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Economic Impact of Continuous Processes, Possibilities of Flow Chemistry and MRT, Integrated Continuous Drug Production

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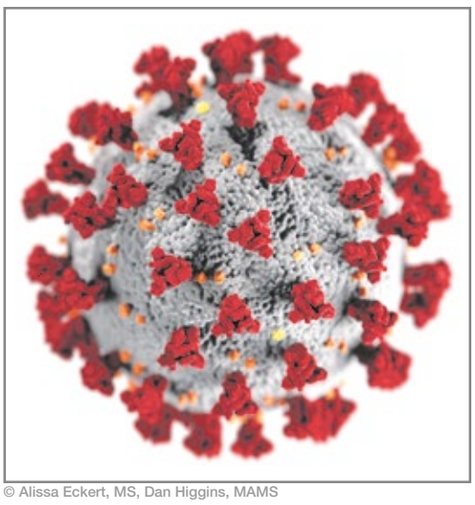

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Continuous Manufacturing

Fine & Specialty Chemicals

Innovation

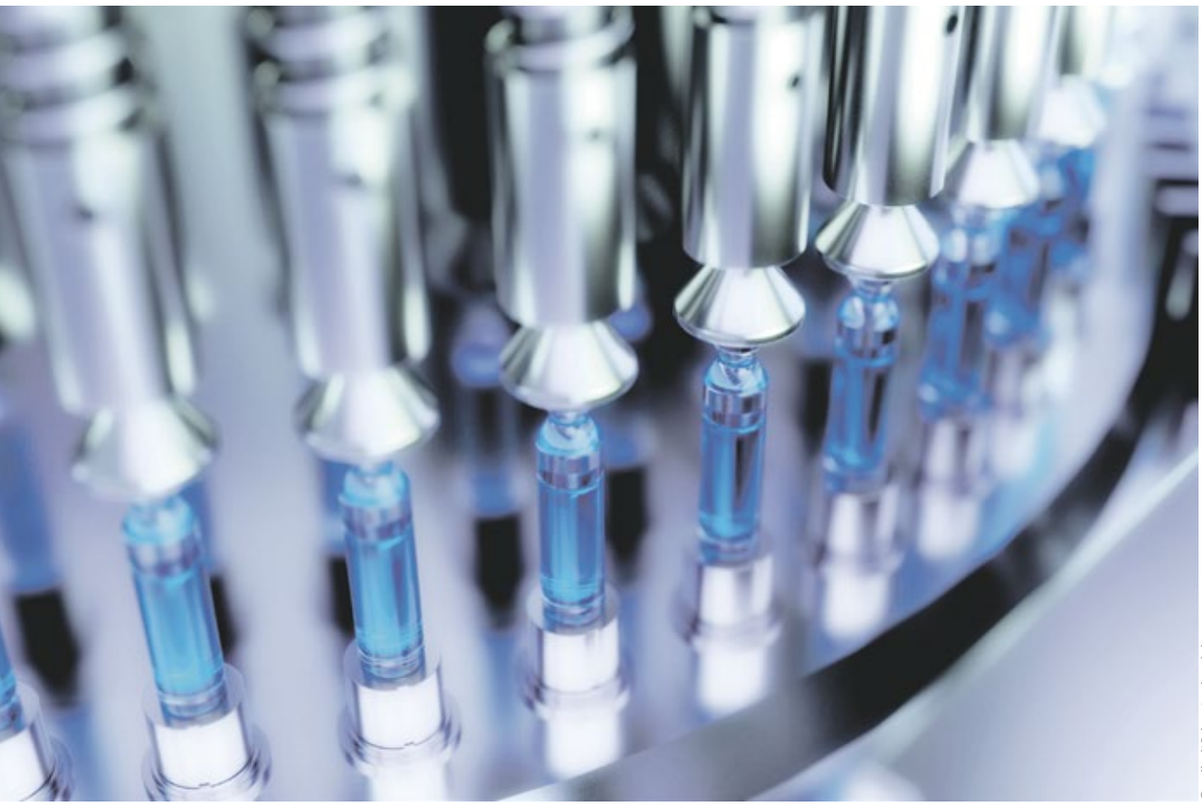
Economic Impact and Challenges of Continuous Pharma Processes

Optimized Production of Active Ingredients and Finished Drugs

The strong focus on supply chain security will increase cost of pharmaceutical production in years to come. In this context, companies considering production in mid to high labor cost countries need to carefully analyze their conversion cost development. It is precisely in this situation that optimized production of synthetically and biologically produced active ingredients and finished drugs is extremely important.

Thilo Kaltenbach,
Roland Berger

Daniel Edinger,
Roland Berger



Compared to the incremental optimization of existing processes, the automation of individual production steps up to complete continuous production offers significantly higher efficiency potentials.

Continuous Production Approach

Continuous production links individual production steps together and quality-relevant parameters are monitored in real time by so-called in-process controls. In the ideal case, the entire production process can be carried out continuously, from the weighing of the sample to the finished drug. In this case, production is controlled by predefined parameters, compliance with which guarantees the quality of the end-product.

Regulatory authorities in several countries support the introduction of continuous production, as the continuous monitoring of relevant parameters guarantees a higher product quality than the random checks used in the classic batch process. In addition to the higher product quality, continuous production offers five economic advantages for the pharmaceutical industry, which will be discussed below.

1. Smaller Production Facilities
In classical manufacturing facilities, the production process is carried out in a stepwise approach. Intermediate products are stored in containers which take up a lot of space, until they are released by the quality department and the process continues. In continuous production, these containers are not needed, as individual production steps are linked together by conveyor systems. Furthermore, continuous production allows the use of smaller equipment for the same production quantities. In consequence, smaller machines and the continuous process are less labor intensive and enable a more efficient production.

2. Increased Equipment Efficiency
Changeover between individual production campaigns has become complex in recent years due to new regulations like the cross-contamination guideline. In addition to the costs for the preparation of these cleaning protocols, the cleaning times reduce the efficiency of the machines used, in some cases considerably. It is not uncommon that the cleaning of the machines used takes longer than the production campaign itself. Continuous production equipment is frequently easier to clean or even dedicated for a specific product and can help reduce this requirement and increase efficiency.

3. Faster Product Release
Real-time monitoring of quality-relevant parameters eliminates the need for quality checks of intermediate products during continuous production. The process is not interrupted when waiting for individual releases from the quality department and there is no need for storage of intermediates. The final release is also much faster and completed to a large extent, by adhering to the described process parameters. In addition to the pure time savings, this helps to reduce the number of quality tests and increases the efficiency in the quality control department.

4. Lower Energy Consumption
Reducing the size of production sites usually has a positive impact on energy consumption, especially for heating, ventilation and air conditioning.

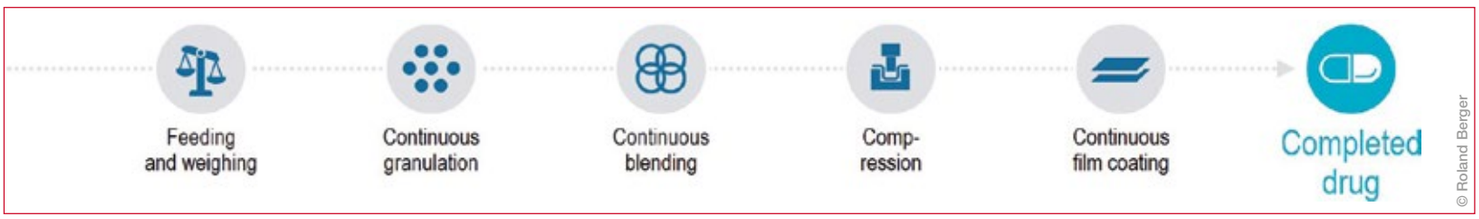


Fig. 1: Example of a schematic continuous production process.

Furthermore, continuous production allows the product to be completely shielded from environmental influences during the production process. This shielding allows, for example, the production of sterile products in clean room classes with lower requirements for air exchange and other parameters. The lower requirements help to reduce energy consumption.

5. Reduced Waste

The elimination of upscaling during product development as well as the use of smaller machines in the production process can help to reduce waste of pharmaceutical intermediates and end products. Furthermore, real-time monitoring of critical parameters allows to react promptly to deviations by adjusting the production process. This can help to prevent the destruction of entire batches in the event of a failed final release.

Summary of Positive Economic Effects

The reduction of operational costs (up to 30%), the higher operational efficiency (up to 80%), the reduced lead times (up to 90%) and the decreased product deviations (up to 50%) contribute to a reduction of variable costs. In summary, this makes production of boarder line products possible and improves profitability of existing portfolio products (Fig. 2). Especially, the labor cost reduction (up to 50%) contributes to the potential reallocation of pharmaceutical production and can help to secure supply chains.

	Batch	Savings	Continuous
Total COGS per 1000 units	$60.00	$18.00 -30%	$42.00
Facility	$21.00	$5.50 -26%	$15.50
Other	$13.80	$4.50 -33%	$9.30
Consumables	$9.60	$2.50 -26%	$7.10
Raw	$9.00	$2.20 -24%	$6.80
Labor	$6.60	$3.30 -50%	$3.30

Exemplary calculation of conversion cost for a batch- and a continuous process

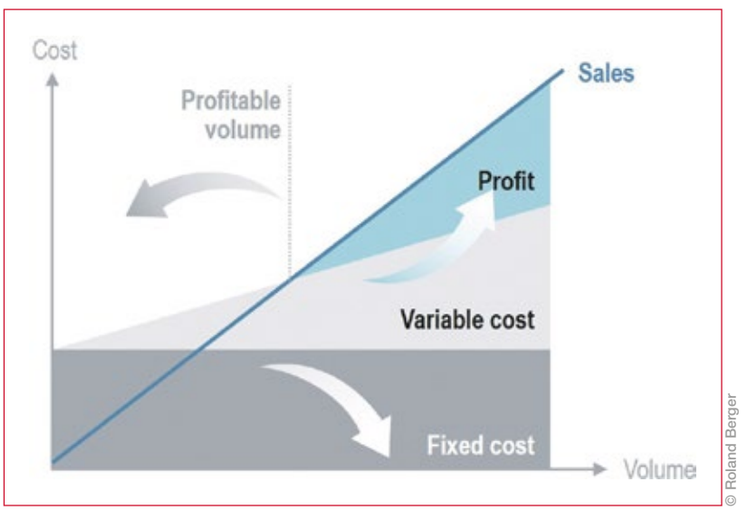


Fig. 2: Continuous production can reduce fix and variable costs and increase product profitability.

Limitations of Continuous Production

However, from a technological point of view not all processes can be converted into a continuous process. The process development is usually still very costly and takes considerable time in the development phase. Therefore, continuous production is mainly recommended for launch products and few existing portfolio products. For these reasons, pharmaceutical manufacturers still rely primarily on classic batch production despite the identified savings potential.

Business Case of Continuous Production

The exemplary calculation of savings potentials per category for an exemplary transfer from a classical batch production into a continuous production process demonstrates a cost of goods sold (COGS) saving potential of ca. 30%. Main contributors are the lower facility costs (ca. 25%) associated to the described smaller production facility and the reduced labor costs (ca. 50%) due to automation and continuous production. Additionally, savings on raw material and consumable consumption (ca. 25%) help to achieve the described COGS saving potential. Saved COGS directly influence the product's profitability and demonstrate the huge potential of continuous production processes.

The Drivers

For equipment suppliers the adoption guarantees new equipment sales, besides that machine manufacturers are extremely interested in obtaining data from production processes. As service providers, the machine manufacturers are establishing a second business segment supporting the pharmaceutical companies in the analysis of their process data. From our perspective, machine manufacturers are ideally positioned for this, as they are both familiar with the technical possibilities of their equipment and can collect data from all production sites using their equipment. Especially in times of increasing competition from low-wage countries, which are now also supplying high-quality machines, the collection, analysis and processing of data is crucial for the future success of machine manufacturers.

Summary

Innovative pharmaceutical companies in particular have a strong focus on delivery reliability of their products from an ethical and economic perspective. Reliable supply chains are often guaranteed by expensive safeguarding mechanisms. Stable and flexible continuous production processes can help to reduce these security mechanisms and thus save costs.

Continuous production fits perfectly into an increasingly data-driven value chain. The collection, analysis and evaluation of data is becoming more and more important and contributes to corporate success. Especially in personalized medicine, as can be seen in the example of recently launched CAR-T cell therapies, better control of one's own supply chain and the offer of digital solutions for coordinating patient-specific production are already decisive for the commercial success or failure of companies.

For these reasons, classical pharmaceutical companies should increasingly rely on digitally networked and automated production in order to optimize the costs of classical products as well as to lay the foundation for the introduction of innovative products today.

Daniel Edinger, Project Manager Pharma & Healthcare and Thilo Kaltenbach, Senior Partner Pharma & Healthcare, Roland Berger GmbH, Munich, Germany

daniel.edinger@rolandberger.com
thilo.kaltenbach@rolandberger.com
www.rolandberger.com

Continuous Pharmaceutical Manufacturing

Why the Industry should Accelerate the Adoption of this Technology

The pharmaceutical industry has been slowly, but surely, embracing continuous manufacturing (CM) over the past decade. In fact, most large pharma companies have invested in continuous technologies, though the range has been broad, from single unit operations to end-to-end solutions. Some companies are just getting started, while others have successfully submitted drug applications with significant CM components.

There have been six such drugs approved in the US (Orkambi, Symdeko, and Trikafta by Vertex Pharmaceuticals; Prezista by Johnson & Johnson; Verzenio by Eli Lilly; and Daurismo by Pfizer), three in Europe (Orkambi and Symkevi by Vertex Pharmaceuticals; Prezista by J&J), and two in Japan (Tramacet by J&J and Verzenio by Eli Lilly).

This steadily growing adoption reflects the undeniable advantages CM provides, when compared to the current paradigm, batch manufacturing. First, as CM processes operate continuously, the process volumes are much smaller, requiring smaller unit operations. This reduces the CAPEX for both equipment and facilities. Second, CM processes are automated and require less personnel for operations. Integrated CM processes allow process material to flow directly from unit to unit, obviating storage and manual transport of process material across units.

Third, quality control (QC) testing and related personnel can be significantly reduced, as off-line testing of intermediate products/API/final product would be largely eliminated. Instead, real-time monitoring with process analytical technologies (PATs) and other sensors would allow for continuous monitoring, coupled with closed-loop control. In this way, the process material is constantly monitored, improving quality assurance. In addition, real-time release testing will be possible, reducing the time and cost to commercialization.

Fourth, in many instances, CM offers higher yield steps and/or ones that require less solvent. In some cases, we have observed that CM reactions can utilize cheaper and less pure raw materials, still yielding in-spec active pharmaceutical ingredient (API) and final drug product.

Fifth, utility costs are significantly reduced. For example, continuous reactors may be maintained at their target temperatures as material flows in and out of them. Conversely, with batch reactors, vessels need to be heated and cooled with each batch.

Sixth, as CM processes operate continuously, cleaning intervals may be performed only as required per validation protocol, and not after every single batch.

Finally, as lead times with CM processes are much shorter, manufacturers may require significantly less inventory and still maintain reliable service levels. Work-in-process inventory can be virtually eliminated, as process material will not be held up at any one point in the process.

These are some of the advantages of implementing CM, many of which will ultimately benefit patients through improved quality and better access; however, there may be others that can become noteworthy as this technology becomes more prevalent.

Bayan Takizawa, Continuus Pharmaceuticals

Integrated continuous manufacturing (ICM) pilot line at Continuus's facility, able to produce coated tablets from raw material.

Integrated Continuous Manufacturing

At Continuus Pharmaceuticals, we are leveraging integrated continuous manufacturing (ICM), a platform that was initially developed at the Novartis-MIT Center for Continuous Manufacturing. ICM spans both drug substance and drug product manufacturing, coalescing these components, which normally reside in different facilities in the batch framework, into a single seamless process that produces final product from raw materials.

The API is not isolated; rather it remains in situ, with its quality ascertained by in-process methods (e.g., PATs). With ICM, an added benefit is that the entire manufacturing process can be engineered intelligently through a systems approach that prioritizes overall efficiency over local performance. Corrective steps can be eliminated as required characteristics are obtained initially, rather than modified downstream (e.g., particle size control through controlled crystallization instead of downstream milling). Finally, incorporating drug substance manufacturing removes the uncertainty of quality and uniformity of sourced API (e.g., if sourced from multiple vendors).

Challenges to Adoption

With all of these benefits, a logical question follows: why the slow adoption? There are several reasons. First, many companies have existing batch

infrastructure in place, enabling them to minimize CAPEX for batch-made drugs. With continuous processes, an investment in new equipment/tools is required.

Second, companies have been batch manufacturing for decades, steadily ingraining this production philosophy within their corporate culture. For example, the idea of integrating drug substance and drug product manufacturing is not only revolutionary to many pharma veterans, but it can also be threatening, as it requires a new skill set.

Third, as pharma has been a high-margin industry, R&D has focused mainly on the development of new products and treatment modalities, not improving manufacturing. Especially in the biotech space, companies hold steadfast to their original manufacturing processes, even if they are decades old. Part of the reason for this position are the costs and regulatory implications of modifying an existing manufacturing process. However, it should be noted that J&J converted Prezista's approved batch process to a continuous one and is looking to extend this strategy to other products due to the expected benefits.

Finally, there is uncertainty among companies on the regulatory risks of implementing novel manufacturing technologies. Fortunately, regulatory agencies are intelligently positioning themselves to better evaluate advanced manufacturing methods, such as continuous manufacturing. The Emerging Technologies Team (ETT) within the FDA's Center for Drug Evaluation and Research (CDER) has been working with companies to advance the regulatory science for CM. The Innovative Manufacturing Technology Working Group (IMT-WG) within Japan's regulatory agency (PMDA) has been tasked with similar responsibilities. Harmonization across the agencies is further evidenced by the ongoing effort to align guidelines for the industry through ICH Q13, which is focused on continuous manufacturing.

A Robust Solution

Recent events have highlighted the fragile nature of pharmaceutical supply chains. An unfortunate consequence of the Coronavirus outbreak has been the disruption of multiple drugs manufactured in India, many of which contain starting materials and APIs originating from China. But health crises are not the only potential triggers — political disputes may also suspend the flow of critical drugs. These problems only add to existing woes that plague many generic manufacturers, as demonstrated by ongoing warning letters, plant shutdowns, and subsequent drug shortages. Janet Woodcock, director of CDER, emphasized some of these vulnerabilities in a 2019 Congressional Testimony.

Continuous manufacturing offers a solution to this problem. Its low-cost structure and environmentally acceptable footprint make it a viable enterprise in countries like the United States. Furthermore, in-country CM of critical drug substances (e.g., ICM) can provide companies a reliable source of these APIs. In fact, Sanofi recently started to build facilities across Europe to bolster its current suppliers. Governments should take note and consider similar strategies, as well as enabling economic and regulatory incentives (see "Why we need continuous manufacturing and how to make it happen" by Clive Badman, et al. for an in-depth analysis).

While slow adoption allows for conservative risk management, it also, in the case of health care, leaves people, often the most vulnerable, behind. Let us take this scourge that has terrorized the entire globe as an opportunity to modernize an outdated manufacturing system and better prepare ourselves for the uncertainty of the future.

Bayan Takizawa, Chief Business Officer, Continuus Pharmaceuticals, Woburn, MA, USA

btakizawa@continuuspharma.com
www.continuuspharma.com

Flow Chemistry Opens up New Possibilities

Milli- and Micro Reaction Technology Can Offer Enormous Advantages in Chemical Manufacturing

The change in the product portfolio of many chemical companies away from commodities to customer-specific specialties is one of the current challenges facing the process industry. Flow chemistry or milli- and micro reaction technology (MRT) is a technology platform that can offer enormous advantages in this respect.

A panel of experts met at the Dechema building in Frankfurt to discuss current topics in flow chemistry. From left to right: Michael Reubold, CHEManager; Joachim Heck, Ehrfeld Mikrotechnik; Joerg Mohr, Saltigo; Karl-Christoph Hoever, Quast; Andreas Haubrich, Sanofi; Kurt Wagemann, Dechema; Volker Oestreich, CHEManager; Bernhard Hettich, CHT; Michael Doludda, Evonik; Anne Kaaden, Ehrfeld Mikrotechnik; Peter Poechlauer, Thermo Fisher Scientific; Manfred Heinrich Schrod, Consultant.

What is the state of the art, the dissemination and acceptance as well as the requirements for further establishment of the flow chemistry technology in the chemical and pharmaceutical industry? CHEManager had invited to the roundtable "Flow Chemistry", Dechema, the German expert network for chemical engineering and biotechnology, provided the appropriate framework, and many experts came to discuss these questions.

MRT replaces the discontinuous batch process with a continuous process in which reactions take place in structures with a drastically reduced size. The main components are mixers with excellent mixing speed and heat exchangers with high heat transfer capacities. This results in improved process control and significant miniaturization of reactive volumes. The excellent mixing and temperature control with hardly measurable temperature gradients over the whole reaction volume cannot be achieved in a classical batch reactor. Due to the exact controllability of the reaction process, the reaction parameters can be better adjusted, resulting in higher product purity and better yields. The small volumes in milli and micro reactors allow the physical process conditions to be extended to higher or lower temperatures or pressures while maintaining a safe and fully controlled unit.

Safety and Process Control

The main advantages of continuous operation in micro and milli reactors are thus ultra-fast mixing, highly efficient heat transfer, simple process control due to low system inertia and high operational safety due to minimal hold-up. These properties of continuous flow reactors are particularly advantageous for fast, highly exothermic reactions with explosive or toxic substances; due to the high safety risk, these processes are often difficult or impossible to handle in batch reactors.

The economic benefits resulting from the technology are mainly due to the high yield and the low proportion of by-products, but also to the sustainable plant safety, lower energy consumption and a smaller carbon footprint.

And yet, MRT has not yet achieved the status in fine chemicals and active ingredient production that one might expect — at least not in Central Europe. What are the reasons for this? Five main topics emerged from the expert discussion: In addition to technology, the question of costs plays a decisive role, approval practice and know-how in the companies need to be improved, and entrepreneurship is needed for medium and long-term strategic decisions.

Well-proven Technology

"We are far beyond the lighthouse project phase," emphasizes Christoph Hoever, who represents the Hoever Group and the company Quast, which builds microreactors: "We are in the implementation phase, in the phase of exploring many smaller laboratory facilities in order to see in which segments and in which areas micro reactor technology can actually be applied on a large scale today. "

Bernhard Hettich, CTO of CHT Group, who has been using MRT in research and production for many years, agrees: "Today, every time a new product is developed, or a new process is introduced into production, we consider whether it can be done continuously. Nevertheless, it has not been widely accepted. Batch also has advantages, for example the flexibility of standardized reactor systems for a certain range of products."

For Peter Pöchlauer of ThermoFisher Scientific, the use of MRT is part of their daily business, namely performing custom synthesis for pharmaceutical developers: "The question these companies ask is: How can I make appropriate amounts of the material of which I have made grams or milligrams in a library synthesis at the appropriate speed and in the appropriate quality? We have established a routine for this request: How do we want to do that? At which of our locations do we want to do that? Which production concept do we want to use? Do we want to do it in standard vessels? Do we want to develop a continuous manufacturing process? Or do we want to use a combination of continuous and discontinuous process steps? Our goal is to make the right decision not only in the choice of chemicals, but also with regard to the production concept. We consider this as part of the normal procedure of a service operation."

Joachim Heck, managing director of Ehrfeld Mikrotechnik, a company that markets micro- and milli reactors for usage from laboratory up to production, refers to a very successful large-scale technical application of MRT: "We have a shareholder from China who is now very successfully operating three production reactors, each with an annual production capacity of around 10,000 tons for an agro-active substance. The first of these reactors went into opera-

tion three years ago. Since then it has been running without any interruptions. It was only opened once after 6 months to demonstrate that no fouling occurred, a consequence of the significant high selectivities.

Summing up, Joerg Mohr, head of Process Development & Analytics at Saltigo, a Lanxess subsidiary in Leverkusen, Germany, confirms: "There are no fundamental obstacles: flow chemistry will continue to compete with conventional batch processes and offer an economically attractive and sustainable solution for suitable problems. The necessary tools are available. However, existing reference plants with their advantages should be made known more widely." In summary, all participants of the roundtable discussion agreed: MRT is proven, reliable, and available.

Cost Considerations

In addition to the technical imperative to support the continuous improvement process through the use of technological progress, there is always the economic imperative in business practice: Cost and benefit must be in an economic balance.

This is also described by Andreas Haubrich from Sanofi in Frankfurt: "We develop continuous processes. In doing so, we look at complete syntheses. And if the building blocks such as selectivity, purity, safety that conti offers have a real benefit, then the process is carried out in conti. But at the top of the list is always the question: How does the process pay off? This is quite normal — also for me as a developer. When I present syntheses, when I work out a process for the production companies, I have to develop it in such a way that it can subsequently be implemented. And that's where cost pressure is quite normal."

When a company must decide between investing in new continuous plant or continuing to operate batch equipment already depreciated, it can be difficult to introduce MRT. Comparing the production costs from this point of view, the batch process is almost always advantageous.

Joerg Mohr also emphasized this aspect: "One must basically differentiate between brownfield and greenfield projects. If I assume that I am going to build from scratch anyway, then I have other freedoms per se. In any case, the bottom line must be that it pays off. And if a new building is not economical, then there are no Conti plants. You can't just realize one step of a multi-stage synthesis in conti mode, because then you would have to make the whole downstream process conti as well. As a consequence, the new process step, including purification and isolation, must be integrated into an overall solution that is suitable for the overall supply chain concept."

Authorization Practice

Is there a connection between the construction of new plants in Germany and the authorization practice in our country? CHT manager Bernhard Hettich sees a particular problem here, regardless of the different federal states and production processes. With regard to MRT, he specified: "We all agree that downsized continuous processes are safer for various reasons, and that can be easily explained even to non-experts. But we

Continued Page 10 ▶

have not yet succeeded in making it clear to an authority that it should be easier to issue a license or obtain a permit for this technology. We are currently in the process of developing a guideline for modular plants that not only favors large-scale chemical companies with their big sites, but also takes into account the requirements of medium-sized companies. This is an important task. We must exert political influence so that the new technologies, which undeniably have safety and environmental advantages, are recognized and correctly assessed by the decision-makers in regulatory organizations."

Manfred Schrod, who has worked for various companies worldwide, has a similar view: "Not much has changed in the last 10 years with regard to approval procedures in Germany. The potential for microreactor technology probably lies outside Europe."

All experts in the discussion group agree, that it should be much easier to obtain approval for a continuous plant with a smaller hold-up for hazardous substances than is currently the case.

Training, Know-how and Thinking in Pigeonholes

The experts also agree on this point: Education and training on the subject of conti and micro reaction technology needs to be improved. "In education, there is still far too much thinking in round bottom flasks", said Bernhard Hettich, and Andreas Haubrich called for two equivalent options, which the chemist can use when planning a synthesis: "He needs two sets: one conti, one normal batch. And then he must know when to make use of which option. However, this is either taken into account too late or not at all during studies or training."

Much of what goes from development to production is done in batches, because people don't know any other way. But then it is often too late due to lack of time to demonstrate and implement the advantages of a continuous process.

In addition to more intensive training in higher education, a stronger emphasis on interdisciplinarity and multidisciplinarity is needed in operational practice. As Peter Pöchlauer puts it: "The chemist must understand his process engineer and vice versa. And the process engineer must understand his plant engineer as well as his analytical chemist — and vice versa. And the plant engineer must understand what the opportunities are in an operational production. Therefore, this kind of multidisciplinarity is what I have to create in my company to be able to make successful developments."

Joachim Heck emphasized that the corresponding training courses, whether in chemistry, chemical engineering or process engineering, are already providing systematic training on the topic of flow chemistry: "There are chairs, where work is being done on this topic, but not yet across the board. By no means every graduate, whether in chemistry or process engineering, has sound skills in continuous process technology."

But the companies are also under an obligation: "Interdisciplinarity is also part of training. And we can promote interdisciplinarity in the companies by recruiting very different people and by regularly integrating them to different tasks and projects. The results are incredible", emphasized Bernhard Hettich.

© Ehrfeld Mikrotechnik

Integration of the continuously operating Miprowa flow reactors into the existing building infrastructure at Shaoxing Eastlake in China near Shanghai.

Sustainability and Entrepreneurship

The CHEMonitor survey, a market trend barometer conducted by CHEManager and Camelot Management Consulting, at the end of 2019 revealed a less than positive mood in the chemical industry, but also encouraged with statements such as "change is necessary, we need a recipe for the future. A change in values can remedy the situation!" With the statement: "Sustainability in the business model is one of the opportunities", the question arises how MRT and flow chemistry can contribute to this, as this technology is particularly characterized by a higher material yield, lower energy input and higher purity of the starting material.

Evonik expert Michael Doludda confirmed: "Sustainability is one of Evonik's top priorities. We are currently conducting massive carbon footprint studies and we are also involving all our suppliers in this process. As a Group, we also want to consider a sustainability factor, that is, an internal CO_2 price, when making investment decisions. This aspect should actually be an advantage for microreactor technology."

"From CHT's point of view", Bernhard Hettich said, "we have had a sustainability strategy based on three pillars for several years: economic, environmental and social — not just carbon footprint. And this is also our decision-making basis. But I would not say that flow chemistry is generally more sustainable. Of course, we have less hold-up of any substances that you don't want to have on a 10-ton scale. MRT is more economical when it comes to production costs or investment costs. And economically it is also more sustainable. To derive a direct link between carbon footprint and flow chemistry seems not to be obvious spontaneously. We do flow chemistry or microreaction technology because it offers advantages. And when we approach something new, we try to find out whether it offers advantages at the point where it is needed. Sometimes it does, but often it doesn't. And of course, we also see that many things work that don't work in batch or wouldn't have worked at all. These are great advantages."

For Peter Pöchlauer, too, a key question for continuous process engineering is profitability: "How can I make MRT fit my business models particularly well?" Of course, the carbon footprint or process mass intensity, a key figure used by pharmacists, also plays a role. But above all, safety considerations are also very important: "When route scouting for a target molecule, not only the brevity or the effort is evaluated, but also the raw material consumption. And here, of course, one often sees that the most hazardous reagents, which nobody likes to touch, are very efficient. With all these considerations, a grip in the Conti drawer can be more advantageous." His summary: "Flow Chemistry will continue to prevail to the extent that it can be shown to fit our business models, our ambitions in environmental protection and our ambitions as a reliable manufacturer of high-quality chemicals. This is where I see our advantage to the Far East markets. These three points mean that Flow Chemistry can make our chemical production in Europe sustainable. And that is what we really want. We have every opportunity to make chemical production in Europe sustainable."

Christoph Hoever is confident: "In the long term, MRT will establish itself because the sum of the advantages from the economic side, both in terms of raw material and energy savings and efficiency, is given. The possibility of upscaling from laboratory scale to smaller reactors up to large-scale production is another big advantage."

Does this mean that there is a lack of willingness to make decisions and take risks, to try out new things? Anne Kaaden from Ehrfeld Mikrotechnik asked the question of entrepreneurial courage: "Is Germany or Europe overperforming? Do I always have to know my return on investment in detail before I enter a new technology? To consider too much details leads to a loss of time and that definitely leads to a loss of money."

More entrepreneurial courage in flow chemistry can therefore bring new opportunities — especially because safety, sustainability and efficiency are inseparably linked to this technology. A continuously and successfully running reference project with a production capacity of thirty thousand tons of product per year proves the possibilities of MRT. Now it is up to the decision-makers in the chemical and pharmaceutical industry to take up the baton and break new ground for process technologies.

Volker Oestreich, CHEManager

Flow Chemistry: A Mature Technology still on the Rise

How to Accelerate the Adoption of Continuous Manufacturing across all Industry Sectors

The change in many chemical companies' product portfolio away from commodities to customer-specific specialties is one of the current challenges facing the process industry. Flow chemistry or milli- and micro reaction technology (MRT) is a platform that can offer enormous advantages in this respect. But MRT has not yet achieved the status in fine chemicals and active ingredient manufacturing that one might expect. What are the reasons for this reluctance?

CHEManager asked executives and industry experts dealing with flow chemistry so share their opinion on why some industry sectors are so reluctant in adopting continuous production processes. We wanted to know:

❶ How would you define the essence of flow chemistry?

❷ Which factors are affecting the global flow chemistry market and the implementation of flow chemistry in the industry?

❸ Should there be simplified approval procedures for flow chemistry processes or plants, and is the technology sufficiently covered in academic education?

Read the insightful answers of the experts here.

A Technology with Enormous Potential

Philippe Robin, CEO and Co-founder, Alysophil

❶ Flow chemistry is a biomimetic process. It reproduces material transformation observed in nature. Nature is known to employ the most efficient process. Developing the chemical industry with intensive use of flow chemistry will enable humanity to make huge progress in the production of goods, in terms of frugality, environmental footprint and safety. In addition, the size of equipment, the seamless scale-up and on-demand production are the kind of fits that are particularly appropriate for fine chemical production

❷ So far, in Alysophil's experience, the industry approaches the implementation of flow chemistry for various reasons.

First, to reach enhanced industrial performance versus batch process (yield, conversion). Going beyond in performance, motivation to use flow chemistry is to improve safety. These processes concentrate at the same place, at the same time, much lower reactive compounds vs batch. In the case of process deviation leading to reaction's runaway or leaks, the impact is restricted in a tiny danger zone vs batch. Then you may think to re-implement forbidden reactions: the ones that are very efficient but also very dangerous to master in batch. For instance, using of phosgene, which can be produced on demand and directly used in a subsequent reaction.

Second, considering environmental footprint examples are more and more focused on solvent-free reactions, energy performance, waste reduction, highly efficient new synthesis by using bio-sourced materials.

Third, the investment and running costs are a factor of differentiation vs batch. For many applications, flow chemistry costs might be 30-50% lower.

Forth the size of the equipment is another key point. Imagine if a surface of 15 sqm could host a process producing 3000 metric t/y. This is definitively not lab scale but really an industrial one on a very tiny area.

Alysophil is convinced that flow chemistry may play a major role to invest in new chemical facilities in Europe. Such decisions may set a new balance in chemical production between Asia and Europe, which will strengthen the supply chain.

❸ Simplified procedures are not necessary as the current regulations are already taking into account the mass involved in processes. So basically, the current regulations are very compliant with flow chemistry. The technology is not really new, but academics have formerly focused their courses on what batch industrials hoped. Beyond the technology, we need a new way of thinking about synthesis imagination, taking into account the capabilities of flow chemistry in terms of catalysis, photochemistry, flash chemistry and low lifetime intermediaries. That's the reason why Alysophil develops artificial intelligence and use for chemistry.

A Growing Need for Modular Flow Chemistry Platforms

Shawn Conway, Director of Engineering, Cambrex High Point

❷ Batch production has traditionally been — and still is — the mainstay of the pharmaceutical manufacturing sector, largely due to quality and regulatory requirements. Continuous flow chemistry had typically been reserved for niche applications, such as highly energetic and/or hazardous reactions where continuous processing allows risks to be managed to avoid catastrophic events as well as expensive infrastructure requirements.

Flow chemistry has become more widely accepted throughout the pharmaceutical industry for several key reasons in addition to process safety, namely volume and cost, as well as quality and reduced development timelines. An increase in the number of highly potent and/or orphan drugs has led to a need for a nimble, smaller-volume capacity model. Existing large batch processing infrastructure is not well suited for these applications for both capability and cost considerations. Developing, designing and implementing modular flow chemistry platforms that can be customized serves this growing need in the industry.

Flow process scalability also allows for fewer scale-up cycles in a development lifecycle, reduces investment cost and speeds time to market for successful drugs. Furthermore, flow chemistry has been shown to provide superior quality for a range of challenging synthetic steps such as cryogenic organolithiations. The ability to tightly control the physical parameters has been shown to afford more consistent products with fewer impurities or unwanted by-products, which can reduce development efforts required to extract, isolate and purify target compounds. This provides a more efficient and streamlined process, and can also reduce timelines, material and energy requirements, enhancing process sustainability.

Recognizing these advantages, the pharmaceutical market has invested accordingly in the technologies, triggering a corresponding investment and growth of process development and equipment providers to enable these powerful technologies.

Tailored Hardware for Demanding Chemistries

André de Vries, Commercial Director, Innosyn

❷ Lately, also the fine chemical industry and the small molecule pharma arena has adopted so-called flow chemistry as one of their focus points to improve manufacturing processes. While the continuous manufacturing of bulk chemicals is state of the art, it faces some challenges in fine and pharmaceutical chemicals, which prevent its introduction on a broad basis.

This is due to the fact that fine, pharma, and agro chemicals are manufactured in multipurpose plants; are complex molecules with many functionalities (many steps / unit operations); are relatively small volume compounds; and that they often have a limited life cycle.

In fact, when the first scalable process is required, in many cases there is no revenue or guaranteed market approval.

Moreover, speed to market is key for the development stages of the pharma or agro product, hence a limited process development time is critical, as well as the flow chemistry equipment being readily available. For the latter, we at Innosyn have adopted selective laser melting (SLM), or 3D metal printing, as enabling manufacturing technology to create the "best fit for purpose" flow reactors and mixers.

Typical chemical reactions to perform preferably in a continuous mode can be divided into two main categories. First, for very fast, highly exothermic reactions, such as nitrations, DiBAl-H reductions, and metalorganic reactions, we have designed, "printed", and applied flow reactors with a relative narrow zigzag channel having superb heat transfer coefficients.

Second, when applying hazardous reagents in relative slow chemistry, e.g. an SN_2 substitution with sodium azide at sterically hindered alkylbromides, we have produced rather large flow reactors (up to 500 mL) with about 1 cm wide channels containing over the full length SMXL elements to secure narrow residence time distribution.

In practice one can now design, "print", and apply within 1 month a new tailored piece of equipment for any type of challenging chemistry.

An Opportunity to Innovate Chemical Processing

Dirk Kirschneck, CEO, Microinnova

❶ I see the essence of flow chemistry in the opportunity to innovate chemical processing in two main ways. The first opportunity is to intensify processing by optimizing space-time-yield, leading to fast, efficient and safe chemical processing. The second opportunity is to work with modular plants that have some on-module flexibility, for example realized by means of 3D-printed reactors. The main driver is to minimize the time-to-produce.

❷ I expect a strong impact of Covid-19 on the flow chemistry and continuous processing community. Governments see that parts of the processing industries are key resources. The ability to have access to modular and flexible pilot plants and manufacturing units offers the option to take action, especially in crisis situations. Sourcing medical diagnostics, treatments and items such as reagents and intermediates are critical for the crisis management. The response to a dramatically changing demand contains a high value, especially in cases where the supply from other parts of the world is not stable. Modular plants using continuous manufacturing can deliver a minimized time-to-produce.

❸ I think that a two-step strategy makes sense. Engineered modules can be delivered with a set of safety relevant documents by plant construction companies. This can be seen as a pre-HAZOP (short for hazard and operability) analysis, which enable the operator to speed up their HAZOP analysis. Another aspect is the existence of reduced worst-case scenarios. If the active volume can be reduced by a factor of 10, especially in the case of hazardous reactions, new safety concepts can be realized. These new opportunities should lead to simplified approval procedures, enabling the industry to react quickly on market opportunities and, therefore, increase the competitiveness.

A Now Well-established Technique

Duncan Guthrie, Managing Director, Vapourtec

❷ Flow chemistry has shifted in the past decades from being a novel field only a few academics were working in, to become an enabling technique for the wider scientific community.

Continuous flow processes allowed scientists of all backgrounds to achieve a better understanding of their chemical reactions. Without heat or mass transfer limitation and with precise control of key reaction parameters (such as temperature, mixing and residence time), new findings have reshaped our existing knowledge previously obtained from round bottom flask chemistry. As flow chemistry expertise built in their companies, more scientists were curious and started to work in continuous flow. As the scientific knowledge increased, our systems had to become more sophisticated to rise to the demands from scientists. High modularity and the ability of running automated reactions with integrated analytical instruments, have also been key factors to ensure more than 500 Vapourtec systems working today in both academic and industrial laboratories.

As a well-established platform, different industries have taken advantage of working in flow for their projects. Accuracy, flexibility, ease of scaling up and automation opened windows for increasing R&D throughput in labs worldwide.

A Fast Road to Innovative Production Routes

Luigi Vaccaro, Professor, Laboratory of Green Synthetic Organic Chemistry, Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia

❶ If I think of flow chemistry, the first concepts that come to my mind are innovation, efficiency and — above all — opportunity. Mastering flow technologies to achieve a chemical process opens a fast road towards a proprietary access route to a desired target material but also to the unquestionably unparalleled optimization of the process in terms of energy, safety and chemical efficiency.

Finally, flow chemistry is an opportunity of incalculable value for academics and industrials to invest in something innovative and capable of creating new science, different professionals and job positions. The opportunities that at the same time involve fundamental and applied research are rare, especially if they can lead to cultural and economic leadership, as flow chemistry can do.

❷ As an academic and as a non-expert of the actual complexity of the economic issues of global chemistry markets, the cost of flow equipment certainly seems to be the main element influencing the actual implementation of this technology. Being fully convinced of the capability of flow technologies of delivering highly efficient processes, I tend rather to focus on the cultural barriers related to its use. We need more professionals who are able to know and exploit the strengths of flow chemistry and to make the technology transfer to real cases more evident and immediate.

❸ There are excellent scientists working at the development of flow technologies for different chemical sectors. Mostly, these activities involve PhD students and more advanced scientists while teaching at an undergraduate level is more limited, but it would be important to present this technology to this audience. Master programs could be organized as a joint effort of universities and companies to include flow chemistry in the curricula.

Cooperation, Not Competition

Charlotte Wiles, CEO, Chemtrix

❷ Continuous manufacturing (CM) is gaining global importance, boasting improved process control and reduced operating costs, leading to increased manufacturing profits and competitive edge. One of the most significant challenges for CM has been a lack of publicity around the technology's implementation industrially. This is changing with CMO's/CDMO's now promoting their capabilities as outsourcing partners for CM.

An often-underestimated part of introducing a new technology into a company is how to navigate the transition from its use in a project to a process. Our view is that a multidisciplinary approach is required to achieve the project goals of safe, efficient, cost effective manufacturing and should involve a mixed team from the outset, obtaining the much needed "departmental buy-in" to accept a "new way" of doing something.

Whilst benefits such as increased process safety, reduced energy consumption and waste generation are widely noted, gaps remain in how to translate these advantages into a clear business case. The future of CM as a production technique rests on appropriate training, awareness of the benefits it can bring, together with its implementation early in product and process development. It is vital that disciplines are combined to identify opportunities for process improvement when assessing use of CM for manufacturing capabilities. This is not a field looking to compete with batch and existing hardware but to complement it, through access to new processing possibilities.

Cooperation, not competition, is key to successful application of emerging technologies!

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Agrochemicals Producers
A strong Link to Europe's Custom Manufacturing Industry

Nanoforming
A Revolutionary Approach in Drug Nanoparticle Engineering

Vaccines
Developers and Manufacturers Are Facing Several Challenges

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Connected Fates

Agrochemical and Custom Manufacturing Industry in Europe have a Long-lasting and Successful Relationship

The fate of the agrochemical innovation, development, product launch and production are strongly linked to the parallel development of the fine chemicals and custom manufacturing industry.

Starting Point

Up to the 1970s and early1980s the market launch of a new plant protection agent was easy from today´s perspective: new successful products were almost always produced in newly erected dedicated production plants, as significant quantities had to be produced due to a high application rate in the kg/ha range. Producing companies purchased — if at all and not backwards integrated like e.g. BASF, Dow, DuPont, Hoechst, Bayer at that time — existing catalogue products as starting materials. Or they could convince fine chemical companies to newly develop and produce new building blocks, which those suppliers could then usually sell to several customers, thanks to the co-launch of similar products on the market. Two examples:

- 2-Methyl-6-ethyl aniline for the herbicides Acetochlor (Monsanto) and Metolachlor (Ciba Geigy).
- 2,6-Diethylaniline for the herbicides Pretilachlor (Ciba Geigy), Alachlor, Butachlor and Amidochlor (all Monsanto)

Furthermore, the regulatory situation was quite "relaxed" in Europe, a fast track launch in France guaranteed a quick launch and a fast payback of money spent in R&D.

Birth of the Custom Manufacturing Industry

From the early to late 1980s onwards, however, products with lower application rates were developed and launched (e.g. sulphonylurea herbicides, strobilurin fungicides, etc.). Also, pressure on payback and investment as well as from the regulatory side started to increase. At peak quantities of such newer products, especially highly active herbicides (sulfonylureas, phenoxys, etc), were forecasted only at 100's of tons and not anymore

Michael Helwig, Independent Consultant

1000's of tons. Thus, the inventing agrochemical companies could not justify in any case to build a new production plant for all such products.

This new situation triggered the birth of the toll or custom manufacturing companies, Lonza being the very first one with the invention of the multi-purpose and multi-product production plants.

In the following decades a highly specialized custom manufacturing industry especially in Europe developed in order to serve the needs of the innovative agrochemical companies. Long-term contracts often secured the supply of specialized starting materials, advanced intermediates or even the bulk active ingredient. Such 1:1 contracts were also necessary from a supplier´s point of view, as those products could not be sold to other customers anymore.

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Today´s Market Players

Looking at the supplier situation first, we have a top-tier of European custom manufacturing organizations (CMO), e.g. Lonza, Saltigo, CABB, Weylchem, Evonik and ESIM, and many smaller Indian and Chinese enterprises.

On the other side of the table today we are facing an extremely consolidated agrochemical industry — by the way much more than in the pharma space — as a result of takeovers and mega mergers which surprised common sense regularly:

- In 2018 the top-4 agrochemical companies had a combined marked share of around 55% (excluding seeds): 1. Chemchina (Syngenta / Adama); 2. Bayer (including Monsanto); 3. BASF; 4. Corteva (Dow + DuPont)
- 14 of the top-50 agrochemical companies are still investing in and launching new molecules (combined market share of close to 70%).

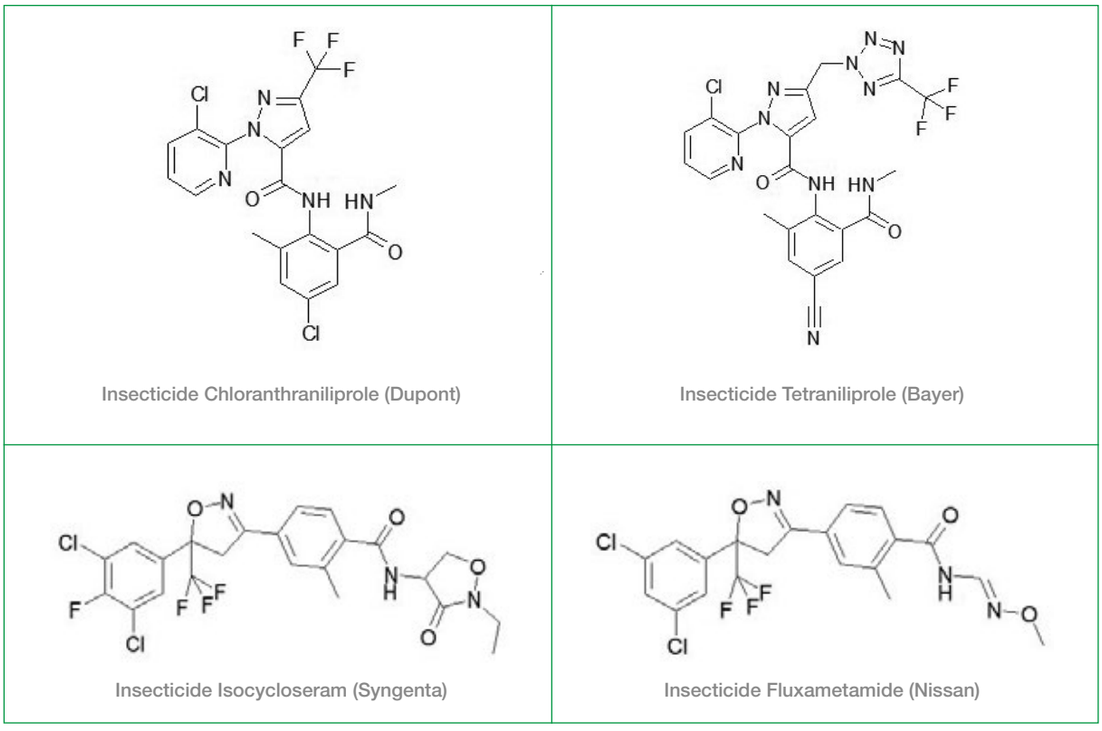

Figure 1: One new lead structure may lead to new molecules of very similar structure but as process patents are well secured – despite the structural similarity – totally different synthesis routes have to be implemented and suppliers cannot make use any more of common building blocks.

Especially for the European / Western CMO industry the proprietary part of the market (new patent protected products) is most attractive. However, the differentiation between proprietary and generic today is not so easy anymore because of two reasons:

- Sales of innovative companies comprise of an increasing share of "in house generic" business.
- Originally generic companies enter the proprietary space by in-licensing or purchasing proprietary product rights.

Today´s Situation for new Products

The pressure on the innovative agrochemical industry to successfully launch a new plant protection agent has become tremendously high:

- Regulatory authorities, not always but very often transcribing the wishes of the end user for a "chemistry-free" environment, have increased and still are increasing requirements for new launches.
- Shareholders expect short term revenues of any pre-investment in R&D, assets or product launch efforts.
- The molecular structure of recent launched or published plant protection agents reveals that it becomes complex and complicated to synthesize those new compounds. Today it is not unusual that more than 15 chemicals steps are needed to put a new agrochemical together.

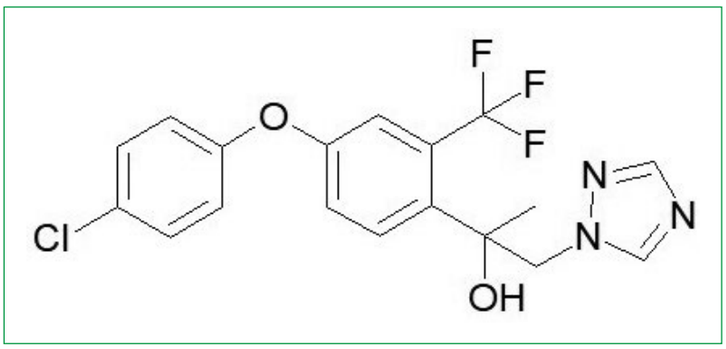

Figure 2: Sometimes a new blockbuster is revealed as a slight variation of an existing chemical class, like BASF's fungicide tradenamed as Revysol, based on mefentrifluconazole.

- As in the past, the publication of one new lead structure still leads to new molecules of very similar structure from the competition. However the difference is that process patents nowadays are much better secured than 30 years ago with the consequence that — despite the structural similarity — totally different synthesis routes have to be implemented and Suppliers cannot make use any more of common building blocks (Fig. 1).

This trend mostly prohibits to develop niche products, nowadays only blockbusters (> $1 billion sales) are being envisaged by the agrochemical industry.

Another observation shows that sometimes a new blockbuster is revealed as a slight variation of an existing chemical class, like e.g. BASF's new fungicide tradenamed as Revysol, based on mefentrifluconazole, a latest member of the fairly old triazole fungicide product class (Fig. 2).

What does this mean to the custom manufacturing industry?

- Fewer products are introduced by fewer companies on the market. These molecules are more complicated to make (more chemical steps, more demanding technologies). Thus, the total business to be outsourced is estimated to remain on a fairly stable level, an important conclusion for the European custom manufacturing industry.
- It has become quite popular and natural to cut the synthesis pathway of a new molecule into different "modules" and source these from different tolling partners depending upon the optimal fit for each part of the synthesis. The often bespoken "one-stop shop" from the past exists only as a niche.
- Due to the above complexity it does not make sense also from an economic point of view to produce everything in house due to huge investments required.

Volatility

The financial crisis of 2008/2009 and subsequent rises and downturns in demand show that those two interwoven industries had to newly define certain relationships and expectations to each other.

The different expectations from both sides during various phases of product related requirement changes are shown in the table.

Especially for the "unexpected" market changes the term "partnership" often needs to be defined in a new way. The whole industry also depends on globalization with all its pros and cons:

Quite significant capacities and capabilities of chemical and fine chemical production have been and are still being erected in China and India. Both, the agrochemical and the European custom manufacturing industry — like many other industries rely and depend upon sourcing different materials and services from those regions. But the often feared move of the whole manufacturing industry out of Europe has not and will not take place.

Recent supply chain interruptions (2008 Peking Olympic Games, 2019 Xiangshui chemical plant explosion, 2020 Corona virus outbreak) prove for the agrochemical and the fine chemical industry that the risk can only be balanced with certain manufacturing industry remaining in Europe (which by the way is also currently discussed on an European level even more for the supply chain security of generic medicines).

Technologies

The invention and launch of new molecules for any industry triggers the

Continued Page 17 ▶

Relationships and expectations between agrochemical companies and CMOs

	Customer (agrochemical company) expectation to supplier (CMO)	Supplier (CMO) expectation to customer (agrochemical company)	Comment
Launch Phase	Implement process as fast and as cost effective as possible	Get reimbursement for all unforeseen hurdles during implementation	Prime value proposition of Western CMO companies
Maturity	Reduce price double digit per year due to learning curve	Get payback of R&D and investment	Intelligent pricing and contracting models secure satisfaction of both industries
Generic Phase	Develop and implement 2nd generation processes and meet LCC price range	Reimburse any additional R&D, handle as a new project	Latest that is the time when new suppliers are implemented, very often from LCC.
Market Downturn	Fill originally contracted and now idle capacity with "other" projects	Pay for idle capacity	Matter of negotiation
Market Upside	Restart / expand production asap	Stick to lead times	Matter of negotiation

Table: The financial crisis of 2008 / 2009 and subsequent rises and downturns in demand show that agrochemical companies (customer) and CMOs (supplier) had to newly define certain relationships and expectations to each other. The different expectations from both sides during various phases of product related requirement changes are shown in this table.

implementation of new production technologies. Some technological developments / milestones for the innovative agrochemical industry and the supplying fine chemicals and custom manufacturing industry are:

- 1990´s: Implementation of low-temperature chemistry (e.g. pyridimidine carbinols, invented by Ely Lilly).
- 2000´s: Broadening of fluorine technologies. Active ingredients containing fluorine atoms became more and more popular (e.g. insecticide Broflanilide by Mitsui with 10 fluorine atoms in the molecule).
- 2010´s: Expansion in Suzuki coupling capacities for SDHI fungicides.

In parallel to such a technological development the materials of construction for reactors also evolved:

- In the 1950s / 1960s production assets largely consisted of stainless steel reactors.
- Then glass-lined reactors have been added, for a long time a good mix of both guaranteed production flexibility for a well-equipped multi-purpose plant.
- During the last 10 to 15 years, Hastelloy reactors became quite popular, in order to cope with special aggressive reaction conditions.
- Nowadays, some latest production requirements demand the usage of tantalized reaction vessels.

The initially promising looking microreactor technology did not significantly enter the toll manufacturing / production situation of agrochemicals as of today.

Michael Helwig, Independent Consultant, Breisach, Germany

michaelhelwig@freenet.de

Corteva Agriscience and AgPlenus Collaborate on Novel Herbicides

Corteva Agriscience and AgPlenus have entered into a multi-year collaboration for the development of novel herbicides. The collaboration will combine the Wilmington-based agriculture company's strengths in crop protection product discovery and development with AgPlenus' expertise in designing effective and sustainable crop protection products using predictive biology.

By leveraging their complementary expertise, Corteva and AgPlenus said, they will address the rise of global weed resistance, created in-part by the absence of new modes of action (MOAs) for weed control over the past 30 years. Successful products resulting from the collaboration will enter a multi-billion-dollar market.

"Weed resistance presents a serious challenge for today's farmers," said Neal Gutterson, Corteva's chief technology officer. "So much has changed since the last MOAs were identified in the early 1990s. It's time to find new solutions; our collaboration with AgPlenus positions us well to do that."

Under the terms of the agreement, Corteva will apply its extensive crop protection research and development expertise, and AgPlenus, based in Rehovot, Israel, will apply a robust computational platform to optimize several of AgPlenus' chemical families. Such chemical families have already been validated for herbicidal activity and are connected to new MOAs. Corteva holds an exclusive license from AgPlenus to commercialize herbicides based on these chemical families. Additional financial terms of the collaboration were not disclosed.

Eran Kosover, AgPlenus' CEO stated: "This collaboration will focus on optimizing our leading chemical families putting us in an excellent position to pursue our target of developing novel herbicides. I am confident that AgPlenus' unique approach in the development of herbicides, alongside Corteva Agriscience's extensive scientific and market know-how, will lead to new and sustainable innovation in the herbicides market." (mr) ■

Delair and BASF Collaborate to Accelerate Agricultural Research

BASF and Delair, a global provider of end-to-end visual data management solutions for enterprises, announced a collaboration to scale up BASF's research and development projects for seeds, traits and crop protection.

The agreement will enable BASF's agricultural research stations worldwide to use the Toulouse, France-based visual intelligence company's delair.ai cloud platform to streamline and standardize the information gained through drone-based field studies. The platform provides enterprise-focused workflows and industry-specific analytics and will help BASF turn its visual drone data into actionable insights and ultimately, new sustainable solutions for the agricultural market.

"As a research driven agricultural company, we want to use the full potential of digitalization to accelerate innovation. Partnering with Delair will help us to get a deeper understanding of the observed crops and their surrounding environments, and reduce the time to market for new products," said Greta De Both, manager of Sensor-based Field Phenotyping for Seeds & Traits at BASF.

BASF recently introduced drones equipped with multispectral sensors to automate and optimize their field data collection, allowing real-time insights into how plants respond to environmental conditions. In delair.ai, BASF will be able to build digital twins of their research fields, as well as map and analyze hectares of plots across all trial sites. The cloud platform will enable field agronomists to automatically vectorize as well as geo-reference microplots and generate biological data and crop behavior per plot.

"While capturing agricultural data is easier than ever with drones, the real challenge enterprises face is harnessing all of this data so that it is consumable, shareable, and actionable," said Lénaïc Grignard, Agriculture and Forestry product manager at Delair. "We are honored to start this new partnership with BASF and help them harness the power of visual data to make the right decisions at the right time." (mr) ■

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International Issues

Your Business 2020 in the Spotlight

Editorial
Dr. Michael Reubold
Publishing Manager
Tel.: +49 (0) 6201 606 745
mreubold@wiley.com

Dr. Ralf Kempf
Managing Editor
Tel.: +49 (0) 6201 606 755
rkempf@wiley.com

Sales
Thorsten Kritzer
Head of Advertising
Tel.: +49 (0) 6201 606 730
tkritzer@wiley.com

Jan Kaeppler
Media Consultant
Tel.: +49 (0) 6201 606 522
jkaeppler@wiley.com

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Nanoforming

A Cutting-edge Solution for Improving Efficiency in Pharma

In 2019, the pharmaceutical industry invested $182 billion in drug development, but only 48 drugs were approved for use. Last year was no deviation from the norm; the great expense and low success rates associated with drug development have long been noted. For example, the period from 2010 through 2018 averaged approval of merely 37 novel drugs per year, despite a 39% increase in investments. It is therefore imperative that the industry adopts technological innovations that can greatly improve the efficiency of drug development.

A leading cause of pharmaceutical attrition is poor drug solubility and bioavailability, with around 40% of promising active pharmaceutical ingredients (APIs) currently suffering from low solubility. Out of the large fraction of drugs administered orally, most only become bioavailable following oral ingestion and penetration through biological membranes within the gastrointestinal (GI) tract. For Biopharmaceutics Classification System (BCS) II substances in particular — defined by low solubility and high permeability — bioavailability can be improved by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids.

As dissolution rates can be significantly improved by reducing the size of the drug particle, advanced nanoparticle engineering technologies are providing a revolutionary answer to this long-standing problem.

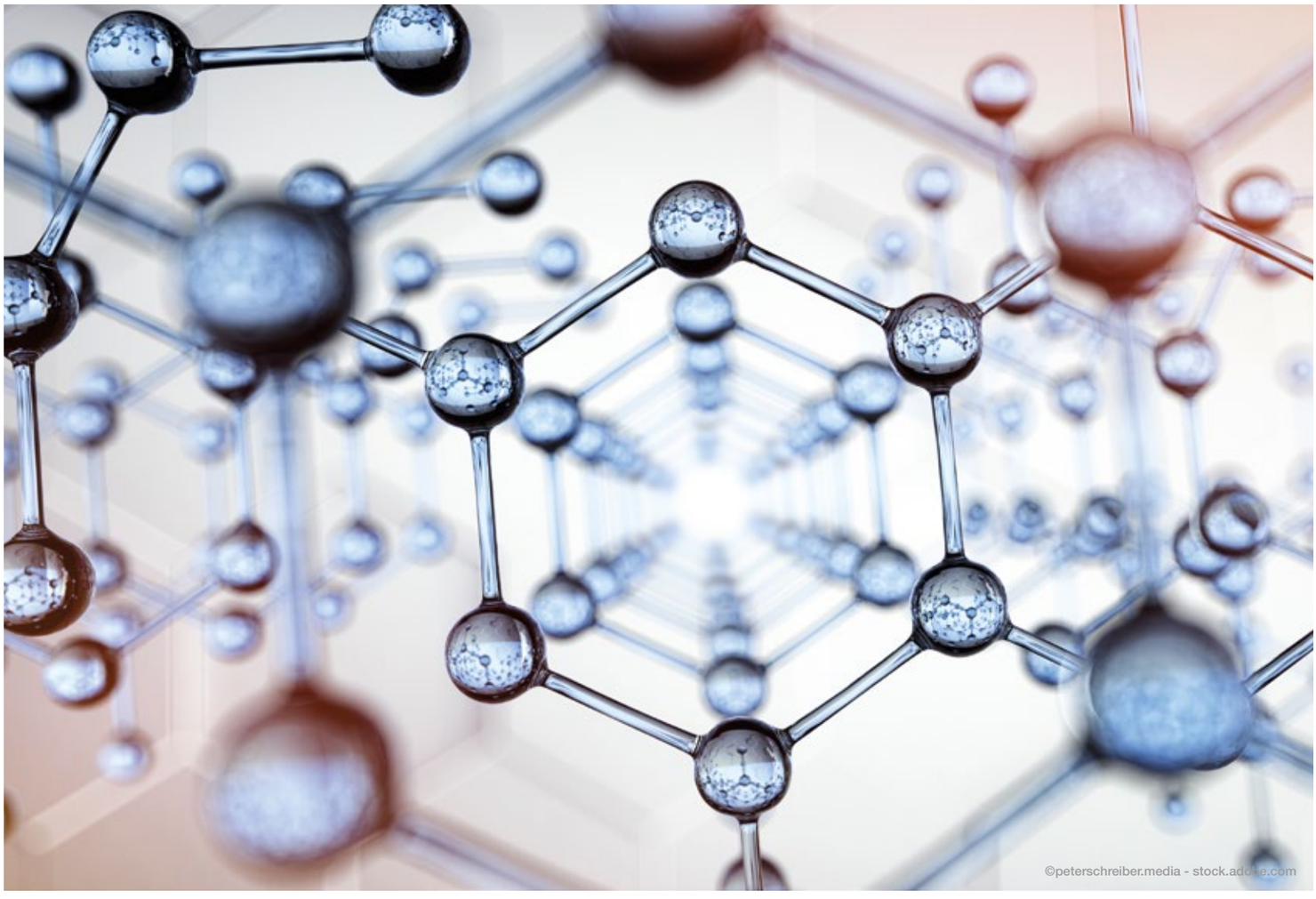
Edward Haeggström, Nanoform

Albert Haeggström, Nanoform

Drug Nanoparticle Engineering

The production of nanoparticles or "nanoforming" can be achieved through either a "top-down" or a "bottom-up" approach. Current top down approaches, such as nanomilling, use a significant amount of energy to achieve 200 nm size materials and require excipients — substances formulated alongside the active ingredient — and often polymers to stabilize materials.

Bottom-up techniques such as solid dispersion often leverage solvent-acting agents and produce physically unstable amorphous particles that lack a crystalline structure.



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The utilization of excipients results in a more complex solubility-enhancing route, which creates scalability challenges.

The latest nanoforming technology, a proprietary process developed by Nanoform, utilizes a bottom-up recrystallisation technique to produce crystalline or stable amorphous materials from solution in a controlled and scalable process. The Controlled Expansion of Supercritical Solutions (CESS) process dissolves and extracts API particles from supercritical carbon dioxide ($scCO_2$) without additional excipients. A key advantage of nanoforming drug compounds without excipients is that it reduces the need for extended compatibility studies and therefore significantly accelerates initiation of clinical trials. The patented technology is the first to produce drug particles as small as 10 nm, while also enabling the tuning of other surface properties through tight control of thermodynamic processes.

Benefits of Nanoforming Drug Particles

Nanoforming offers many benefits for the pharmaceutical industry, with projections indicating that the technology might be able to double the number of drugs reaching clinical trial. By enhancing the bioavailability of drug compounds, the latest nanoparticle engineering technology can reduce the quantity of API required to achieve the same therapeutic effect. This has wide-ranging implications, from reducing side effects for patients to facilitating the development of more environmentally friendly drug manufacture.

Studies have found that Dv50 ~350 nm API particles provide a 54% increase in the area under the curve (AUC) compared with Dv50 ~2 micron particles for Piroxicam which could translate to a 54% dose reduction. It is therefore expected that 50-100 nm API particles will display a 90% reduction in dose, which will significantly lower the quantity of API that is ingested by patients. It is also expected that this dose reduction capability will be highly relevant for BCS II and possibly also for BCS IV compounds, the two classes into which 70-90% of all drugs in development fall. This can help to reduce side effects for patients, and also reduce the cost of manufacturing.

Pharmaceutical companies have an increasing responsibility to adapt their processes as the industry moves towards a more carbon neutral footprint. Nanoforming can help the industry considerably in this endeavor by reducing the quantities of API that are manufactured. Moreover, the utilization of supercritical CO_2 permits a greener particle engineering process for the production of nanoformed APIs. With a production process that is free of excipients and organic solvents, the latest nanoforming technology is well positioned to decrease the environmental impact of drug development.

Not only does a significant reduction in dose through enhanced bioavailability imply patient and environmental benefits, it is also a novel way of improving manufacturing efficiency, of reducing volumes of drug substance and drug product manufacture, as well as manufacturing footprints and capital expenditure required for manufacturing. This is a step change that could enable major pharma companies to increase efficiencies in their supply chains by using such techniques.

Facilitating Novel Drug Delivery Routes

Shrinking drug particle size has exciting implications for drug delivery, opening up previously inaccessible routes. Ultimately, this results in the development of more effective treatments for patients. Enhanced pulmonary delivery is a prime example. While nanoparticles can be exhaled from the lung due to their low inertia, nanoparticle medicines can be coupled to a larger delivery framework of 1-5 µm or can be delivered in suspension as a pressurized metered-dose inhaler (pMDI) or through nebulized delivery. This enables drugs to be delivered into the periphery of the lung and can also facilitate systemic circulation of the drug following absorption from the lung into the blood. This is followed by a rapid onset of action, making it an appealing option for pharmaceutical developers. By facilitating transport of nanomedicines into the deep lung, a wide array of new opportunities can be realized for treatment of respiratory disorders. In addition, it is expected that if the particles were tuned to 10-50 nm size, they could become entrapped by the cells in the lung and not cleared effectively. This would therefore permit increased local delivery and potentially provide advantages for lung cancer treatments.

Nanoparticle engineering creates new possibilities for ocular delivery. A notoriously challenging target, drugs penetrating through the human eye must overcome numerous physical barriers such as the ocular surface epithelium and tear film. Nanotechnology can help to overcome the challenge posed by the natural barriers present in the human eye, offering benefits over nanocarrier technology — including high drug loading and increased adhesiveness to improve both transportation and retention of the drug formulation in the ocular sac.

Nanoforming and the Challenges of Tomorrow

One of the greatest challenges society faces is the dramatic increase in age-related diseases as a result of shifting global demographics. Indeed, the number of people in the world aged 60 years or over is expected to grow by 56% between 2015 and 2030. This will place an unprecedented demand on healthcare systems and requires the development of novel and more efficient therapies to treat age-related diseases.

Nanoforming technology will be critical for the delivery of these new treatments, as the innovation provides a number of benefits for elderly patients. For instance, enhancing bioavailability and lowering drug dosage can reduce the risk of adverse drug reactions (ADR). This is particularly important for elderly populations, as twice as many patients over the age of 65 are hospitalized due to ADR-related events when compared to younger people. Moreover, the smaller quantity of API also enables a significant reduction in the overall size of the tablet, which can help elderly patients suffering from xerostomia — difficulty swallowing caused by reduced or absent saliva flow — continue their drug regime.

Age-related diseases of the brain, including Alzheimer's disease, are also expected to increase with aging populations. Treating Alzheimer's disease still presents a great challenge to drug developers as drug delivery to the central nervous system (CNS) is limited by the blood-brain barrier (BBB). Nevertheless, research has shown an inverse correlation between nanoparticle size and successful penetration of the BBB. This indicates that advanced nanoforming technologies may permit the development of effective therapeutic options for Alzheimer's in the future.

Looking to the Future

Nanoparticle engineering increases the likelihood of successful drug development and provides multiple benefits to the pharmaceutical industry. With the invention of advanced nanoforming technologies capable of producing stable nanoparticles smaller than 50 nm by size, new opportunities for novel therapeutics and drug delivery applications have been introduced. Nanoparticle engineering is therefore an incredible example of the power of nanotechnology for advancing the field of medicine.

Edward Haeggström, CEO, and Albert Haeggström, CFO, Nanoform, Helsinki, Finland
edward.haeggstrom@nanoform.com
albert.haeggstrom@nanoform.com

https://nanoform.com

Chemical Process Research and Development

How a CRO Can effectively Work with Global Clients

Increasing demands for outsourced solutions has made contract research organizations (CROs) an important facet of the pharmaceutical landscape. Innovator pharma will regularly approach such organizations in order to meet their growing chemistry, manufacturing and controls (CMC) needs. When coupled with the globalization of goods and services, it is common for pharma to work with a CRO whose location could mean your research travels from Cardiff to California, or even Canberra.

For a CRO to efficiently meet the needs of its global customers, it is essential to overcome any logistical challenges. Vastly differing time zones and scheduling could therein prove a difficulty for some. Moreover, companies based around the world will need to comply with differing regulations. However, there are clear strategies that help negate these to ensure optimization through to product launch and life-cycle management.

Update, Upgrade and Upkeep: Regulatory Alignment

Staying on top of the multitude of regulations found throughout the world remains a key part of ensuring efficient business. These evolving regulations across multiple continents ensure it is vital that a CRO develops processes and uses products that comply to the country where its customer is based.

Moreover, simply aligning with one regional regulatory body, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), provides a limited coverage of the global standpoint on many new implemented rules. For example, as China is one of the main suppliers of active pharmaceutical ingredients (APIs) to the EU, it is paramount to ensure both the EMA and National Medical Products Administration (NMPA) are harmonious in manufacturing standards.

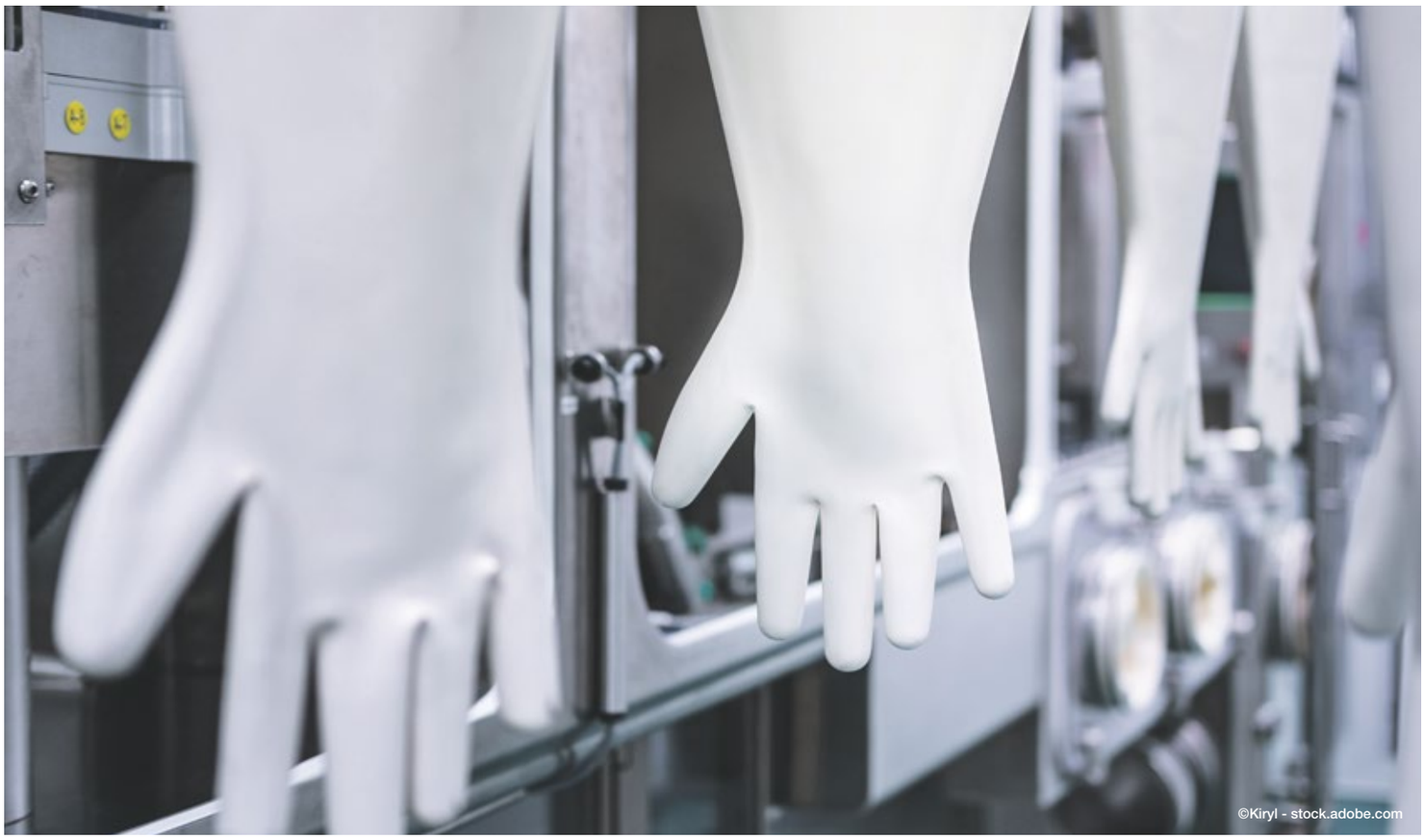
A CRO can ensure they remain at the forefront of regulatory information and trends in a range of ways. Attending regular compliance training, seminars and conferences are all essential, while signing up to newsletters and website alerts ensure a CRO stays a step ahead on anything applicable to a client's business.

The consequences of neglecting the upkeep of regulatory alignment can be incredibly damaging. Financial penalties and damage to a business's reputation are two possible consequences, with legal action and external audits also conceivable. Ensuring a partnership with a CRO who navigates the ever-changing environment of global regulations can prove to be crucial to negating potential problems like these.

Jas Douville, CatSci

Custom Services, High-quality Output

However, the geolocation of an organization is often not the key variable when it comes to fostering an effective partnership in a global landscape. Typically, an approach to a project will



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not be influenced by the customer's location, but instead by the company size and experience and expertise of its staff. Whereas a larger company may require a more streamlined approach, a less mature company with limited experience in a market may require more involvement and support from a CRO. Such support may go beyond technical advice and also include guidance on business development and regulations. The outcomes of such a partnership may vary — they could help to shape a smaller company and refine the capabilities of a larger one.

An important commonality for an effective partnership, no matter the size, experience or location, is communication. A consultative relationship enables a CRO to understand the objectives and challenges faced by a customer. This can be achieved through both the virtual world and real time. Connective tools and advances in digital technology enable instant access and regular updates, in addition to remote access. However, when possible, face-to-face contact can help to ensure that the needs of all companies are met. If conditions allow for physical presence, this can play an important step in building and maintaining client relationships.

Innovation and Location

The transfer of technology is another step that, when optimized, helps to provide an efficient service to global clients, and commonplace in the pharmaceutical industry. In the pharmaceutical industry, this term refers to a manufacturing process dissemination: taking the protocol from a CRO production site and implementing it in a scaled-up facility. This transfer still faces a number of challenges, especially with a global client base, to ensure speedy transitions overseas.

Companies based in different locations will often operate under different technological constraints. A CRO therefore needs to be adaptable and proactive in order to accommodate such differences. With the emergence of new routes to high-value products, promoting rigorous protocol updates is a key enabler to efficiency. Indeed, ensuring protocols are developed thoroughly is a key cost consideration, especially in the early stages of technology transfer. If the transfer of technology is neglected, the results achieved can differ between sites. To ensure that results are reproducible and concerns with cost are eased, a CRO should provide on-site support for the early stages of technology transition.

Worldwide Scientific Excellence

With the exponential growth of the pharmaceutical industry and the lines between CRO and company beginning to blur, the role of a CRO is constantly changing. To succeed in the global marketplace, both CROs and pharmaceutical industries alike are developing new global partnerships.

Driven by constantly updated regulations, many companies are now finding a common goal in environmental sustainability, alongside economically viability. No matter the locational or size differences, the pharmaceutical industry speaks the same language — chemistry.

As CROs are increasingly sought after to develop therapeutics that meet the evolving healthcare needs of the world, there is an increasing need for improved connectivity and finger on the pulse of global trends. CatSci, which has a global client base but undertakes the bench chemistry in Cardiff, UK, provides a vivid example of how this can be successfully achieved.

Jas Douville, Head of Business Development North America, CatSci, Cardiff, UK

enquiries@catsci.com
www.catsci.com

Building a Culture of Analytic Excellence

Design of Experiments: Why Do I Need Data Analytics?

Researchers, developers and engineers may question whether they have the capacity to adopt data analytics into their busy working lives. When there is always more to achieve than there are hours in the day, how is it possible to become an expert in data analytics as well? Colleagues and management teams do not always see the benefits of data either, happily entrenched in decision making based on a combination of subject matter knowledge, anecdotal evidence and traditional approaches to experimentation. The resistance to change can be overwhelming.

For those who have worked through the challenges and overcome the initial hurdles, however, the results can be transformational. With the right data analytics tools geared to the way scientists and engineers think about their data, tasks that previously took days, weeks or even months can be reduced to minutes and hours. The benefits include greater predictability, improved efficiency, and the freedom to focus on the next challenge. It is enough to make proponents of data analytics passionate about the possibilities.

Looking at the Data

One example is an experience I had while working on a root cause investigation for an issue with yield in a vaccine manufacturing process. The problem had been ongoing for some time, and analytics was almost the last resort for finding a solution. The various teams involved all had theories: The downstream scientists were convinced the problem was in the chromatography steps; the upstream scientists thought a raw material change was the culprit; the lab people didn't think it was their fault because they had made some improvements to analytical testing at around the same time. The operators running the process had noticed some changes, but no one was listening to them. The organization had reached an impasse.

The decision was made to gather the data and put it into electronic format, then begin to apply analytics to uncover the best way forward. By looking at the data and acting on what it revealed, rather than searching for evidence to support existing theories, the organization achieved a break through. The early results of the analysis changed everything and the whole investigation turned at that moment. The data helped all to focus. Analytics allowed the teams to build consensus and to start listening to the process technicians and what they had been trying to tell them all along.

In this kind of situation, it is often those who shout loudest who get heard. Data analytics can help to level the playing field and allow members of the team to relinquish erroneous beliefs that may be holding the whole operation back. By trusting the data and allowing analytics to be a "myth killer," greater advances come within reach.

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Julia O'Neill, Direxa Consulting

Demonstrating Success

Solving a high-profile problem for your organization will certainly raise the profile of an analytics approach. People should take risks and tackle the big problems with data analytics, rather than the projects that allow them to hide. High-profile projects are more likely to get resourcing and management attention, which in turn help to drive momentum and organizational change when people start to see the results.

In the vaccine manufacturing example mentioned earlier, the problem with yield had been ongoing for 2 years and was solved in 3 weeks once the data was available. There are many other examples of massive reductions in total development time — the total time it takes to reach a stated goal — achieved through data analytics. The scale of change may be dramatic. The resulting freedom to innovate, to move on to solving

JMP Webinar

Julia O'Neill has more than 30 years' experience using statistics and chemical engineering to solve problems in chemistry, vaccines, biologics and pharmaceuticals. In a free webinar on May 5, 2020, she will give an introduction for scientists, engineers, product development team leads and portfolio managers who are interested in how practical strategies for stability assessment can support accelerated commercialization timelines for drug products. To attend the presentation, please register here:

bit.ly/2JAMMHm

other problems, to adopt proactive approaches rather than reactive, can make all the difference to the motivation levels of the teams involved. Data analytics can cut the time required for research and development, helping R&D to support twice as many products, and bring them to market twice as fast. And because knowledge accumulates, researchers can innovate more predictably over time.

Building Momentum

The clarity and certainty of data-driven decision making can transform the outlook of a team and help to drive a problem-solving culture based on analytics excellence. There may be an initial investment of time required to plan the approach, but if data is available in electronic format it can be used and analyzed effectively. It is only by starting to ask questions of your data that you can understand whether you have the right data in the first place.

It is also advisable not to use lack of data availability as an excuse. The results can quickly convince colleagues, teams and the wider organization that there are significant time savings and cost reductions to be achieved if they embrace new techniques. Sometimes it can be the production of a single compelling graph, or an interactive visualization of the problem, that helps generate consensus. Data analytics can help to focus the team and deliver the certainty and predictability to reassure the wider organization. It can also reduce the stress levels of the individuals involved, leading to a more productive, fulfilled team able to reach its potential.

"The resistance to change can be overwhelming."

Achieving Scale

Delivering results and solving high-profile problems can rapidly generate interest from the wider organization. Management and leadership teams will want to understand how to capture the value of a data analytics approach once they start to see its positive impact. Scaling data analytics to help transform an organization requires the right tools. Selecting a tool that guides non-statisticians through appropriate ways of analyzing their data helps to ensure the willing adoption of new ways of working. In a head-to-head comparison, a tool designed around the way scientists and engineers think about data in the first place is a winning choice. Avoiding a silo mentality is also crucial. By enabling researchers and developers to conduct their own analysis, organizations can scale from the ground up. By putting data analytics capabilities into the hands of the subject matter experts — those who understand the data, its origins and its quality — organizations can scale capabilities more rapidly to meet the growing demand for analytics excellence.

Julia O'Neill, Founder and Principal Consultant, Direxa Consulting

julia@direxaconsulting.com

Local Injection, Global Impact

Vaccines Protect the Lives of Millions, but Developers and Manufacturers Are Facing Several Challenges

The worldwide spread of the corona virus shows once again that despite all technological progress, humanity is still exposed to health risks. The biotech and pharmaceutical industry often succeeds in developing protective vaccines against such diseases. However, the companies take a high economic risk and have to comply with strict requirements. View of an industry that plays by special rules.

It all started very small on the fish market in the Chinese city of Wuhan. When the first reports of a new type of virus made their way into the media in early January 2020, only a few suspected that it would develop into a global health challenge. At the latest when the first people fell ill with the new corona virus (image page 25) in a Bavarian company, when Italy cordoned off whole villages and areas of land and the stock markets worldwide collapsed, it was probably clear to most that this was much more than just a local fish market affair.

With the rapid spread of the corona virus, the question also arose of how mankind could protect itself against this threat. The ideal would be prophylactic vaccination. But it could take a year or two before this is developed and approved — in the best case.

Time and again, infectious diseases take hold of humanity, often resulting in thousands or even hundreds of thousands of deaths. Smallpox and measles have taken a heavy toll for many years. According to the German Robert Koch Institute, 290,000 to 650,000 people succumb to influenza, which regularly afflicts large parts of humanity, every year.

Eradication Through Vaccination

On the other hand, numerous diseases have been completely or largely eradicated through consistent vaccination. The last cases of smallpox were recorded in Somalia in 1977, the last case in Germany was reported in 1972. Measles has also been largely eliminated by widespread immunization.

Other infectious diseases, however, are persistent, such as the annual influenza or „real“ flu. The World Health Organization (WHO) even warns of an influenza pandemic, i.e. a wide distribution on several continents simultaneously: „The world will face another influenza pandemic — the only thing we don‘t know is when it will hit and how severe it will be.”

To protect against the flu, the vaccine is adjusted annually. For example, the Paul Ehrlich Institute (cf. page 26), which is responsible for vaccines in Germany and monitors their quality, efficacy and safety, has approved a number of influenza vaccine products for the 2019/2020 season for strain adaptation.

The Chikungunya virus poses a threat of a different kind. It is transmitted by Aedes mosquitoes such as the Asian tiger mosquito and leads to Chikungunya fever in humans. The virus is mainly found in the tropics and subtropics. Since the Asian tiger mosquito now also occurs in Germany, a further spread of the virus must also be expected here.

Nothing Protects Better Than Vaccination

We can keep our distance, sneeze into our arms, wear face masks or disin-

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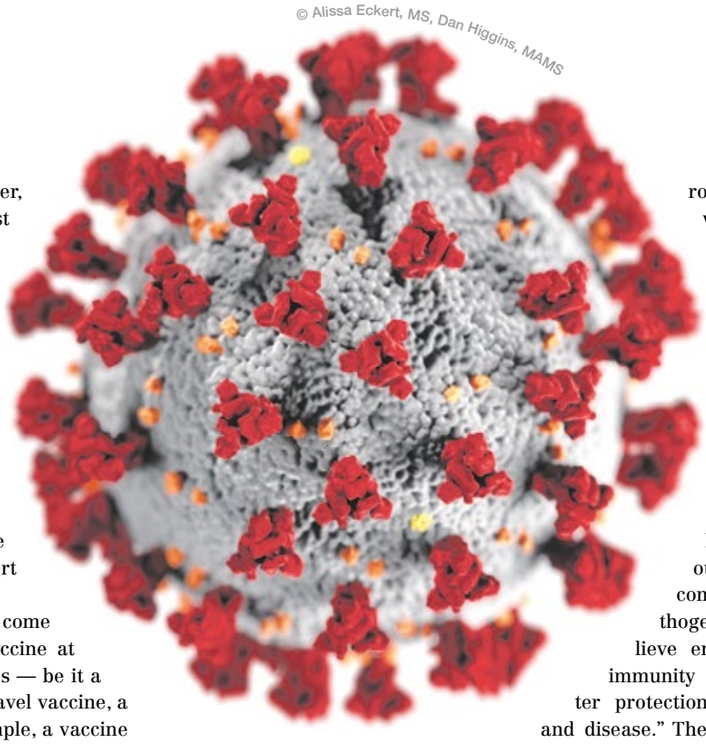
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fect our hands. However, nothing protects against a viral infection as effectively as vaccination. „Vaccinations are among the most important and effective preventive measures available in medicine. Modern vaccines are well tolerated and adverse drug reactions are only observed in rare cases," says the Robert Koch Institute.

In fact, most people come into contact with a vaccine at some point in their lives — be it a childhood vaccine, a travel vaccine, a flu vaccine or, for example, a vaccine against cervical cancer.

Vaccines can be divided into different classes: Live vaccines use attenuated pathogens as carriers, which are equipped by the researchers in such a way that the immune system is feigned to be infected, thus creating immune protection. In this way, for example, a vaccine against Ebola has been developed. In turn, dead vaccines are based on inactivated pathogens. There are also gene-based vaccines. They try to activate the body to produce viral proteins that build up immune protection. Such vaccines are not yet on the market, but could possibly be produced quite quickly.

The development of a vaccine poses particular challenges for biotech and pharmaceutical companies. On the one hand, the preparations should be available quickly after the appearance of a new pathogen. At the same time, the quality requirements for vaccines are particularly high. Since they are usually administered to healthy people, vaccines should have no or only minor side effects. The starting position is therefore completely different from that of oncological products, for example, where considerable side effects are accepted if the patient simultaneously receives a survival benefit from the product.

Furthermore, some vaccines are real multi-purpose weapons that immunize against several diseases with just one injection. Producing a vaccine that is effective against 13 different serotypes, for example, to prevent infection with pneumococci is a challenge: „It's like making 13 different vaccines. The production process is divided into 581 individual steps," says the pharmaceutical company Pfizer.

Development In Stages

The development of a vaccine is a multi-stage process. First, the virus has to be analyzed and the question needs to be answered what of it causes immune reactions. The next step is the design of the active substance: which parts of the virus and which additives should be contained in the substance? Finally, the vaccine candidate has to be first tested on animals and then on humans.

However, the development and production of a vaccine is also an economic challenge. Vaccine manufacturers run the risk of developing and producing in the void. Once a vaccine against a new type of viral disease has been developed to market maturity, it is possible that the virus is no longer virulent and hardly anyone will need the vaccine. The companies can produce in stock or for government-guaranteed quantities; it is also possible that the virus will come back to life in a year or two and the vaccines will then be needed. But a solid business base looks different.

In the past, the high demands on vaccines have led to many companies withdrawing from this business. Globally, the vaccine market is now dominated by a good dozen companies, including GlaxoSmithKline (GSK), Merck & Co, Sanofi and Pfizer. GSK confidently claims to be one of the largest suppliers of vaccines worldwide: „We develop, manufacture and deliver more than two million doses of vaccine every day to people in 150 countries." The portfolio comprises approximately 40 vaccines, including preparations that protect against pneumococcus, meningitis, hepatitis, rotavirus infections, whooping cough and influenza.

The much smaller US company Novavax, however, argues with the strengths of its technology. „Our carefully designed genetic constructs allow us to tailor our vaccines to key components of pathogens, which we believe enhances functional immunity and leads to better protection against infection and disease." The company also relies on speed in development: „Unlike traditional influenza vaccine manufacturing, we do not need to grow an actual influenza virus, obtain embryonated chicken eggs, adapt the virus or optimize new strains to grow in eggs. This 50-year old method requires four to six months lead time to produce a new strain of virus and significant investment in fixed production facilities."

But the best vaccines are of no use if they are not taken. The WHO sees a great danger especially in the refusal of some to vaccine: „Vaccine hesitancy — the reluctance or refusal to vaccinate despite the availability of vaccines — threatens to reverse progress made in tackling vaccine-preventable diseases". Vaccination, according to the WHO, currently prevents 2-3 million deaths a year. This value could be increased. If global coverage of vaccinations improved, a further 1.5 million could be avoided, according to the international health authority.

Currently, all hopes rest on the development of a coronavirus vaccine. This could also save the lives of many people.

Read the interview about vaccine research on page 26

Universal Influenza Vaccine Clearly a Strategic Goal

Interview with Klaus Cichutek, president of the Paul Ehrlich Institute

The Paul Ehrlich Institute is the German federal institute for vaccines and biomedicines. Klaus Cichutek has been president of the research institution and medical regulatory body since 2010. He earned a doctorate in biochemistry, is associate professor of biochemistry at the Johann Wolfgang Goethe University in Frankfurt and a member of numerous scientific and medical committees. We asked Klaus Cichutek about the vision and goal to develop a universal influenza vaccine.

Klaus Cichutek, Paul-Ehrlich-Institute

CHEManager: Professor Cichutek, many vaccines are still being developed using chicken eggs. Is this process still up to date?

Klaus Cichutek: The manufacture of vaccines using chicken eggs or chicken fibroblasts is an established and proven process. Not every virus can be propagated in every cell culture system and the quality-assured manufacture as pre-defined in detail is an important part of the marketing authorization of each vaccine product. Therefore, it would not be appropriate to modify the production process of vaccines that are effective, of high quality and safe to use. In the case of influenza viruses, there is now also a cell culture vaccine. However, this represents a new development with its own specific marketing authorization, not a product variation.

Most established virus vaccines rely on other cell culture systems, such as human diploid or animal cell cultures. In addition, there are new approaches — so-called vaccine platforms — based on genetic material (RNA, DNA) or gene vector-based concepts such as the Modified Vaccinia virus Ankara (MVA) or attenuated measles virus, which are used to inoculate the genetic material of relevant and innocuous virus proteins. These three platforms (DNA, RNA and vectored vaccines) are also used by the currently most advanced developments against SARS-CoV-2.

What are the current major challenges in the development of new vaccines?

K. Cichutek: In vaccine development for the prevention of infectious viral diseases, some important prerequisites must be met. First of all, antigen structures (usually surface proteins of the pathogen) must be identified that mediate the induction of a protective immune response and remain conserved so that changes in the pathogen surface, such as those that constantly occur in influenza viruses during a season, do not lead to a loss of efficacy.

Prior to the first clinical trial it is tested in animals, whether the chosen antigen(s) or the gene(s) encoding the antigen(s) will mediate a specific immune response (immunogenicity). This means that they must not only trigger antibody formation, but also a sustained protective effect through the formation of neutralizing antibodies. Neutralizing antibodies inhibit virus spread in the body by inhibiting the entry of new viruses into additional somatic cells. In order to induce a real protective effect and the formation of these neutralizing antibodies, inactivated vaccines and vaccines consisting of purified or recombinant single pathogen components require a formulation including adjuvants as potentiators of the immune response. This applies to vaccines against viral diseases such as e.g. influenza, tick-born TBE and Japanese encephalitis. Attenuated live vaccines, such as those against measles, mumps and rubella, do not require adjuvants.

Manufacture under conditions of „Good Manufacturing Practice" (GMP) must consistently result in and identical vaccine product, and ideally be fast and cost-effective.

As with all vaccines, local and systemic tolerability and the possibility of use in groups of persons particularly vulnerable to the infectious disease must be ensured. Ideally, the protective effect should also last for many years.

Which diseases pose particular challenges for vaccine developers?

K. Cichutek: With regard to the development of vaccines against SARS-CoV-2 infection and Covid-19 disease, it has been shown based on the experience gained during the development of vaccines against MERS coronavirus that neither inactivated adjuvanted vaccines nor live attenuated vaccines will be the preferred vaccine types.

To date, attempts to develop vaccines against for example human immunodeficiency virus HIV, hepatitis C virus (HCV), but also against novel pathogens such as Zika viruses and West Nile virus, have been less successful. The same applies to a universal influenza vaccine.

Initial successes with the new vaccine platforms have been achieved for Dengue and Ebola. Still, these vaccines are still under surveillance because open questions remain.

You mentioned the universal influenza vaccine. How far has development progressed in this area?

K. Cichutek: The development of a universal influenza vaccine is clearly a strategic goal, also of the WHO. Initial approaches are in the preclinical trials stage, and at least two vaccine concepts are in the first stages of clinical trial development. However, there is still no approach that seems to provide both very long-term protection and protection against „all" possible variants or strains of influenza virus. All current approaches seem to solve only one of these two problems — which would still be an important first step. Cautious optimism is therefore permitted in this matter.

CHEManager INTERNATIONAL

INNOVATION PITCH

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Software Tools Help Chemical Plants Adopt Advanced Analytics

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Analytics Software for Chemical Plants

Powerful Software Tools Help Chemical Processing Plants Adopt Advanced Analytics

Chicago, Illinois-based start-up company 6C Solutions has developed a data platform that integrates IOT and contextual data at chemical plants. Founded in 2019 by Keerthan Vantakala, who was joined shortly thereafter by Zak Kann, the company wants to help plant owners and operators raise their processing plants further up the analytics value curve. We asked the founders about their motivation to start a company, their technology and their goals.

Keerthan Vantakala, 6C Solutions

Zak Kann, 6C Solutions

CHEManager: You founded 6C Solutions about one year ago. How did it all start?

Keerthan Vantakala: The idea for the initial version of 6C came up after I already made the switch from working as a chemical engineer to being a data analytics consultant. I was teaching myself how to code and learning new tools. As I was being exposed to these new technologies, I kept thinking of how they could be used in a plant setting. This idea just stayed in my head and I finally acted on it a bit over a year ago. I started calling up old co-workers and pitched them what I wanted to build, ultimately cold-calling plants to see if I could get a meeting with the plant manager. I had a few positive meetings and that's all the motivation I really needed to quit my day job and pursue the venture.

What does 6C actually stand for?

K. Vantakala: Initially, it was supposed to be named C6 Analytics, which was going to be a play on Carbon being the 6th element. Turns out a lot of other people had a similar idea. Branding is not my expertise so at that point I just wanted to pick something and move forward, ultimately, I chose to just reverse C6 to 6C.

What is the USP or differentiating feature of 6C Solutions?

Zak Kann: What differentiates 6C Solutions from all the other analytical platforms for plants is the attention we put into contextual data. Not only do we integrate with the majority of other software used at chemical plants, but we also put an emphasis on creating tools that easily capture operators & engineers feedback. This feedback can be anything from the classification of an event that occurred to textual notes. This allows us to build relationships among the various data sources that a plant has, as well as start to curate labeled data sets. These labeled data sets are the key to creating more effective machine learning and artificial intelligence tools for the plants.

How has the response from the processing industry been so far?

Z. Kann: So far, the response from the chemical industry has been positive. Although we are still early in our start-up cycle, the companies we have given demos to and that are using our tool at the moment have given us very interesting feedback. We are taking all that feedback and are about to release our first non-beta version!

How easy is it to start up a company in the US, what kind of support did you receive to venture into your entrepreneurial career?

K. Vantakala: Starting a company in any country is difficult. We are both first-time founders and have run into many challenges as we move 6C forward. We have received a lot of support from various individuals as well as entities. Before Zak joined 6C, I went through the Iowa Startup accelerator, which was key in helping build the foundation. At that point all I really had was a sketch and a PowerPoint presentation, they helped me ensure I was taking the right steps to actually build the start-up. We recently went through the 5-HT program in Mannheim, Germany, and met numerous helpful individuals. The biggest thing in terms of support was learning to make the ask. Most people want to help if you put yourself out there and ask for it, I believe you will be surprised by the response!

What will be the next steps to develop 6C Solutions?

Z. Kann: We are about to release the first non-beta version of our app for the ethanol industry in the US and we are currently working on getting test clients for the waste-water treatment and the chemicals & pharmaceutical industry. Apart from that it's a lot of listening to our clients and figuring out how we can help them!

Personal Profile

Keerthan Vantakala, CEO, is a chemical engineer with experience in big data analytics. He has worked as a chemical engineer, big data consultant for fortune 500 companies, and on an analytics operations team for an Ad-Tech company before founding 6C Solutions. After seeing firsthand the amount of manual analysis done at chemical plants, he saw an opportunity to leverage his experience to build tools that allow engineers and operators to spend less time making sense of data and more time taking action on insights.

Zak Kann (CTO) received his PhD in chemistry from the University of Wisconsin - Madison with a focus in molecular simulations and spectroscopic and time-series analyses. Since then, he has worked as a data scientist in the advertising and travel industries. His primary passion is making the integration between the real world and the information world as seamless and intuitive as possible. He joined 6C Solutions because the company's vision brought together his background in chemistry and sensors with the data-in-context approach that he believes is the future of data science.

Business Idea

Modern Analytics Technology for Chemical Plants

6C Solutions is creating analytics applications that increase productivity and profitability at chemical plants. Rather than replace a plant's current software, the company's tools aim to integrate with and merge data from these software sources. Below are a few example of the type of tools 6C is creating:

The **Experimentation** tool has two main benefits:

- Allows an engineer to easily quantify process changes without the need for manual data extraction, cleaning and analysis.
- Uses detected correlations to create and suggest experiments that maximize the likelihood of large process improvements

The **Batch Analytics** tool connects data from a historian, LIMS, and any other data source to give engineers and operators a holistic view of every batch. Batch quality is indicated via a predictive 'batch grade' that tells you what batches are likely to need the most help. The application also allows one to compare the current batch to historical ones and ensure all metrics are in line with where they should be.

The **Alarm/Downtime Recommender** tool helps ensure operators to have the information they need to quickly troubleshoot the issue when an alarm is triggered or a downtime event occurs. To aid in this 6C created a tool that users machine learning to match real time data to historical trends to compare the current alarm/downtime event to past events and provide a recommendation for what the issue may be. This tool also aids in 'alarm overload' by recommending changes to or deletions of alarms that are typically false or non-actionable.

6C currently sells its tools directly to plants as well as via 3rd party integrators. Another avenue 6C is currently exploring is partnering with OEM's and other vendors to create a white labeled analytics application that they can offer to their customers.

- 6C Solutions
  www.6csolutions.com

The Experimentation tool by 6C allows an engineer to quickly analyze results of any chemical trial or process changes across the entire plant.

Elevator Pitch

Data Analytics Consulting and App-Building Services

6C Solutions is building applications to increase advanced analytics adoption and collaboration at chemical plants. The start-up company has developed a data platform that integrates IOT and contextual data at chemical plants to help plant owners and operators to push their processing plants further along on the analytics value curve.

Milestones

2019

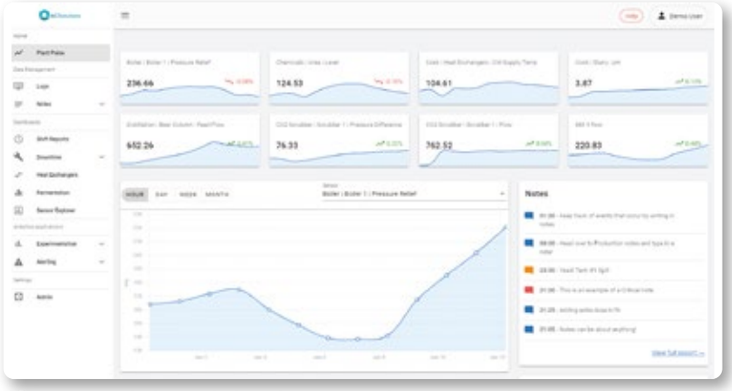
- Foundation of 6C Solutions by Keerthan Vantakala (CEO)
- Participation in Iowa Startup Accelerator
- Zak Kann joins 6C Solutions as co-founder and CTO
- 6C releases beta platform

2020

- Further development of tools and applications
- 6C releases its first non-beta version for the US ethanol market
- Participation in the 5-HT X-linker start-up boot camp for digital chemistry & health, Germany
- Expansion into waste water treatment, chemicals, oil & gas and the pharmaceutical industry

Roadmap

6C is in the early stages of getting traction within the industry, thus the start-up's roadmap is malleable at the moment, especially given the current economic climate. The founders have been starting with the ethanol and wastewater treatment industries in the US but are ensuring all of the tools and applications they develop can be used in any industrial process. The next step is to expand into oil & gas, pharmaceuticals, chemicals and food manufacturing 6C is currently working on getting test clients for the wastewater treatment and the chemicals and pharmaceuticals industry.



6C has been starting with the ethanol industry and plans to expand the use of its tools into oil & gas, pharmaceuticals, chemicals and food manufacturing.

In February 2020, 6C Solutions (K. Vantakala front row far right) participated in the 5-HT X-linker start-up boot camp for digital chemistry & health, Germany.

Bridging the Gap between Virtual Planning and Reality

Industrial Augmented Reality Solutions for Engineering and Manufacturing

Founded in 2015, the rapidly growing start-up company Holo-Light has garnered a great deal of industry attention so far. Holo-Light is a pioneer of the augmented reality (AR) revolution. The AR expert offers software and hardware solutions to improve engineering workflows — focusing on factory planning, plant design, prototyping and quality control. Florian Haspinger, CEO and co-founder of Holo-Light, speaks about the beginning and growth phase and the future goals of the start-up.

CHEManager: Holo-Light was founded 5 years ago. How did it all start?

Florian Haspinger: We founded Holo-Light at a time when augmented reality was still new in the industrial sector. A big step was the announcement of Microsoft´s first AR smart glasses HoloLens. We saw a huge potential for industrial use, managed to get a device quite early and used this market advantage to build first solutions. With our engineering background we also knew first-hand where the challenges lie. We decided to bridge the gap between virtual planning and what is ultimately real.

Besides being pioneers, what are the differentiating features of Holo-Light?

F. Haspinger: Our augmented reality engineering space (ARES) enables engineers not only to visualize their own CAD files — including the whole hierarchy level — but also to manipulate and work collaboratively on them. With interactive streaming for augmented reality (ISAR) we also created a way to visualize large amounts of 3D data in real size — for example, a large chemical plant. Our software solutions are complemented by Stylus XR, the most precise AR input device on the market. It allows engineers to perform millimeter-accurate work, measurements and movements in an AR environment.

Florian Haspinger, Holo-Light

How has the response from the chemical industry been so far?

F. Haspinger: Without the feedback from the chemical industry, we would not have the solution we provide today. In one project we simulated the behavior of different plastics and faced the challenge to visualize high volumes of data. This triggered us to develop our remote rendering solution ISAR. The close cooperation with industry players helps us to create added value. And we want to develop together with the companies, not over their heads.

What have been the most exciting projects?

F. Haspinger: A flagship project is how BASF uses our AR software and digital twin to significantly reduce time and material cost in factory planning processes. The planning of complex assemblies on 2D screens can be tricky: The digital plan and reality oftentimes diverge. By means of AR, BASF visualizes and manipulates envisaged pipework and assemblies directly on site. This allows engineers and planers to determine on the spot whether everything is in order or further modifications are needed. "What if" testing scenarios also give them a better understanding of their projected designs.

What will be the next steps to develop Holo-Light from a start-up to an established company?

F. Haspinger: We have a very good technological basis and are now working more and more towards scalability. With the help of our investors, we can strengthen our support structure and distribution channels in order to bring our software even faster to the customer and deliver updates to them quickly. And with Microsoft´s HoloLens 2 recently released, we also incorporated new exciting features in our solution for a very intuitive AR experience.

With Stylus XR engineers can perform highly accurate operations in AR like the precise marking and measurement of objects.

Personal Profile

Florian Haspinger, CEO of Holo-Light, born in Tyrol, studied physics at the University of Innsbruck before specializing in aerospace engineering in his master's degree. He has a fable for computers and loves to write software programs in nearly every kind of computer language. Together with his fellow students Susanne Haspinger (COO), Alexander Werlberger (CTO) and Luis Bollinger (CMO) he founded Holo-Light in 2015.

BUSINESS IDEA

Redefine Engineering with AR

How to overcome the barriers between people and technology? How will engineers work in the future? And what new possibilities does augmented reality (AR) offer in factory planning, plant design, prototyping, and technical education? These questions were asked by the German start-up Holo-Light. Consequently, the AR player developed one of the most collaborative AR software suites to efficiently cut costs and improve engineering workflows.

The augmented reality engineering space (ARES) enables engineers to visualize and interact with 3D CAD data in an AR environment — leading to better planning processes, shorter development cycles and seamless product designs. Engineers or industry designers can securely import all their CAD files into the software and can visualize them in the real world with a head mounted device like Microsoft´s HoloLens 2.

Furthermore, the AR workspace enables tight collaboration. Any team member can dial into an AR session and see the exact same model just as all other viewers can. This is not only useful for prototyping or factory planning. Sales or Marketing departments can also use the multi-user mode for presentation purposes.

With interactive streaming for augmented reality (ISAR) Holo-Light also created a remote rendering solution to visualize data-intense content via local or cloud processing power. In real size and time, with every detail, and without using polygon reduction. A software development kit (SDK) also allows other companies and developers to stay in control, while crafting their own bespoke remote rendering AR solution.

Holo-Light's software solution package is complemented by Stylus XR, an AR input device with artificial-intelligence-based tracking technology. Allowing engineers to perform millimeter accurate operations in AR like the precise marking and measurement of objects. It is also possible to sketch and design fully interactive 3D holograms, using the environment as a personal canvas.

■ Holo-Light GmbH, Ismaning, Germany
www.holo-light.com

HOLO-LIGHT

ELEVATOR PITCH

AR Expert with Strong Partners

Founded in 2015, Holo-Light operates out of their primary offices in Munich, Germany, and Innsbruck, Austria. The company´s mission is to develop the industrial Augmented Reality workspace for enterprises and market leaders; optimizing and simplifying their engineering performance, leveraging industrial data, and generating competitive advantages in the age of digital transformation. The AR expert has received numerous awards both in Europe and across North America for its continued success in improving Augmented Reality through cutting-edge technologies in both hardware and software sectors. Major customers are BASF, Festo, TÜV, Magna and BMW.

Milestones

2015
- Foundation of Holo-Light

2017
- Launch of first AR software product Holo View
- Holo-Light joins Microsoft´s Mixed Reality Partner Program

2018
- Nominated for the Austrian State Prize for Innovation
- New Investor Innogy Innovation Hub
- Launch of AR input device Holo-Stylus
- Holo-Light wins German Innovation Award
- Named community prestigious AWE Auggie Award Winner

2019
- Winner of BAUMA Innovation Award
- Cooperation with Deutsche Telekom's tech incubator, hub:raum
- Holo-Light receives €4M Series A financing
- New lead investor EnBW New Ventures

Roadmap

2020
Microsoft HoloLens 2 global roll out
- New augmented reality engineering space (ARES) software suite
- Launch of next generation AR input device Stylus XR
- New interactive streaming for augmented reality (ISAR) remote rendering solution

2021
- Start of Series B funding round

Holo-Light founding team (from the left): Michael Oberlechner, Alexander Werlberger, Susanne Haspinger, Florian Haspinger, Luis Bollinger.

Collaborative plant planning in the chemical industry with augmented reality: Time and material cost can be saved by this progressive way of AR-collaboration.

Smart Tools for Chemical Research

Speeding up Research Discovery with Artificial Intelligence

Iris.ai was founded at Singularity University at NASA Ames Research Park in 2015. Challenged to come up with an idea that would positively impact the lives of 1 billion people, the team was formed and problem areas were explored. What sounds like having put the cart before the horse turned out to be a brilliant strategy for this company working to have machines make sense of written scientific content for us. According to Fast Company, Iris.ai is the world's first AI researcher and was named one of the Top 10 Most Innovative Companies in AI in 2017. Michael Reubold met the founders.

Anita Schjøll Brede, Iris.ai

Victor Botev, Iris.ai

CHEManager: Iris.ai was founded 5 years ago. How did it all start and what was there first: the idea or the company?

Anita Schjøll Brede: A balanced and dedicated team of A-players, in our view, is the most crucial and important factor in a start-up, and that was where we started! The fundamental problem we then decided tackle is and was simple enough: we have an unprecedented and exponentially growing body of scientific knowledge, but it is too much for humans to make sense off — so we need smart machine systems to help.

Why did you pick the name of the Greek messenger goddess for your firm?

A. Schjøll Brede: We thought of Iris.ai as a messenger bringing important knowledge from powerful beings — such as researchers — into the right hands, at the right time.

What is the USP or differentiating feature of Iris.ai?

Victor Botev: We allow smart leverage of the knowledge in millions of scientific text documents: without pre-indexing and any other substantial training by humans. This allows our users to do things like: finding new application areas for their existing compounds; extract all key data from a set of documents; build smart knowledge graphs from their own written expertise; and do superior literature searches.

Which obstacles did you have to master so far?

A. Schjøll Brede: Obstacles we have had to master include attracting top-level talent, which we have been able to do both by unifying around a big vision, and by being a remote team where we will hire people wherever they are — especially for Machine Learning engineers, because it allows us to find people who would prefer not to move an AI hub. We've also had to work hard to attract VC funding: it becomes extra hard when you receive a lot of attention so everyone wants to talk to you, but you work with complex technology in a complex industry so no one really has you as their core investment thesis. Luckily, we have managed to build an incredible team who stands by us founders in thick and thin, and can pull of absolute miracles when needed!

What have been the most exciting projects so far?

V. Botev: We are right now working with a great client on an extraction tool for key data from patents. It is so satisfying to work in proof of concepts with companies where they know very well what needs they have and what problem they want to solve but recognize that building it themselves is outside the scope of their core expertise. We won the proposal and have been working for 8 months on the project; now we're getting close to completion and seeing the client happy because they get exactly what they wanted from a very challenging technical task is very exciting.

In a broader perspective, we were recently announced as a Top-10 semi-finalist in the "AI for Good" XPRIZE, which we have been competing in for more than four years. It has been amazing to go through the judging stages and see that our research, our technology, its impact, and our team, has been repeatedly vetted and deemed solid, sound and contributing to the field of Artificial Intelligence. It is such an accomplishment by our researchers!

What will be the next steps to develop Iris.ai?

V. Botev: We need to find more of the brilliant and forward leaning chemistry companies to work with and get our smart tools to full scalability! We thoroughly enjoy exploratory discussions with potential new clients.

Personal Profile

Anita Schjøll Brede is CEO and Co-Founder at Iris.ai. She is also Faculty in AI at SingularityU Nordic. Forbes claims she's among the world's top 50 women in tech. The past decade her career has spanned 10 industries including developing an e-learning tool in Silicon Valley, reducing energy consumption in the process industry, facilitating solar light business in Kenya and trying to disrupt the recruitment industry. She also dropped by six universities on the way. And built a race car.

Victor Botev is the CTO and Co-Founder of Iris.ai, previously a researcher from Chalmers University of Technology. He studied individual master's degrees in Artificial Intelligence and Computer Systems and Networks at Sofia University St. Kliment Ohridski and Chalmers, respectively. At Chalmers, he conducted research on clustering and predictive neural network models and the usage of signal processing techniques in studying Big Data. He has put his unique combination of AI research, software development lead and ambitious vision to the ultimate test at Iris.ai.

Business Idea

The AI Chemist

Over the past five years, Iris.ai has built an award-winning Artificial Intelligence/Machine Learning engine for scientific text understanding. Now, it has been trained and specialized in chemistry research. That allows the Oslo, Norway-based start-up to build a new suite especially for the chemical industry.

Iris.ai is offering smart tools for Chemical R&D, allowing researchers effortless leveraging of information from millions of documents; research papers, patents, internal documentation etc. The smarter literature search tool 'Discover' allows users to visually map out all papers, patents and other documents related to their research question. Teams using this tool are scientifically proven to outperform teams using keyword-based search tools on overview, spot-on papers found, and conclusions drawn.

The 'Identify' tool helps users find new applications for their chemicals, materials or compounds, by scouting millions of interdisciplinary, unstructured documents. This systematizing of serendipity is simply not possible with only human brain power and can open up new revenue opportunities for the company.

The 'Extract' tool automatically extracts key data from patents, papers and other scientific literature. At 90% accuracy, two full person-months of tedious labor can be automated down to a few hours performed by a machine.

The core engine is based on recent years' breakthroughs in AI, Machine Learning and Natural Language Processing. The algorithms deal with scientific text understanding:

- Similarity: proprietary WISDM metric measuring how similar two pieces of text are.
- Compositionality: on word level or text piece level, to identify parent/child concepts.
- Causality: advanced knowledge graph connections and basic reasoning to determine causal relationships.
- Corresponding ranking metrics: to give contextually fitted results.

The Iris.ai Chemistry engine can also be used to make custom fitted tools from the modular system.

■ Iris.ai, Oslo, Norway
www.iris.ai

IRIS.AI

Elevator Pitch

An Ambitious Team

Iris.ai was founded at Singularity University at NASA Ames Research Park in summer 2015. Challenged to come up with an idea that would positively impact the lives of 1 billion people, the group soon found a common frustration with the access to and passion for the value of scientific knowledge. The founders spent the next four years building a core AI engine and a suite of tools for academic researchers, which has been successfully deployed at University libraries across the Nordics, before taking on the next challenge: specializing the machine on chemistry research and building more pointed tools for industry. All of this leads Iris.ai toward the final goal: «The AI researcher», an AI system that will become an invaluable team member of any human research team in the future.

Milestones

2015
- Iris.ai was founded at NASA Ames Research Park.

2016
- We were admitted to 500 Startups in the Nordics, launched our first simple tools, attracted the first round of angel financing and joined the AI XPRIZE competition.

2017
- Iris.ai was announced by Fast Company to be among the world's Top-10 most Innovative companies in Artificial Intelligence, the start-up was admitted to Founders Factory in London, and the WISDM paper was published.

2018
- The scalable tool suite for University Libraries was ready, the first full licenses were sold and the Scithon paper was published.

2019
- The decision to focus in on Chemistry was made, the first tools iterated, and the first Proof of Concept clients from the Chemical industry were onboarded.

2020
- Iris.ai was announced as a Top 10 Semifinalist in the AI XPRIZE.

Roadmap

2020
- Sign on an additional limited number of Proof of Concept clients to co-design unique tools.

2021
- Commercial Chemistry tools ready to be scaled with SaaS licences.

2025
- Learnings from Chemistry and other specializations re-generalized, and birth of the first version of the fully fledged AI Researcher.

Iris.ai was founded at Singularity University at NASA Ames Research Park in 2015. Challenged to come up with an idea that would positively impact the lives of 1 billion people, the team over the past five years has built an award-winning Artificial Intelligence/Machine learning engine for scientific text understanding.

Specialty & Agro Chemicals America

On July 28-30, 2020, Specialty & Agro Chemicals America, to be hosted in Charleston, South Carolina/USA, focuses on the chemical products and technologies that have specific applications for the agrochemical and specialty chemical manufacturing markets. Participants cover a diverse range of chemical end-uses including adhesives & sealants, agriculture & crop protection, coatings & paints, cosmetics & personal care, flavors & fragrances, pharmaceuticals, plastics & composites, and water treatment. **www.chemicalsamerica.com**

CPhI Worldwide

CPhI Worldwide, taking place on October 13-15, 2020, in Milan, Italy, hosts more than 45,000 visiting pharma professionals over three days. 2,500+ exhibitors from more than 150 countries gather at the event to network and take advantage of free industry seminars. Every sector of the pharmaceutical market is represented under one roof. In 2019, two new podiums were introduced: Natural Extracts, based in the Natural Extracts zone, with content that covers this segment of the industry; and World of Pharma, which looks mainly at regional trends and updates. **www.cphi.com**

ChemOutsourcing

ChemOutsourcing, to take place on September 13-15, 2020, in Long Branch, New Jersey/USA, is the largest USA-based API show. It focuses on API development spanning early drug discovery through chemical development and commercial supply. Attendees are executive scientist "buyers" from pharmaceutical companies responsible for sourcing starting materials, intermediates, active ingredients, and commercial supply and experienced in working with Contract Research and Contract Manufacturing Organizations. **www.chemoutsourcing.com**

Chemspec Europe

Chemspec Europe will take place from November 11-12, 2020, in Cologne, 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 international exhibition covers a maximum range of fine and specialty chemicals for various industries. Excellent networking opportunities and top conferences presenting the latest results of ongoing R&D projects round-off the show. **www.chemspeceurope.com**

Index

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General Managers
Sabine Haag
Dr Guido F. Herrmann

Publishing Director
Dr. Heiko Baumgartner

Product Management
+ Managing Editor
Dr. Michael Reubold
Tel.: +49 6201 606 745
michael.reubold@wiley.com

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

Freelancer
Volker Oestreich
Thorsten Schüller

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

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

Production Managers
Jörg Stenger
Melanie Horn (Advertising)
Oliver Haja (Layout)
Ramona Scheirich (Litho)

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

Lisa Colavito
Tel.: +49 6201 606 316
lisa.colavito@wiley.com

Beate Zimmermann
Tel.: +49 6201 606 316
beate.zimmermann@wiley.com

Wiley Reader Service
65341 Eltville
Tel.: +49 6123 9238 246
Fax: +49 6123 9238 244
E-Mail: WileyGIT@vuservice.de

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Contact

Dominik Vogt

Conference Manager

+49 (0)2233 4814-49

dominik.vogt@nova-institut.de

Organiser:

nova Institute for Ecology and Innovation

nova-institute.eu

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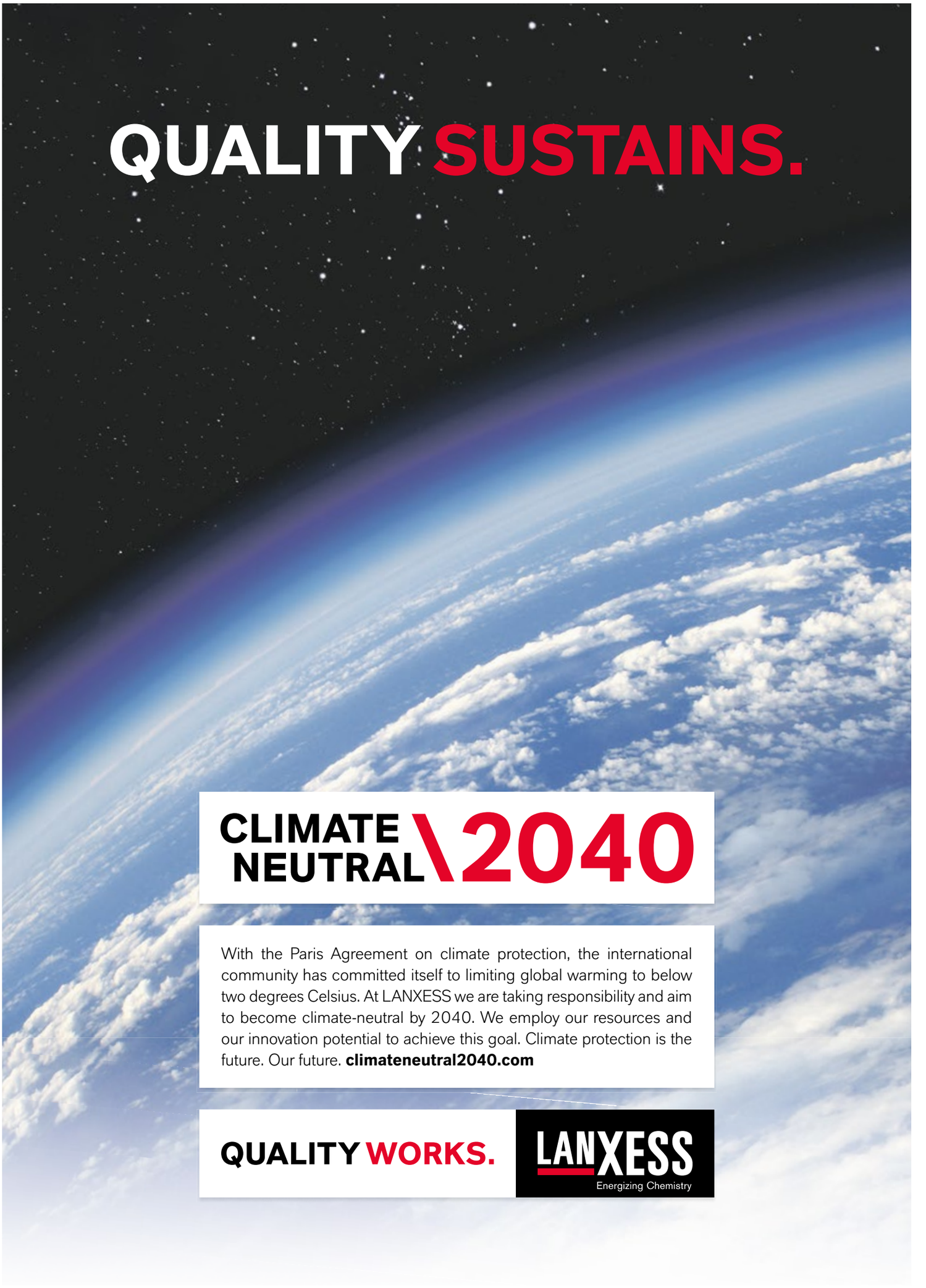
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