, Germany. The event is the key platform for manufacturers, suppliers and distributors of fine and specialty chemicals to showcase their products and services to a dedicated audience of professionals in the industry sector. The product portfolio of this event covers fine and specialty chemicals for various industries. Conferences presenting the latest results of ongoing R&D projects round-off the show.

■ www.chemspeceurope.com

Specialty & Agro Chemicals America 2024

The Specialty & Agro Chemicals America show—scheduled to take place on June 25–27, 2024, in Savannah, GA/USA—is a forum that promotes chemical manufacturing, chemical technologies, and related chemical industry services that have specific applications for the agrochemical and specialty chemical markets. The event will focus on the chemical products and technologies that have specific applications for the agrochemical and specialty chemical manufacturing markets.

■ www.chemicalsamerica.com

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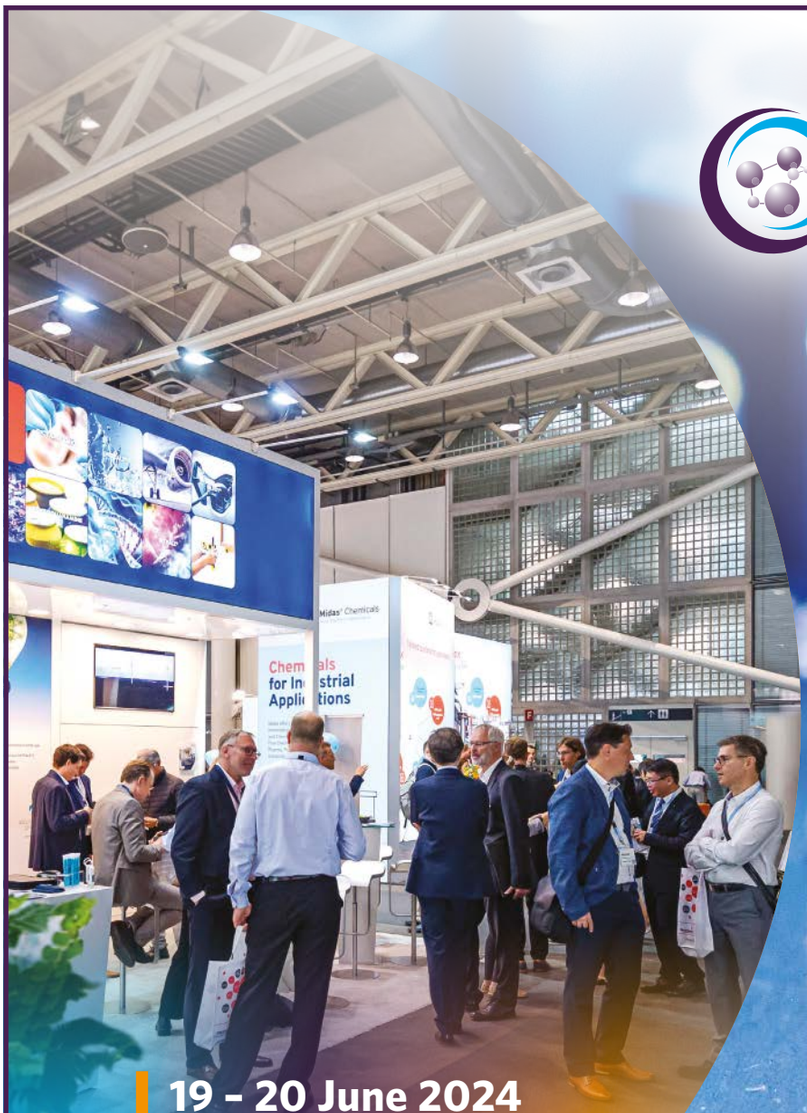

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