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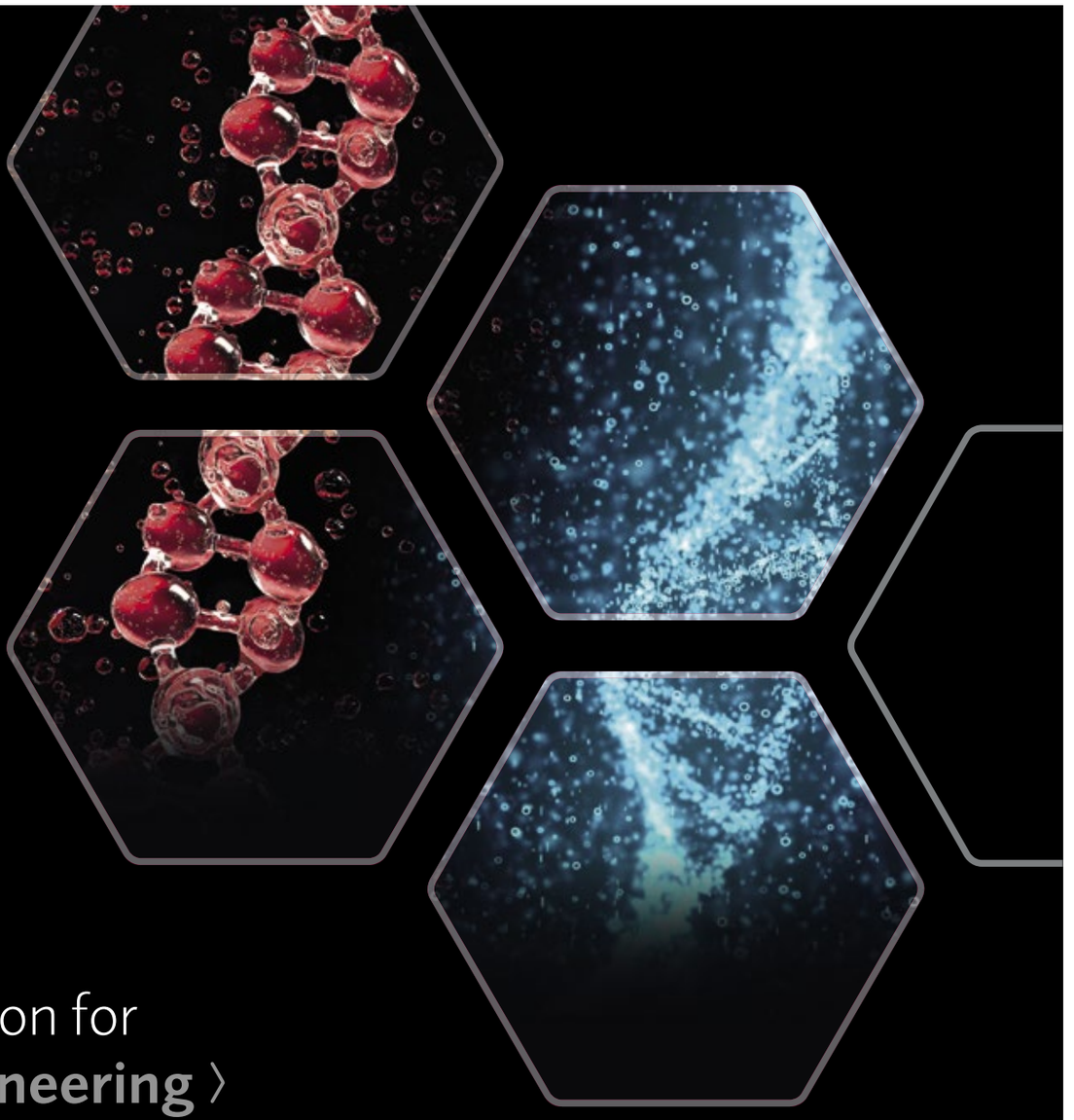

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Pharma & Biotech

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Expansions in High-Potency API Manufacturing

HPAPI Capacity Increase is an Active Area of Investment by CDMOs/CMOs

Driven by the growth in oncology drugs, several CDMOs/CMOs have made or announced capacity expansions to manufacture highly potent active pharmaceutical ingredients (HPAPIs) and drug products.

Patricia Van Arnum, Chemical & Associated Technologies Association (DCAT)

Several CDMOs/CMOs have made or announced capacity expansions to manufacture highly potent active pharmaceutical ingredients (HPAPIs) and drug products.

Biologics and newer approaches, such as immunotherapies, are part of the oncology-drug market, but small molecules, including cytotoxics, and hybrid approaches, such as antibody-drug conjugates (ADCs), are also part of the market and represent opportunities for CDMOs/CMOs. DCAT Value Chain Insights rounds up recent expansion activity for highly potent drug substances and drug products.

CDMOs/CMOs and their Investment Projects

Lonza: In June 2019, Swiss CDMO Lonza announced an investment to expand HPAPI capacity at its site in Visp, Switzerland, by adding two 4-m³-scale, multi-purpose production lines. The expansion complements the company's existing production capacities from lab to large commercial scale and further involves a subsequent capacity optimization in existing production lines. The expansion was scheduled to come on line this July. The company has the capabilities in place to handle HPAPIs to exposure levels up to 100 ng/m³ across all manufacturing scales.

In addition, in July 2019, Lonza initiated a two-year expansion of bioconjugation capacity for ADCs at its facility in Visp. Last year, it received

US Food and Drug Administration (FDA) approval for the commercial manufacture of its third ADC from the facility.

WuXi AppTec: STA Pharmaceutical, part of WuXi AppTec, opened in the first quarter of 2020 a HPAPI facility at the company's site in Changzhou, China, its second HPAPI facility. WuXi STA's first HPAPI facility, located at its Shanghai Jinshan site, supports process R&D and kilo-scale production. The newly added HPAPI facility includes HPAPI labs and a pilot plant (250-L-1,000-L reactors) capable of handling APIs with occupational exposure limits down to 0.05 µg/m³.

Catalent: Catalent reported in August 2020 plans to expand its site in Loma Hermosa, Buenos Aires, Argentina by adding over 1,020 m² of production space to handle cytotoxic and highly active products for prescription softgel manufacturing. The new facilities are due to be completed in December 2021.

Helsinn: Lugano, Switzerland-based pharmaceutical company Helsinn, focused on cancer-care products and a CDMO of APIs through its manufacturing subsidiary, Helsinn Advanced Synthesis, opened in late July 2020 a dedicated anti-cancer bay at its manufacturing plant in Biasca, Switzerland. The new bay will be used for the development, analysis, and manufacturing of clinical and commercial anticancer APIs.

Seqens: In 2019, Seqens invested approximately $30 million for a new facility for HPAPI manufacturing in Villeneuve-La-Garenne, France, located outside of Paris. The modular unit, with initial capacity of 10-15 t/y, further allows for future investments as customer needs evolve. The potent-compound manufacturing unit maintains a maximum level of particles in the working environment of 100 ng/m³ to allow for the production of SafeBridge Category 3 potent compounds, which is classified as molecules with occupational exposure limits (OELs) ranging from approximately 30 ng/m³ to 10 µg/m³.

Cambrex: Last year, Cambrex opened a new $24-million HPAPI manufacturing facility at its site in Charles City, Iowa. The 550-m² facility is part of an overall multi-year investment plan by the company in small-molecule API development and manufacturing across its facilities, which included a $50-million, 700-m² multi-purpose manufacturing facility at Charles City, which opened in 2016.

Piramal: In January 2020, Piramal Pharma Solutions (PPS), announced an investment of $19 million to expand its facility in Aurora, Ontario, Canada, with the addition of 975 m² manufacturing space in a new wing for API manufacturing overall and including HPAPI manufacturing for potent compounds down to an OEL of 1 mcg/m³. It will also include filtration and drying capabilities. The expansion is expected to be completed and running by April 2021.

In June 2019, PPS opened a new $10-million HPAPI unit at its site in Riverview, Michigan. The new wing, consisting of two kilo labs and a quality control analytical lab, was designed to handle HPAPIs with OELs of < 1 mcg/m³ and as low as 20 ng/m³.

CordenPharma: A contract provider of both small-molecule APIs and drug products, CordenPharma acquired a former Pfizer facility in 2017. The 5,000-m² API manufacturing facility in Boulder, Colorado, included additional capabilities in high-potency manufacturing and specializes in the development, scale-up, optimization, and production of highly potent and cytotoxic/cytostatic APIs from development quantities to commercialization. The acquisition of the Boulder facility is aligned with a broader corporate strategy of of-

Continued Page 6 ▶

fering fully integrated supply (APIs, drug products, packaging, and logistics), including development and manufacturing of highly potent and oncology products.

Fareva: In 2019, Fareva expanded HPAPI capabilities with the completion of a $34-million investment across two sites in Europe. The company's Excella facility in Germany expanded OEB 6 (< 0.1 µg/m³) capabilities with the completion of an analytical building, addition of jet milling with an isolator, and expansion of roller compaction for high-potency products. Fareva's La Vallée site in France completed construction and qualification of analytical and chemistry R&D Labs, pilot plant, and commercial manufacturing buildings capable of handling OEB 5 (0.1 –1 µg/m³). This investment more than doubled Fareva's HPAPI capacity. The company provides high-potent capabilities across two sites with volumes ranging from 100 L to 4000 L for development and manufacturing of both APIs and drug products up to OEB 6 (< 0.1 µg/m³) from early phase to commercial.

Flamma: Last year, Flamma acquired Teva Pharmaceuticals' Chemical Synthesis Center in Malvern, Pennsylvania. Among the capabilities of the 3,700-m² facility was one cGMP HPAPI kilo lab suite with isolators (classified Band 4 by SafeBridge). Flamma has two cGMP facilities in Italy, located near Milan: Chignolo d'Isola and Isso. Additionally, Flamma is established in China, where its 100 %-owned Chinese subsidiary, Flamma Honkai, operates in Dalian in the Liaoning Province.

Cerbios: In 2019, Cerbios announced the investment of new production lines in a building dedicated to HPAPIs to enable accommodation of larger volumes and batch sizes. The expansions will accommodate SafeBridge Category 3 for batches ranging from 5 kg to 30 kg. At the time of the announcement in January 2019, completion was scheduled for the second half of 2020. Additionally, in December 2019, the Lugano, Switzerland-based CDMO announced successful SwissMedic authorization of a new cGMP bioconjugation suite for up-to commercial scale manufacturing of ADCs.

Evonik: German chemical manufacturer Evonik increased its assets and added additional capacities to support the small-, medium- or large-scale production of HPAPIs at its facilities in Tippecanoe, Indiana, and Hanau, Germany. The expansions, reported in 2018, enable the company to run several HPAPI projects down to an exposure level of 5 ng/m³.

AGC: A Tokyo-headquartered manufacturer of glass and chemicals, AGC expanded its facilities in 2019 in Chiba, Japan, to increase the company's manufacturing capacity for pharmaceutical intermediates and APIs, including HPAPIs.

Novasep: In 2017, French CDMO Novasep opened a new €11-million bioconjugation facility at its site in Le Mans, France, for clinical and commercial manufacturing of ADCs. The new facility completes Novasep's ADC manufacturing platform, which includes ADC payloads, drug linkers, and monoclonal antibody commercial-scale production capabilities.

Ajinomoto: In 2018, Ajinomoto Bio-Pharma Services opened a new ADC and highly potent fill–finish facility near its existing campus in San Diego, California. The 5,300-m² manufacturing facility includes areas dedicated to bioconjugation, formulation, purification, quality control, and sterile fill and finish, including lyophilization. The facility can accommodate early clinical phase through commercially approved programs. In addition, the company, in March 2019, announced further investment for the reconfiguration of GMP manufacturing suites in Belgium to support increased HPAPI capacity and improve process safety with additional instrumentation.

BSP: BSP Pharmaceuticals, a Latina Scalo, Italy-based CDMO of oral solid dosage forms and injectables, announced an expansion of high-containment capacity dedicated to oncology compounds and the addition of new capacity for innovative molecules and immunotherapies. The investment involves expansion of the company's existing facilities for oncology products and cytotoxics by approx. 2,800 m^2 to increase its total conjugation capacity for ADCs. The new high-potency manufacturing capacities, as announced in 2019, are scheduled to be completed by the end of 2020.

PCI: PCI Pharma Services completed late last year an expansion of its Rockford, Illinois, facility to include 2,800-plus m^2 dedicated to specialty drug-product capabilities with four high-potent compound suites and three new secondary packaging areas.

Recro: In 2018, Recro Gainesville, a CDMO of oral solid dosage products, added a 2,200-m^2 facility, which included high-potent material processing space, near its existing 9,000-m^2 contract pharmaceutical development and manufacturing plant in Gainesville, Georgia. The expansion provides capabilities from formulation development to clinical-trial material supply to commercial manufacturing with clinical packaging capabilities to be added in 2020.

Sterling: Sterling Pharma Solutions, a Dudley, UK-headquartered CDMO of APIs, opened a pilot-plant facility in 2019 following a £6-million investment to increase API capabilities, including the handling of potent compounds. Overall, the expansion included three new reactor trains at scales of 225 L, 500 L and 1,360 L and enables small to mid-scale clinical supply and commercial batch production.

Heraeus: Hanau, Germany-based technology group Heraeus announced last year that its subsidiary, Heraeus Pharmaceutical Ingredients, is expanding production capacities for platinum-based HPAPIs.

Minakem: Minakem, the CDMO division of Minafin, a Mont-Saint-Guibert, Belgium-based fine chemicals producer, opened in 2018 a new closed-controlled environment high-containment HPAPI production facility at the company's plant in Louvain-la-Neuve, Belgium. The new facility extends Minakem's capacity to develop and manufacture highly potent APIs from small-scale development to full GMP batch releases.

Procos: Procos, a wholly owned subsidiary of the Japanese company CBC, expanded to add a HPAPI manufacturing unit at its facility in Cameri, Italy, located near Milan. The expansion, which started in 2016, was completed in 2018.

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The Rise of HPAPI Molecules

Trends in Highly Potent API Manufacturing: Safe Handling, Containment and Production

Several convergent trends increasingly define the small molecule landscape. A growing proportion of the drug development pipeline is made up of more complex, highly potent APIs (HPAPI). These molecules are commonly associated with innovative cancer treatments, such as antibody-drug conjugates (ADC), but they also have shown effectiveness in treating autoimmune diseases, diabetes and a range of other indications. HPAPI molecules now make up over 30 % of the drug development pipeline.

Alongside the growth in HPAPI molecules, smaller companies are increasingly driving the development of innovative molecules and products. These companies are submitting higher numbers of drug products for regulatory approval as specialty medicines, which often requires meeting accelerated timelines to market. Additionally, when these products are designed to treat rare diseases with small patient populations, they face uncertain demand if or when they reach the market. This uncertainty underscores the importance of flexible manufacturing capacity that can help avoid regulatory changes (e.g., due to change of scale) in response to an increase or decrease in demand.

For biopharma leaders, these trends mean it is more critical than ever to secure the capabilities to contain, handle, develop and manufacture increasingly complex molecules, including HPAPI. For many companies, particularly small, emerging and even virtual biopharma companies which lack extensive in-house manufacturing capabilities, the path forward typically includes working with an external partner such as a contract development & manufacturing organization (CDMO). In these cases, it is essential to select a partner with the appropriate experience and capabilities to help advance and develop innovative, life-saving HPAPI products. The optimal partner will also anticipate clinical fluctuations throughout the entire clinical development timeline, make proactive suggestions on process improvements and manufacturing concepts and thereby minimize time to the next clinical milestone and to the market.

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Pharma & Biotech

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Multi-purpose, kg-scale facility for highly potent payloads for ADCs at Lonza's Center of Excellence for HPAPI development and manufacturing at the Visp site in Switzerland.

HPAPI Molecules: Efficacious at Extremely Low Concentrations

HPAPI molecules represent a new way to use small molecules to deliver innovative patient therapies, often incorporating more precise delivery mechanisms. The shift toward the use of HPAPI has led to the emergence of a pipeline of more effective medicines, with potentially lower dose requirements and fewer side effects. These molecules are efficacious at extremely low concentrations, in doses as low as 1 mg/d. On the downside, their high potency means they can cause harm if handled improperly; they frequently have occupational exposure limits (OELs) at or below 10 µg/m³ of air as an 8-hour time-weighted average.

Interest in highly potent drugs is largely driven by oncology research and more targeted therapies across a number of indications. Currently, over 1,000 highly potent small molecules are in development, with approximately 30 % targeting oncology, 20 % for antidiabetics, 20 % for autoimmune diseases and the remainder for other indications.

Due to their wide range of potential uses and benefits for patients, the growth in the HPAPI market is outpacing the overall API market by almost two-to-one. The segment is growing at about 10 % compound annual growth rate (CAGR), compared to 6 % for the overall small molecule market. The market value from existing and new HPAPI product launches is

expected to double between 2018 and 2025, from around $18 billion to $35 billion.

Safety Is a Top Priority in HPAPI Manufacturing

This trend towards greater use of HPAPI molecules presents significant potential benefits for patients, but it also comes with handling, containment and manufacturing challenges for innovators and their development partners, since these molecules can be dangerous if mishandled. Safe HPAPI handling can be ensured by focusing on facility design, protection strategy & procedures and personal protective equipment.

Sophisticated facility design elements include several tools to ensure safe handling of potent materials. Units are available for primary and secondary containment of the entire process including solid charging containment, sampling and unloading, with ranges from 50 g to 200 kg of starting material. For product sampling, liner ports can help lock in and lock out glass sampling bottles. To aid in the product unloading process, manufacturers can use endless liner systems and customized flex isolators (in some cases more rigid, hard-walled isolators may be preferred).

Well-designed protection strategies include nuanced and detailed processes for how workers can use and clean HPAPI manufacturing assets. For example, cleaning procedures should include clear acceptance criteria for opening equipment after precleaning. And the safest equipment start-up sequences are embedded into the risk assessment process, with leak test and rinse prior to production and defined criteria allowing for production release.

Personal protective equipment is of course extremely important to keep workers safe. Reliable equipment including coveralls, hoods, gloves, chemical suits, supplied air and other implements should be available in ample supply for anyone working with highly potent materials. However, the use of PPE should be the last resort and not the main method of protection for routine operations. Adequate organizational measures and procedures can often accommodate PPE-free operations, keeping the PPE only for non-routine operations.

An important complement to technical containment equipment is a well-trained workforce with a strong commitment to a culture of safety. While a culture cannot be bought and installed like a piece of manufacturing equipment, leaders can take steps to encourage the right mindset among workers. When it comes to building out a training program, facility operators must stress that there are no compromises possible in compliance. And fielding idea submissions from employees and managers for how to improve safety further can increase motivation and dedication among staff members.

The Trend toward HPAPI Outsourcing

In response to the growing need for sophisticated HPAPI manufacturing, some CDMOs are building flexible, integrated capabilities dedicated to HPAPI development from preclinical to commercial production. These programs place an emphasis on safe procedures from equipment start-up to handling, cleaning and decontamination, and they come as outsourcing of HPAPI production is increasing at a rapid pace. Demand for highly potent small molecule API manufacturing and development services is keeping pace with the overall HPAPI market value, and is expected to exceed $7.5 billion by 2023, more than doubling the $3.5 billion market size in 2015.

"Demand for highly potent small molecule API manufacturing and development services is expected to exceed $7.5 billion by 2023."

One example is Lonza's Center of Excellence for HPAPI Manufacturing and Development at our Visp (CH) site, which features a comprehensive platform including a highly skilled team, extensive evaluation and training procedures and state-of-the-art facilities. Lonza has capabilities in place to safely handle HPAPI to exposure levels up to 100 ng/m^3 across all manufacturing scales (up to 10 m^3), allowing for production to scale up and down flexibility as needed. For more potent compounds such as ADC payloads (containment down to 1 ng/m^3), Lonza has separate and segregated capabilities at the Visp site, where quantities from grams to multiple kilograms of compound can be safely handled (Fig. 1).

What it Means for Biopharma Innovators

For biopharma innovators, working with a single partner across the development pipeline can shorten timelines and reduce risk. CDMO partners can access in-house experts across a range of drug substance and drug product challenges, engage in technology transfer activities and exchange information, ideas and best practices across the drug development cycle. A study from Tufts Center for the Study of Drug Development has found that a single-source outsourcing model can shorten the drug development cycle by 14 weeks and lead to financial gains of up to $45 million. For HPAPI compounds, drug product capabilities will include parenteral formulations/sterile fill-finish services and oral delivery options such as liquid-filled hard capsule technology. Contained particle engineering can also be required for safe and effective jet milling or spray dry processing. Outsourcing development to a qualified CDMO can help meet accelerated production timelines and help deliver life-saving therapies more quickly to patients who need them.

Conclusion

As HPAPI molecules continue to play a growing role in new pharmaceutical products, biopharma companies will need access to flexible, sophisticated manufacturing assets to bring their innovative products to market and to patients. Given the high potency of these molecules, safety and containment are key components of effective HPAPI manufacturing.

"Alongside the growth in HPAPI molecules, smaller companies are increasingly driving the development of innovative molecules and products."

Working with a qualified CDMO can help biopharma companies advance HPAPI compounds and products at high speed and low risk. When evaluating external partners, biopharma innovators should base their choice on the CDMO's experience in the HPAPI space and the containment, handling and manufacturing assets the partner brings to bear.

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References can be requested from the author.

Understanding the Requirements of Safe HPAPI Manufacturing

Growing HPAPI Demand and Project Complexity Make CMO Partners Critical for Success

The pharmaceutical industry is increasingly focused on the development of specialized drug products with new treatment modalities, including previously undruggable targets for oncology and other areas. For many pharmacologically active substances behind these products, biologic activity is exhibited at extremely low concentrations. Such highly potent active pharmaceutical ingredients (HPAPIs) now account for around one quarter of all new pharmaceutical entities, and half of those in clinical development.

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When it comes to facilitating the efficient design of containment solutions, Evonik has long relationships with external partners for the engineering design and maintenance of hard and flexible containment solutions such as isolators, flexible glove bags, charge/discharge technologies and HPAPI packing and sampling.

A typical HPAPI has a therapeutic daily dose of less than 10 mg and an occupational exposure limit (OEL) below 10 µg/m³ of air as an eight-hour time-weighted average (TWA). However, a growing number of pharmaceutical compounds under development, known as ultra-HPAPIs, can require even more extreme levels of exposure control down to an OEL range of 1-20 ng/m³. Most HPAPIs and ultra-HPAPIs in clinical development are outsourced to contract manufacturing organizations (CMOs) that have the necessary process expertise, qualified facilities, development labs and track record for compliance with key quality, regulatory and safety requirements. While many CMOs have made significant investments in their HPAPI capabilities over the last two decades, pharmaceutical companies can still find it challenging to select a partner to reliably support them throughout all project stages including process development, clinical scale-up and commercial manufacturing.

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Complex Processes Require Substantial Expertise

Only a few CMOs have a long history of execution in optimizing safety and containment control processes to handle and manufacture HPAPIs from small-scale development lab quantities up to large-scale commercial volumes. The ability to demonstrate extensive project experience with other comparable HPAPI projects, and a strong track record for audits and supply security, is also considered essential.

Furthermore, many HPAPIs require between several and a dozen or more process steps for synthesis. For many of these steps, multiple advanced technologies can be required including peptide coupling, mPEG/PEGylation, continuous processing, chiral resolution, catalysis or biocatalysis and cryogenic reactions. In many instances, only a few CMOs will have the necessary technology portfolio to coordinate the safety and special process engineering capabilities required for such complex projects.

Most importantly, the CMO must be able to demonstrate strong technical competencies in the development of effective risk control systems that are based upon a comprehensive assessment of exposure hazards and other safety risks for each process step required for chemical synthesis. Various disciplines must be aligned together under a HPAPI project team including process engineers, R&D and manufacturing experts, toxiologists, industrial hygiene specialists, and safety and hazard assessment experts. Specialist analysts are also required to implement in-process, intermediate and final HPAPI analyses, and to develop trace analytical methods to support plant cleaning protocols. Additional resources and software for project management, employee training and cleaning protocols should

also be available. Often, the CMO will lack the desired technical experience or structural versatility to provide peace-of-mind during the development and implementation of a risk control system.

Key parties and processes that should be utilized under a best-in-class system for hazard assessment, risk assessment and risk control are summarized in the table.

It is a key regulatory requirement that prospective hazards which may be encountered during HPAPI handling are identified and understood to enable OEL development. This highly complex process requires extensive technical know-how. Together with occupational exposure banding (OEB) and other factors including short-term exposure limits (STELs), the development of an OEL enables organizations to conduct assessments for various acute, allergenic, corrosive, carcinogenic, mutagenic, toxic, reproductive, and other occupational risks. These assessments in turn help establish and maintain safety and containment control procedures that minimize exposure risk regardless of manufacturing stage or production site.

Thorough Consideration of Quality and Safety Procedures

Conformance to regulatory requirements and ICH guidelines also requires a thorough consideration of quality and safety procedures to prevent either the release of an HPAPI or intermediate, or cross-contamination with other products manufactured within a multi-purpose facility.

In order to optimize the risk analysis strategy for HPAPIs, Evonik utilizes a system of five Occupational Exposure Bands (OEBs) that incorporates global containment guidelines for its manufacturing sites (cf. figure).

"It is a key regulatory requirement that prospective hazards are identified and understood."

The compound's OEL classification is based on toxicology data, pharmacology, bioavailability, clinical trial results, and physicochemical evaluations. In-house toxicologists will refer to the data set provided by a pharma customer and also conduct an extensive evaluation of available literature. The most relevant pharmacological and toxicological data set linked to the most serious health effect is selected as the point of departure (POD) for the acceptable daily exposure (ADE) and OEL calculation. This POD value is then adapted applying different standardized toxicology safety factors to calculate the ADE used to determine cleaning requirements of pharmaceutical reactors and equipment, and the OEL (in µg/m³ or ng/m³) to assess containment measures regarding inhalation exposure.

The occupational banding system provides an initial guideline to help the CMO select the most suitable facility and design the containment

Continued Page 12 ▶

	Hazard Assessment	Risk Assessment	Risk Control Systems
Involved Parties	▪ Industrial Toxicologist ▪ Toxicology Review Committee	▪ Industrial Hygienist ▪ IH Technicians ▪ Quality Assurance Specialists ▪ Operations Personnel ▪ Engineering	▪ Industrial Hygienist ▪ Engineering ▪ Maintenance ▪ Analytical Laboratories ▪ Operations Personnel

Utilized Processes	▪ Hazard Classification
	▪ Dose/Response Evaluation
	▪ Safe Exposure Levels (OEL's, STEL's)
	▪ Derivation of Acceptable Daily Exposure (ADE) values
		▪ Control Strategy
		  ▪ Engineering Controls
		  ▪ PPE Selection
		  ▪ Administration Controls
		▪ Reproductive
		  ▪ Risk Assessment
		▪ Operator Awareness
		▪ Operator training
			▪ Cleaning Methods and Limits
			▪ Air Space Monitoring
			▪ Spill Procedures
			▪ Operating Procedures
			▪ Facility Controls
			▪ Process-Specific Controls
			▪ Waste Handling
			▪ Medical Surveillance
			▪ Respiratory Protection
			▪ Emergency Response

Key parties and processes that should be utilized under a best-in-class system for hazard assessment, risk assessment and risk control

of unit operations. This is followed by thorough task-by-task exposure risk assessments of the whole drug substance handling process to evaluate specific exposure risks based on the established OEL, as well as pharmacological and toxicological actions of the compound, to protect the operators and prevent potential cross-contamination.

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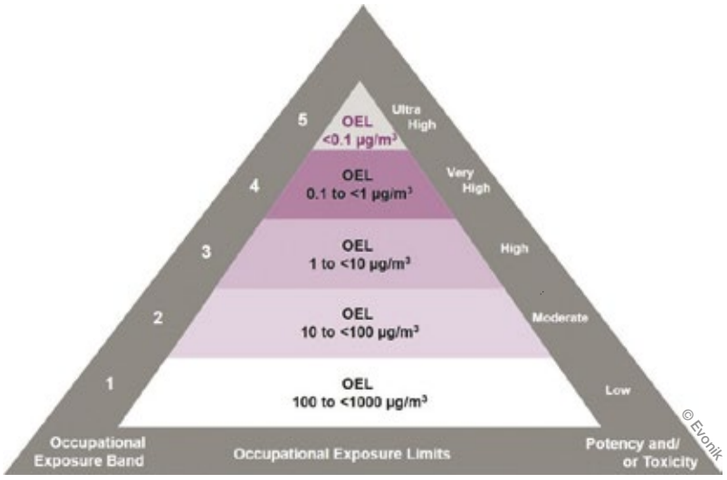
Evonik's Hanau site in Germany can produce HPAPIs on small-scale under GMP for clinical trials.

Each process step requires significant attention to the development of safe handling and containment system protocols that can prevent workforce exposure, accidental release of the substance or another pharmaceutically active intermediate, and cross-contamination with other products manufactured in the facility. To facilitate the efficient design of containment solutions in pharmaceutical plants, collaboration with external equipment vendors and engineers is also becoming a key CMO requirement.

Best-in-class Policies for HPAPI Handling

Taking these and other factors into account, Evonik has implemented what it considers to be a set of best-in-class policies for the hazard and risk assessment of highly potent compound handling:

- Toxicological assessment of compounds with pharmacological and/or toxicological activity and setting of OEL and ADE values. In a case where data is not sufficient to derive an OEL, a basic hazard review is conducted to assign a default OEB range. The application of estimated in-silico predictions of mutagenicity using FDA-accepted software tools is provided.
- Industrial hygiene risk assessments prior to handling HPAPIs, and an ongoing program to monitor the performance of containment systems.
- Guidelines for facility design and exposure control approaches to establish the safe handling of potent compounds and their pharmaceutical dosage forms at laboratory, pilot and large-scale production scales.
- Training and communication guidelines and programs to ensure that employees are aware of the occupational hazards presented by potent compounds and that they have sufficient knowledge of the controls used to prevent exposure.



Classification of Occupational Exposure Bands (OEBs) at Evonik

- An effective project management system to ensure potent compounds are managed appropriately throughout the project and product life cycle, including project evaluation, R&D work, analytical, manufacturing and waste disposal.
- Technical guidelines for the design, installation, qualification, and maintenance of glove box, glove bag, and potent compound isolator systems Guidelines for the qualification of personnel using highly potent compound containment systems

A History of Excellence

Since the early 1990s, these policies have been used at Evonik's Tippecanoe facility and helped make the facility in the US state of Indiana the world's largest contract manufacturing site for HPAPIs with the ability to run six different HPAPIs in parallel. The site has a total capacity of 170 m^3 with containment capabilities down to an OEL of 0.1 µg/m^3 and features multiple QC and process development lab support areas. The main T29 multi-unit, multi-product facility for HPAPIs was designed upfront to achieve effective product cross-contamination protection and worker safety.

„Many HPAPIs require between several and a dozen or more process steps for synthesis."

Thanks to the efforts of industrial hygienists, maintenance teams, operations teams, quality assurance experts, engineering, and automation personnel, the site has maintained an unparalleled record for safety and containment control over more than 25 years of HPAPI manufacturing.

Evonik's Hanau site in Germany also provides customers with process and analytical laboratories for the development and optimization of HPAPIs or ultra-HPAPIs requiring containment down to an OEL of 5 ng/m^3. The facility can produce HPAPIs on small-scale under GMP for clinical trials.

A combination of process and containment system expertise, technology portfolio flexibility and manufacturing versatility is increasingly considered essential to identify suitable CMO candidates for HPAPI and ultra-HPAPI projects. Beyond these necessities, pharmaceutical customers are increasingly making their final selection decisions on the ability of a CMO to demonstrate a history of excellence for regulatory audits, quality consistency and supply security.

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Wake-up Call

The Impact of Covid-19 on the Pharmaceutical Industry

Being in the public eye, the pharmaceutical industry has responded extremely well to the coronavirus pandemic. However, the Corona crisis has uncovered some issues that are smoldering under the surface and need to be addressed by the industry and by politics alike. For instance, the pandemic puts pharmaceutical research and development strategies to the test and challenges manufacturing planning and supply chain management. Andrew Badrot, CEO of C² Pharma, a Luxembourg-based manufacturer, and distributor of active pharmaceutical ingredients (APIs), is a senior pharma expert and a close observer of industry trends. For CHEManager, he analyzes the current situation and how this pandemic may kick of changes in the pharma market. Questions by Michael Reubold.

Andrew Badrot, CEO, C2 Pharma

CHEManager: Mr. Badrot, the Covid-19 pandemic is having an unprecedented worldwide impact. After a half year of living and working under pandemic conditions, what in your opinion are the most important lessons learned so far?

Andrew Badrot: Across the board, we have learned the hard way not to take anything for granted. In the industry, the hardest lesson has been about what true supply chain security means. Over the past few decades, many industries have worked to redesign supply chains to reduce costs, which has led to a greater reliance on global sourcing and networks. But the leveraging of global supply chains has gone so far in the pharma industry that quality and reliability of supply have suffered. There was a naive belief that these global networks could not be disrupted, but Covid — and a resulting trade war — have shown us otherwise.

Do we have to halt or even turn back the wheel of globalization?

A. Badrot: Looking at the big picture, just a while ago in 2016, it was still unconceivable to go against the wind of globalization in the mainstream western world. Politicians took the stance that globalization was the inevitable direction of history for our civilization and this narrative was supported by economic theory and large corporation activities.

Carrying forward to pharma, the threat of temporary bans on raw materials exports from China during Covid has sent shivers around the world. This was further amplified by the reality of India's partial and temporary ban on some APIs. With China and India being two of the largest providers of APIs and source materials in today's pharma market, the reality that this industry could be "held hostage" without exports became very real.

In today's market, I do not believe any politician would continue arguing that globalization is a "necessary thing" because we now see that the core theory underlying the concept of globalization has been proven wrong. Wealth will not transform dictatorships into democracies. Quite the opposite, in fact. New wealth in dictatorships combined with open communication platforms will threaten democracies at their core and transform some of them into populist authoritarian regimes. And while pharma will continue to be a global industry, business as usual is going to look a little different going forward.

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The pandemic has uncovered the limits of the pharma manufacturing model, in particular its reliance on China and India for many starting materials and even some APIs and drug products. Will this lead to a relocation of certain manufacturing back to the US and Europe?

A. Badrot: We believe that the most enduring consequence of Covid-19 in this industry will be a re-evaluation of pharma supply chains with a more regional and failsafe approach. We expect that manufacturers will look to redesign their supply chains with multiple suppliers, and with a much greater reliance on regional manufacturing hubs in the United States, Europe, and Japan.

This will not happen overnight, of course. We expect that it will be a

10-year long journey where the industry looks at how to re-shore pharmaceutical manufacturing. Initially the challenges will be based on finances and capacity because so much of the existing capacity for chemical assets in the US, Europe and Japan no longer exist. This means that a great deal of money will need to be spent to re-build infrastructure. Another challenge will be the politics of reshoring, as these types of facilities are often misunderstood and unwelcomed by residents.

Still, these challenges can be overcome, and from a longevity perspective, they will have a great deal of positive impact if addressed properly. Not only will re-shoring bring dependable jobs back to the west, but it will increase the quality of drugs being manufactured, and ultimately lower costs over time.

Apart from reshoring manufacturing, what else can Western countries do to reduce the risk of supply shortages and safeguard their healthcare systems in future crises?

A. Badrot: We believe that three decisive actions by Western governments can change the course of affairs in pharmaceutical manufacturing and eliminate the reliance on imports for essential drugs:

First, the creation of preferred access regulations mandating domestic supply of essential API and drugs via a combination of financial grants and import duties. This will be most effective if the supply chains are built to allow drug products to be made from the "cradle to the grave". This means the APIs, solvents, and excipients must all be readily available for sourcing at the quality level needed close — or closer — to home.

Second, strengthening of global quality standards for medicine by allowing the US FDA, European, Japanese, and other regulatory authorities to audit foreign manufacturing facilities without notice. No notifications mean no time to cover-up bad behavior, resulting in a rise in quality compliance.

And **finally**, transparent labelling at the pharmacy, listing the "country of origin" that the ingredients were sourced from and where the final drug product was formulated and filled in, will allow patients to make more informed decisions.

If these three things are done concurrently, there would be strong incentive to build innovative and flexible local manufacturing assets for essential materials and drug product manufacturing because there would be sustainable profitability in the supply chain. Ultimately, a lack of profitability — which is necessary to keep a business running — is what lead to so much outsourcing of the supply chain in the first place.

While change in the pharma business is continuing, M&A are one element of pharma companies to strengthen their position and create value. Will this consolidation even intensify due to the Corona crisis?

A. Badrot: Mergers and acquisition activity ebb and flow but is always an underlying factor of growth in this industry. Due to the pandemic, we may see companies that were already in weaker positions go into bankruptcy,

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and perhaps this could create a bargain-hunting mindset. But this pandemic has also presented new opportunities for companies to enhance strengths and leverage financial interests.

Even if Covid-19 encourages more of a buyer's market, there will be big winners. For instance, Biontech will likely be an acquisition target. Its collaboration with Pfizer has sent its valuation sky-high, tripling in value since January to reach nearly $18 billion, which is immense for any company, but particularly for one with no track record of products or sales.

Undoubtedly, the shifting acceleration of R&D will certainly drive intense M&A activity with big winners and bigger losers.

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C2 Pharma, a Luxembourg-based manufacturer, and distributor of active pharmaceutical ingredients, operates a facility in Ingelheim, Germany.

Speaking of R&D: In the past, pharma companies worked on their R&D projects internally. Today, external innovation is a key success factor, and collaborations with industry peers or research organizations are a daily occurrence. How do you expect the R&D model to evolve in the post-Covid era?

A. Badrot: We do not believe Covid-19 will have a negative impact on pharmaceutical R&D and its reliance on a mix of internal/proprietary and external partners to drive innovation. The overall approach to development and manufacturing have not proven to be a pain point. Rather, we expect that governments will get more active in financing, or even dictating, R&D and manufacturing programs catered to pressing public health interests. This would be a positive development for the local market and the global markets, as innovation happens and inspires true change. We would be hopeful to see programs such as this have an impact on the search for things like novel antibiotics.

Does consolidation in the pharma industry also create a necessity for the CMO industry to consolidate? Which other trends do you see that are changing the CMO industry?

A. Badrot: The CMO industry does not necessarily need to consolidate, but most likely will. Re-shoring will create tremendous opportunity for players who can expand their manufacturing asset base quickly and organically. In parallel, we expect massive private-equity liquidity to be injected in the industry. Private equity does not do "organic growth" particularly well, so the liquidity will drive a flurry of consolidation of small and mid-scale players. This will push the big players to continue accelerating their growth bigger and bigger, which will change the overall landscape of outsourcing. In the coming ten years, we may finally see the emergence of a handful of very large CMOs — that has been a topic of debate in the last 5 years — because of re-shoring.

You established C² Pharma combining the strengths of Brazil's Centroflora and Switzerland's CMS Pharma. This explains the origin of the company name.

A. Badrot: Yes, C² Pharma is a name that nods to our past and looks ahead at our future. The company was originally named Centroflora CMS, and when we branched out in 2014, this created a lot of confusion with many customers. Looking to overcome this challenge, we changed the name to C² Pharma, and subsequently split from Centroflora Brazil, which no longer held any ownership in the company. The C² refers to the past with the C from CMS Pharma and the C from Centroflora. And it looks ahead at the two C's our team is driven by for the future: competence and confidence.

In 2014, you acquired assets from German drug maker Boehringer Ingelheim along with a multi-year agreement to supply the market with phytochemical APIs. How did this deal expand your technology base and market reach?

A. Badrot: The transaction established C² Pharma in the API manufacturing business. The portfolio we acquired was mainly a phytochemical portfolio of APIs, meaning APIs extracted from plants. Although much of this portfolio was marred with quality problems, we managed them transparently with our customers and gradually eliminated the problems one by one. We concurrently tech-transferred those APIs to a new manufacturing site.

Today, most of our API developments are based on chemical synthesis, but we have also kept our phytochemical heritage in the company and worked to enhance competence in that space. We have established our own source of Digitalis leaves for the manufacturing of Digoxin API, and are engaged in early stage R&D work in the field of hemp and Cannabis and other undisclosed naturally derived raw materials.

How do you evaluate the potential of plant-based APIs in the future?

A. Badrot: Plant-based APIs are considered a niche business in pharma. Phytochemicals require sustainable crops to source from and can often be expensive and complex to extract, which requires the expertise to do so. Even though the industry has trended towards more reliable organic synthesis, phytochemicals will always have a place. Nature is valuable and can surprise us with the resources it offers.

Take the recent pharma industry interest in cannabis and CBD. Globally, interest is growing in these products, and the plant-based approach has shown to have features that may not be reproducible in a chemical facility. This means that phytochemical expertise, while niche, remains valuable and necessary to innovation.

A key sponsor of the "Partnerships for a Better World" program, C² Pharma is committed to build a sustainable pharma supply chain. What are the goals of this program and does it have in its tool box to reach them?

A. Badrot: The "Partnership for a Better World" program started in 2003 with Centroflora to support sustainable, traceable, and ethical harvesting of medicinal plants used in the manufacturing of phytochemical APIs for pharmaceutical and nutraceutical products. The program was designed to positively impact all aspects of the supply chain for harvests of various native plants from the Amazon forest and other Brazilian biomes, such as Pilocarpine.

The program's focus on longevity recognizes the critical importance harvesting has on biodiversity as well as the fact that it is the only source of income for more than one thousand families in Brazil. Five core principles of the program actively infuse and promote ethical trade and sustainability concepts into the harvesting process, including:

- Fair Trade principles to improve working conditions for families of pickers by increasing their income by 5 to 10 times.
- Socio-environmental development of local communities from Brazil's most disadvantaged regions, whose livelihoods depend on the gathering of native plants. Rather than depending on single- plant harvests, multiple harvest cycles are created for different plants to ensure a year-round income stream for families of pickers.
- Sustainable harvesting techniques to help end illegal picking and reduce the risk of extinction for native plants and preserve biodiversity.
- Increasing the quality of phytochemical markers in the harvests by implementing Good Harvesting Principles.
- Enhancing traceability of harvests to build in long-term quality and sustainability of ingredients.

At C² Pharma, we carry forward this work by providing firm purchase commitments and full pre-payments of harvests a year in advance. We pay 30% higher prices for the harvests than equivalent farmed crops and ultimately accept lower product margins for the API with the knowledge that these crops have extended lifespans and value.

www.c2pharma.com

Facing Strong Headwinds

In Light of the Covid-19 Pandemic the Pharma Industry has to Reinforce Supply Chains and Review Business Processes

So far, the pharmaceutical industry — including CMOs/CDMOs — has responded well to the outbreak of the Covid-19 pandemic. However, the Coronavirus crisis has uncovered some issues that were smoldering under the surface and need to be addressed by the industry and by politics alike. For instance, the pandemic puts pharmaceutical research and development strategies to the test and challenges manufacturing planning and supply chain management.

CHEManager asked executives and industry experts about how this pandemic may kick off changes in the pharma market. We wanted to know:

- After half a year of living and working under pandemic conditions, what in your opinion are the most important lessons learned so far, and how will the current pharma business model change in the post-Covid era?
- Read the insightful answers of the experts here.

A Paradigm Shift that Is Here to Stay

Sauri Gudlavalleti, Global Head of Integrated Product Development Organization (IPDO), Dr. Reddy's

The Covid-19 pandemic has been one of the worst crises to hit mankind, but has inspired tremendous resilience and innovation in all parts of the healthcare industry. Pharma R&D teams across the world have been working relentlessly to develop treatments, prophylactics and vaccines to combat the virus, and are experiencing a paradigm shift that is here to stay beyond the pandemic. The first and most significant realization is that pharmaceutical development, which is thought to be a long-drawn process, can create tremendous impact in the short term. The fervent pace of development over the last few months has shown that there is a tremendous scope for higher speed and efficiency in this space. Researchers have demonstrated this by simplifying development protocols, digitizing processes, using in-silico modelling and data analytics tools. The deployment of virtual collaboration tools helped integrating physical R&D activities across multiple global locations. Pharma researchers understood that it is critical to keep up and accelerate the development of all categories of medicines — not just those that are directly relevant to the crisis at hand. We have seen that several existing drugs can be repurposed (e.g. antivirals like Remdesivir and Favipiravir, IL6 inhibitors, corticosteroids, anti-parasitics are all being tested for Covid-19) and several other drugs become essential for supportive therapies (e.g. ventilation aids, anticoagulants etc.). On the chemistry and manufacturing side, disruptions in supply chains have highlighted the need for greater backward integration of key starting materials and simplification of manufacturing processes during development. Finally, this period has reminded us of the value of enhanced partnerships across pharmaceutical companies, academia, government and non-governmental agencies. Multiple organizations are collaborating to combine their respective strengths in discovery, development, manufacturing, clinical trials, regulatory management, and last-mile distribution to accelerate product availability to every corner of the world. All in all, this crisis has brought out a new sense of speed, urgency and purpose in the pharmaceutical industry, and with it, a series of shifts that are here to stay.

Effective Management Is Required

Mark Benger, Site Director, Cambrex Edinburgh

The six months spent working in pandemic conditions have seen the industry reflect on the next steps in the drug research and development pipeline, with companies having had to delay or even stop programs. This applies to the larger pharma companies, and also the smaller, virtual companies where funding may be an issue without clinical data to support next steps.
Delays have been caused by the interruption of vital supply chains and lockdown of areas where the drug substance may be under preparation, but also due to the delay in decision making because of remote working and working through video conferencing.
There have also been large operational changes for many staff working in drug development labs or in offices, such as the introduction of changed working practices, or shift patterns to minimize social interactions and distancing, which could lead to progressive mental and stress-related problems building up.
Breaking up teams when staff are asked to work from home or lone work could have long-term implications. Not everyone is comfortable working from home, and in drug development, problems are often solved best by teams in the same space. Although remote conferencing has improved, it does not replace the dynamic of a team meeting. Effective management is required to maintain the focus on key projects, and to ensure continuity of work within laboratories and plants to ensure staff safety. Even industry veterans with long drug development careers are dealing with new challenges in these times.
All of the measures that have been introduced to protect staff, such as wearing PPE, social distancing, mixing remote and on-site working, may become normal over time, so looking forward, safeguarding staff's mental well-being as well as physical health could well be the greater challenge for managers of drug development facilities.

Excellent Program Management Is Vital

Kay Schmidt, Senior Vice President, Technical Operations, Catalent

Early on, as the virus spread internationally, we took advice from someone with experience of the deadly Ebola outbreaks: "Take action fast, because otherwise the pandemic will outrun you." Organizations have needed to be both engaged and focused to make agile decisions on what's important. As suppliers of life-changing medicines, pharma companies needed to continue operations and keep employees safe. At Catalent these measures included remote working, shift re-alignments, unidirectional corridors, cohort work assignments, and line layout changes.

Excellent program management is vital as we have integrated capabilities across our global network. To meet program demands, we have worked on more tasks in parallel and, with constant communication with and the trust of our partners, taken measured risks to compress timelines. The need for transparent and technically-sound risk management and mitigation is critical. For example, to support clinical trials we have worked with partners to turn repurposed API into patient doses in just days, and we have worked 'at risk' to supply patients even before formally signing contracts.

The pharma industry will undoubtedly make more use of connected technologies to speed processes and reduce in-person contact; for example, we have already implemented virtual tours and remote viewing, negating the need for some visits, and further use of e-signatures where possible.

The industry was already transitioning from the 'blockbuster' era to a future of treating orphan conditions and more personalized medicines. The increased flexibility and agility these new 'small batch' programs require has helped Catalent deliver solutions for the pandemic. Focusing on providing the appropriate and efficient infrastructure and equipment to meet multiple customer needs, and the introduction of, for example, more flex suites and micro environments, has meant Catalent has been able to initiate programs quickly to supply more than 50 antivirals, vaccines, diagnostics and treatments for Covid-19.

A Real Leap in Efficiency and Productivity

Jan Kengelbach, CEO, Aenova Group

At Aenova we had two simple objectives to navigate through the global Covid-19 pandemic: First, to protect the health and safety of our colleagues and their families, and second, to fulfill our role as a critical supplier of essential medications including those to mitigate the symptoms of Covid-19 to patients and healthcare customers around the world. Our countermeasures were strict and achieved the desired success. And, of course, they still apply.

Let me sum up in three points: First, CDMOs depend on a large and complex global supply chain and given that raw materials are often by definition in the dossiers single-sourced, the supply of certain APIs or their transport routes may be negatively affected. The pandemic has highlighted were supply chains are at greater risk of being disrupted. Our strategic procurement team has done a fantastic job in proactively addressing these, but the identification and approval of alternative resources is absolutely fundamental for our business.

Secondly, our operations and service levels depend on the 4,500 people who contribute to making products for our customers. Safety and hygiene measures have always been part of our daily operations, but through Covid-19 we were able to make them even better in this respect, we are proud that our absenteeism rate during the pandemic has been lower than ever before.

Thirdly, we have also learned that the Covid-19 pandemic accelerates digitization and virtual work. This even goes so far that customer meetings and negotiations of new contracts, onboarding of new colleagues, customer and regulatory audits and even due diligences can be performed digitally now plus administrative staff can work from home. All this leads to a real leap in efficiency and productivity.

Collaboration Is more Important than Ever

Dago Caceres, Global Strategic Marketing Leader, DuPont Nutrition & Biosciences

The pandemic has demonstrated that all members of the pharma community — from regulatory agencies to suppliers — can join forces and leverage their respective areas of expertise to develop safe, efficacious and cost-effective products, and deliver them swiftly to market. At DuPont, we've learned that the development time of novel APIs, of biologic or synthetic origin, can be further optimized and streamlined to bring crucial solutions — such as vaccines for prevention or medicines for treatment — to market faster. Now more than ever, pharmaceutical companies need to collaborate with their partners and stakeholders to facilitate the development of new medicines.

We've always known that business continuity is critical, but 2020 is a great reminder of its importance. The pandemic has shown that the pharmaceutical supply chain is a global, complex and interconnected web that needs to be assessed holistically, as it's only as strong as its weakest link. Each member of the chain plays a vital role in ensuring that products can be produced and made available to patients and consumers, even under the most challenging of circumstances. We'll likely see more companies focus on inventory build strategies to secure product in the event of unplanned shutdowns due to lack of resources. Additionally, we expect to see more suppliers expand the "flexibilization" of assets/materials on the systems side, to produce the same products in different assets and in various regions. This has always been a priority for DuPont, but it will become even more crucial as the industry visualizes what may lie ahead.

We've learned that digitizing our production capabilities, investing in improved technology and bolstering data infrastructure can produce even better products. We've invested in better planning and reporting tools, as well as in-depth digital and analytics, to enable faster decision-making, more efficient solutions and better understanding of variability in our processes — and we're already seeing outstanding results. Moving forward, we'll likely see increased digitization efforts across the industry, as well as virtual technical support throughout the supply chain and enhanced tools for remote communication and verification. This will allow us to keep our fingers on the pulse of the supply chain, without even being there.

Agile Companies Have Benefited from the Crisis

Andreas Bonhoff, CEO, TTP Group

In 2020, the pandemic will present us with a completely new situation: the process chains and flow of goods from outside Europe have been halted.

The trend in the pharmaceutical industry is: Find solutions to increase innovation, investment, value creation and jobs in the EU. Therefore, in the medium term, increased investment should flow into production in Europe. Investments in domestic production can be expected in particular in the area of pharmaceutical API.

Since the core of TTP Group is in Europe, we do not expect Covid to cause any persistent downturn. We are focusing on organic growth — particularly in times when pandemics may not remain isolated cases. And this is where we see our greatest market opportunities in the next two years as a specialized engineering service provider.

We are currently seeing that the pharmaceutical industry is doing generally well. We have responded to this trend with a broad range of services. Our local presence with competent employees directly in the customer's environment is of great benefit to us in these times. So, it is possible for us to be there for our customers during the whole Covid time and we are able to serve every customer requirement within the scope of the respective hygiene regulations.

Still, due to the higher coordination effort, the effects were mainly felt internally: deployment plans had to be optimized; home office infrastructure and networking capabilities had to be ensured.

Agile companies have thus benefited from the crisis. We have seen that modern companies are capable of implementing changes in just a few weeks.

Through the merger of TTP-Pharmaplan-Triplan, we already initiated a transformation process a year ago, which enables us to use cross-industry optimization processes.

The development of digitalization was definitely driven by Covid, which will also be of benefit to us after the crisis. The new situation has forced us all to deal with the new technical tools and to use them now in our day-to-day work.

Thanks to digital networking via a cross-group platform with over 900 experts, we are now bundling outstanding knowledge competence, across sectors and countries. This year was therefore also marked by an uninterrupted increase in the number of employees, which we were able to achieve with the help of digital tools, even during the Corona crisis.

Safeguarding the Reliable Supply of Essential Therapeutics

Wolfram Schulze, Vice President Information Systems, Organization & Digital Transformation and Head of Infection Prevention Task Force, Rentschler Biopharma

Cooperation in times of Covid-19 is key to weathering the crisis. In these unprecedented times, we at Rentschler Biopharma are deeply committed to safeguarding the reliable delivery of essential, sometimes lifesaving, therapeutics for our clients and their patients. At the same time, we are strongly dedicated to ensuring the safety of our employees and our partners.

We understand the change initiated by Covid-19 as an opportunity for further development and optimization of existing processes along the entire biopharmaceutical value chain – together with partners and clients.

A continuous optimization of operational fitness regarding processes, business continuity and digital maturity has always been an integral part of our company's strategy, even before the outbreak of the Covid-19 pandemic. We had previously started an initiative to focus on establishing second sources for raw materials and to balance global and local vendors to become more resilient against disruptions in global supply chains. Leveraging and further growing our strategic partner ecosystem will furthermore ensure the reliable delivery of premium services to our clients. The Rentschler Digital Agenda and its initiatives will complement and further enhance our existing services with digital capabilities, which become more and more important in our fast-paced and interconnected partner ecosystems.

In short, the Covid-19 pandemic helped us to verify that the direction set forth by the Rentschler Strategy 2025 is now even more valid than ever and allowed us to re-prioritize related strategic implementation projects.

United We Withstand the Corona Crisis

Thomas W. Büttner, Managing Director, Gemini PharmChem

In May 2020, at the height of the coronavirus crisis, Gemini PharmChem successfully launched commercial production of anthracycline anti-cancer active pharmaceutical ingredients (APIs) at its production facility in Mannheim.

This was a concerted push on behalf of Gemini's employees, shareholders, suppliers and other stakeholders. We are incredibly thankful for the efforts of the entire team to advance the company's strategic goals during these times of unprecedented challenge.

Gemini's production, now ongoing, is beginning to alleviate a worldwide product shortage in the anthracycline product category and helping doctors provide patients with the therapies needed to fight a range of cancers.

Gemini, a subsidiary of Synbias Pharma, plans to strengthen its product portfolio by launching the production of additional anti-cancer APIs later this year and is exploring other strategic initiatives to grow its production business. With this in mind, the group expects to increase its team in 2020 to meets its growing production needs and will continue to invest in its facility in Mannheim.

Collaborations and Partnerships Leveraged the Industry's Collective Knowledge

David Ginivan, Vice President Corporate Communications, Vectura

It has been remarkable to see how our industry has come together. Collaborations dominated the news headlines and the pharma industry was lauded for mobilizing quickly to try to help contain and treat the fast-spreading Coronavirus.

Collaborations and partnerships leveraged the industry's collective knowledge to expedite development and approval of new vaccines and therapies. These include compounds formerly tested on other viral pathogens, such as Ebola and HIV, and the repurposing of existing medicines to help in the fight against Covid-19.

It usually takes over a decade to develop a safe, effective anti-viral therapy. But, when it came to Covid-19, we didn't have that kind of time. One way to speed the process was to look at old drugs to work against this new disease threat.

One of those drugs was low-dose dexamethasone, an anti-inflammatory steroid which has been in use since the early 1960s. Scientists found that dexamethasone helped hospitalized patients who needed oxygen or were on a ventilator. It appeared to dampen the immune response, giving the lungs a better chance to recover. A breakthrough with a repurposed drug during the crisis.

Repurposing and repositioning projects offer the prospect of a faster route to patients than a discovery project for a new molecule; and, if the drug is already on the market, most necessary safety trials will have been completed.

As a result of the Covid-19 crisis, a key reminder for medical scientists and the industry is that, before embarking on new expensive discovery projects, we should look at what is in our medical arsenal as the solution might already be in our hands. In some ways, this crisis has laid out a blueprint for scientists to research the properties of existing and marketed molecules as one of the options to solve and treat emerging new diseases.

Business Continuity Planning, Agility and Flexibility are Crucial

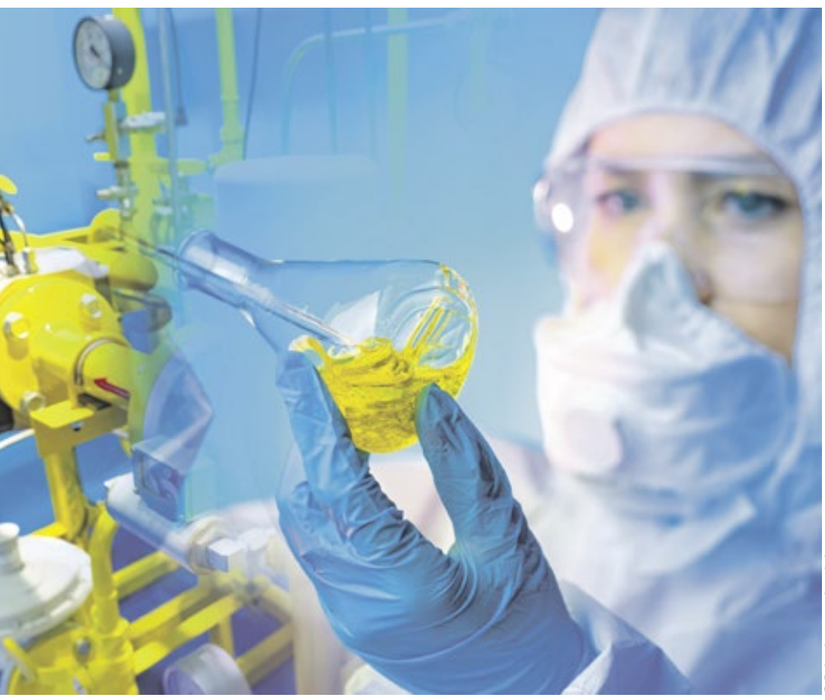
Leon Wyszkowski, President, Commercial Operations, Pharma Services, Thermo Fisher Scientific

As the world leader in serving science, Thermo Fisher Scientific has been involved in virtually every aspect of the ongoing fight against Covid-19, including more than 200 projects in vaccines, antivirals and treatments over the past several months. Over this time, there are several important learnings for pharma services businesses to keep mind: 1. Robust business continuity planning is crucial. The plan should be flexible and agile — since you will need to adapt. Importantly, you can't wait for a major event to happen — it needs to be in place and tested well before you need it. 2. Create simplicity and agility in the supply chain. It is more important than ever to work closely with supplier partners and monitor and reassess your supply chain. It is equally critical to validate alternative sources of supply and expedited transportation modes wherever possible to ensure critical inventories for both Covid and vital non-Covid medicines. 3. Ensure redundancy in supply chain. The pandemic has underscored the need for redundant capacity across the network to eliminate single points of failure. Second sources either within a single network or leveraging multiple supply organizations will be a priority in the future. 4. Continue to invest. While the Covid-19 pandemic continues to create uncertainty, continue to invest in your business. For pharma services, this means growth in capabilities, capacity and supply to ensure that critical medicines are never delayed in reaching patients. 5. Innovate and leverage digital. The adoption of digital technologies are critical to ensure business continuity and connectivity with colleagues and customers in new, virtual ways. For example, virtual and augmented reality technology can provide virtual site visits and inspections for regulatory agencies and customers alike, without the need for them to physically travel. These solutions create new opportunities for agility, flexibility and cost reduction at sites.

Resource Efficiency Pays Off

Development and Optimization of Biotechnological Processes

The production of biobased products using biotechnological processes offers great potential for resource efficiency. Good practice examples show that companies can save considerable amounts of natural resources every year, and also have less waste to dispose of. This reduces material, energy and waste disposal costs.



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The use of biotechnological processes in material-converting industrial goods production helps save resources thanks to more efficient production methods. In addition, the utilization of renewable raw materials conserves natural resources. Compared to conventional processes, a product made using biotechnological processes can be manufactured in milder reaction conditions (e.g. lower temperatures and pressure) and with fewer synthesis and processing steps. At the same time, higher space-time-yields can be achieved. This leads to lower volumes of raw materials, lower energy requirements as well as reduced water consumption. Furthermore, it generates fewer by-products and toxic substances, which as a rule have to undergo resource-intensive treatment, processing and possibly disposal. This often results in lower overall operating and waste disposal costs.

In industrial biotechnological processes it is primarily renewable raw materials that are used. Their use in industrial production reduces our dependency on finite resources and contributes to environmental protection and the reduction of CO_2 emissions, since the CO_2 emissions released during energy consumption at the end of the product life cycle are partly reused in the formation of renewable raw materials, whereas this possibility does not exist naturally with fossil fuels.

The use of renewable raw materials creates biobased products, which now have a positive image among consumers thanks to their positive ecological aspects. The performance and user-friendliness of such products used to be scrutinized and compared with conventional products. The higher price in some cases deterred consumers too. However, with the growing climate crisis, this skepticism is giving way to a change in thinking, and higher prices are increasingly being accepted by consumers. This is also reflected in the constantly growing market share of biobased products.

Process Development

In order to produce and process biobased products new biotechnological processes must be developed, or existing conventional processes must be modified and enhanced. This often represents a considerable undertaking, requiring innovative ideas and a high level of technical and scientific expertise in the process development. Moreover, the development process is marked by economic uncertainties arising owing to the difficulties in gauging the feasibility, productivity and competitiveness of the process to be developed, a development timeframe that is difficult to predict as well as a fluctuating raw materials base.

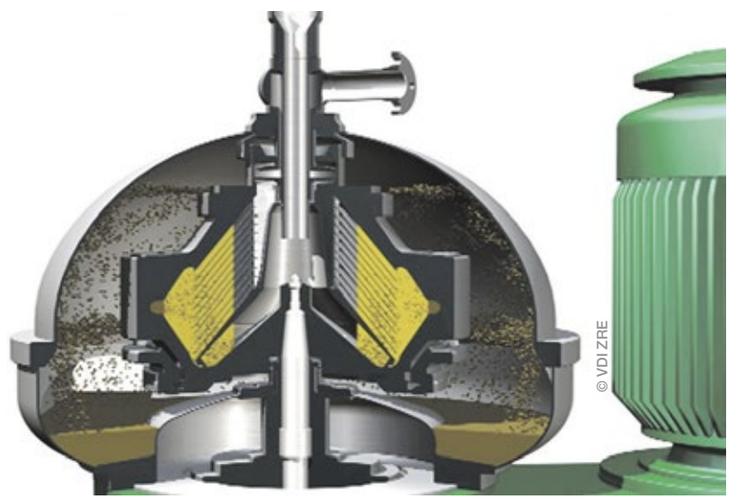
Mastering this challenge requires solutions such as miniaturization, automation and digitalization. It is already possible to accelerate bioprocess development today using high-throughput technologies in combination with bioinformatics algorithms. Future developments in innovative technologies could contribute to overcoming and mastering the existing risks and challenges in process development. This would ensure that the development of biotechnological processes is seen as a lucrative endeavor for companies and that more and more companies decide to develop and implement such processes.

Katja Saulich,
VDI Zentrum
Ressourcen-
effizienz (VDI ZRE)

When a company embraces the technological and economic challenges and converts its production process to biotechnological production processes, it can benefit from considerable economic and ecological advantages. Taking the example of vitamin B2 production, the resources used (material and energy) decreased by up to 60%. The waste generated shrank by up to 95% and the CO_2 emissions fell by up to 30%. The annual production cost savings amount to up to 40%.

Biocatalysts

In order to put in place a resource-efficient and economically viable biotechnological production process, the identification of suitable biocatalysts (enzymes and microorganisms)



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In the biotechnological production of ethanol, a separator enables the reuse of yeasts.

is an important requirement. Suitable biocatalysts can be selected with the help of innovative screening and analysis methods. Efficient biocatalysts demonstrate high catalytic activity and long-term stability — combined with a low deactivation rate. In addition, highly efficient catalysts are characterized by high reaction and binding selectivity as well as a high reaction speed.

Bioprocess Monitoring

Online sensor systems are a central element of bioprocess monitoring for biotechnological production processes. They are instrumental in ensuring that a bioprocess is resource-efficient and achieves the production target with a minimum of faulty batches. Biochemical target parameters are necessary for optimal bioprocess monitoring, although the direct measurement of these is normally not possible. Alternatively, data sets of other process parameters are gathered using indirect measurement methods and are used to glean relevant information about the process status with the help of intelligent evaluation algorithms.

Trends towards increasingly compact measuring systems (miniaturization) as well as the major progress in laser technology and detector design have widened the field of application of these analysis methods considerably. The integration of sensor technology, often complicated, is made easier by combining it with intelligent software. It provides automatic recalibration and thus significantly longer lifetimes. The intelligent sensor systems created thereby are able to conduct self-monitoring and diagnosis, integrated data evaluation with logic and control functionalities or interactive networking with other components in the process environment.

Making Know-how Available

On behalf of the Germany Federal Ministry for the Environment, the VDI Centre for Resource Efficiency (VDI ZRE) provides companies with free-of-charge instruments that aim to support the development and optimization of their own biotechnological process: The process visualization and the resource check "Industrial biotechnological processes" contain further examples and measures for increasing resource efficiency in production using industrial biotechnological processes.

Conclusion

The use of biotechnological processes for the industrial production of biobased products offers great potential for resource efficiency. Although the development and implementation of biotechnological processes carry a certain economic risk, in many cases the ecological and economic advantages outweigh the commercial risks. It is a challenge worth embracing. The development of highly efficient biocatalysts and high-performance bioprocess monitoring are considered the foundations for successful implementation.

Katja Saulich, Research Assistant, VDI Zentrum Ressourceneffizienz GmbH (VDI ZRE), Berlin, Germany

www.ressource-deutschland.de

Smart Trial and Error

Transforming Research and Development with Design of Experiments

Gaining and maintaining competitive advantage requires today's organizations to innovate at increasing speed. As products and processes become more complex, subject matter expertise alone does not always deliver progress at the pace demanded. "Trial-and-error" methods do not always yield optimal solutions when time is limited. A more systematic approach is required.

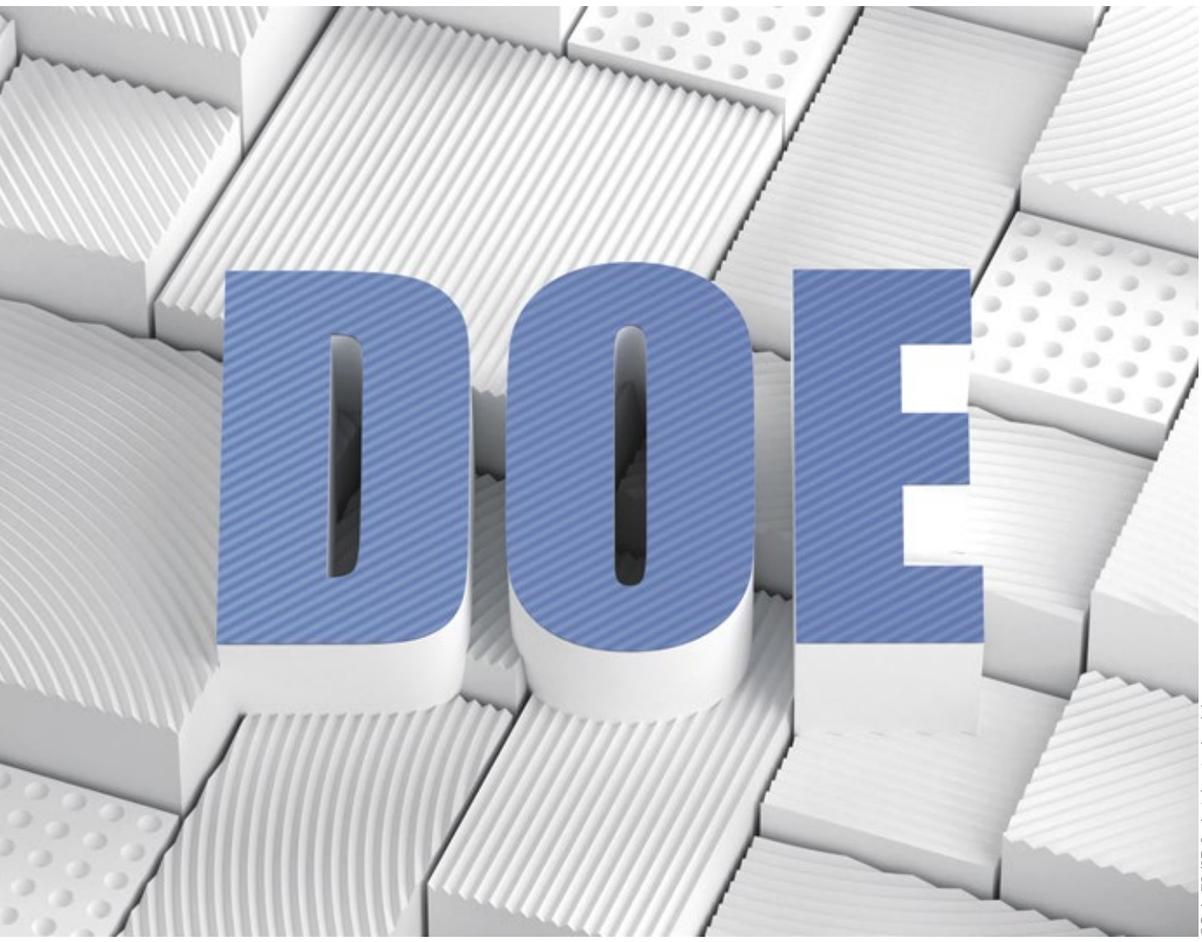
Many experts working in R&D rely on a traditional approach to this problem, changing one variable at a time. It might seem to offer the structure for more predictability, but such an approach can end up constraining innovation and decreasing efficiency in the long run. One-factor-at-a-time methods have some shortcomings, as they overlook synergistic and antagonistic interactions. They do not use proper randomization, and lurking variables might spoil results and lead to false conclusions.

The answer for an increasing number of organizations is design of experiments (DOE). DOE enables scientists to look at interactions, utilize randomization and change multiple factors — all leading to a better understanding of processes with fewer experiments. Proponents of DOE claim significant advantages, so why aren't more scientists seizing the opportunity to optimize processes while saving time and money through adoption of designed experiments?

Overcoming Objections to DOE

Pilar Gomez Jimenez, Principal Scientist at Johnson Matthey, has a master's degree and a PhD in chemical engineering. She has been working in R&D of catalysts and materials for over 15 years and is an enthusiastic practitioner of DOE.

At Johnson Matthey, DOE has delivered 50% to 70% savings in time and resources. She says that gaining management support has not been a problem. According to Gomez Jimenez, the main obstacle when encouraging others to adopt DOE is always the human factor: "As humans, we struggle to visualize a multivariate experimental space. We are able to imagine the effect of changing temperature, but if we are moving temperature and pressure at the same time, then analyzing the data gets more complicated and our minds struggle to visualize it."



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Peter Goos, University of Leuven

Perhaps because many scientists are taught to work with one factor at a time or because they have been doing things a certain way for a long time, it can be difficult to persuade teams to overcome their initial fear of statistical approaches to experimentation. Gomez Jimenez says it is essential to support colleagues to explore something new, particularly where a statistical approach is required.

Widespread adoption of DOE can often be hampered by initial fears that the process will be onerous, or that the scale and type of problem is not suited to DOE. In fact, DOE is a methodology that scales regardless of the size of the problem. It provides the ability to thoroughly explore the opportunity space, enabling scientists to define an efficient and effective data collection plan that enables them to build a model of the product or process. That model can then increase understanding of the problem, drive decisions and enable consensus with other stakeholders. The more complex a problem and the more factors involved, the bigger the opportunity space to be explored — and the greater the impact of DOE.

Achieving Life-Changing Results

Tim Gardner is a scientist and the CEO and founder of Riffyn, an organization enabling scientists to easily combine DOE with efficient data management and contextualization. Gardner said recently that DOE has changed his life, just as it has changed organizations where he worked in the past. Some plants where he worked with DOE experienced a productivity boost of 10-15%. Time to market for new products reduced fourfold, sometimes more, in one case shrinking from 15 months to 3 months.

Results like this inspired Gardner to found Riffyn and seek to make DOE a standard way of operating for more organizations. But he recognizes that people fear change, and for many, DOE represents the unknown. Whether there is confusion over the term DOE and what it actually means, or uncertainty over the use of maths and statistics, fear can prevent many organizations from seizing the opportunity. Seeing the transformational results of DOE first-hand is often an excellent motivator for organizations to embrace a new approach.

DOE helps scientists design and analyze results rapidly and in a visual way, enabling them to understand analyses quickly and explain them to other people. Visualization is key to demonstrating the value of the process to the wider organization without needing an in-depth knowledge of statistical analysis. Whether supporting the delivery of better solutions, products or services, a statistically designed approach to experiments can accelerate the discovery and creation of viable new solutions and ensure that they can be delivered at pace and at scale.

DOE offers plenty of advantages beyond saving time and resources. Improved predictability helps with planning and enables more efficient ways of working. This efficiency can help to ease the pressure levels within teams under pressure to deliver. Organizations can make better decisions faster and meet project milestones more predictably. Reducing the stress on individuals by giving them the right tools to be productive and efficient can benefit the whole organization.

JMP Webinar

On October 8, 2020, the webinar "Smart Trial and Error for Rapid Innovation" will feature a keynote presentation by Peter Goos on DOE, followed by a panel discussion with industry experts about the power of using smart trial and error to speed up innovation, achieve faster, more predictable cycles, and save time. To attend the presentation, please register here: https://bit.ly/3gSQmdS

Creating the Time and Space for Innovation

By actively manipulating factors according to a pre-specified plan, it is possible to gain a new understanding of relationships between inputs and outputs; achieve faster, more predictable cycles; and save time: in short, to know when a concept will work and when it will not.

Gomez Jimenez explains that because "you're looking at the full experimental space and getting a proper map of what the results will be and the interactions between the variables, the result is greater insight and confidence in the conclusions."

With the right tools, it is easy to get started and experience some quick wins, which in turn helps to convince colleagues, teams and the wider organization that there are significant benefits to be achieved with DOE. Bradley Jones, Senior Research Fellow at JMP, calls DOE "active learning" and highlights how it gives organizations the ability to "fail fast", which in turn drives rapid innovation. Perhaps reframing DOE in these terms would help to demystify it and encourage more scientists and organizations to make the leap.

Peter Goos, Professor at the Faculty of Bio-Science Engineering, University of Leuven, Leuven, Belgium

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Randomized Clinical Trials / Development of New Therapies

Is Real-Time Data the Key to Accelerating Drug Development?

The development and production of new vaccines and medicines is a time-consuming process. In the face of the Covid-19 pandemic, how can we utilize modern digital technologies to accelerate the development of new therapies and enable the earliest possible access to promising, potentially lifesaving, new treatments?

In order to accelerate therapy development, the process of randomized clinical trials (RCTs) in drug development needs to be re-evaluated, as current practices are too slow for acute states of emergency like the Covid-19 crisis. We can accelerate the analysis of the efficacy and safety of specific drugs that have demonstrative potential by looking in real-time at real world evidence/data (RWE/D).

Digital Technologies Enable and Simplify RWE Studies

Accelerated studies should happen under the umbrella of a simplified, pragmatic RWE study. Patient data should be collected, continuously monitored and analyzed, almost in real-time, from electronic health records and electronic medical records (EHR/EMR). Digital technology has evolved to the point where, in a global health crisis like this, it allows us to react quickly, efficiently and for a large number of patients. Today, there are platforms and technologies available that can provide real-time insights into data across provider networks, combining real-time access to longitudinal clinical data with analytics and advanced visualization capabilities.

Digital Technologies Allow Patients to Report Symptoms Remotely

Another technology option in a health crisis is electronic patient reported outcomes (ePRO). In the case of Covid-19, it is deemed that the majority of afflicted individuals exhibit mild symptoms and may be under self-quarantine. While they may be unable to visit clinics and record clinical data for obvious reasons, they can easily use mobile apps for reporting clinical outcomes, such as simple measurements like the severity of cough and fluctuations in temperature. Remote monitoring can easily be orchestrated to support these efforts through this real-time data collection. This provides vital data streams for clinical analysis and avoids the protracted rigmarole of setting up new investigator sites and traditional means of patient recruitment.

Digital Technologies to Enable an Integrated Data Hub

Recent advances in digital engineering allow for mobile apps to be deployed and updated within days, thereby even rendering the RWE study "adaptive" in addition to real-time. It is possible to set up "visual command centers" for pandemics. For example, data streams from EMR systems and electronic clinical outcome assessment (eCOA) apps could come together from across the country to provide a daily/weekly snapshot of how the infected patient population is reacting to potential treatment for Covid-19. The whole system could be set up as an integrated research platform using umbrella designs where new treatments are seamlessly added, while ineffective ones are removed, determining safety and effectiveness in real-time and moving closer to successful treatments.

Srinivas Shankar, Cognizant

New Regulatory Framework Necessary

Regulations for drug development have evolved over the latter part of the earlier century and may be apt for treatments such as psoriasis, hyperlipidaemia — in essence, diseases whose progressions are incomparable to that of a pandemic. In a globalized world, we need to have a regulatory framework that enables the industry to switch to operating in an emergency mode with accelerated decision-making, drug testing and development in the wake of pandemics situations. We need to act at the speed of viral replication. In order to protect humanity from future pandemics, we need to have a new regulatory framework that allows us to develop, study, and test new promising compounds in a matter of weeks rather than in months or years.

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CHEManager INTERNATIONAL

INNOVATION PITCH

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Bioprocessing
Spectroscopic Online Monitoring and Control of Bioreactors

Composite Structures
Surface Functionalization with Innovative Plasma Technology

Start-up Community
Key Factors for Evolving a Local Entrepreneurial Ecosystem

WILEY

Glucose Control of Bioprocesses

Online Monitoring and Control of Bioreactors by Mid-Infrared Spectroscopy

Irubis is a biotechnology start-up based in Munich, Germany. It was founded in 2017 with the aim to make online monitoring and control of bioreactors by mid-infrared spectroscopy to become standard. Biopharmaceuticals are predominantly expressed by mammalian cells in so-called bioreactors. A major challenge is to ensure the optimal nutrient concentration for the cells. Currently, in most bioreactors samples are taken manually once per day to measure the nutrient concentration in a separate analytical device. Irubis enables continuous monitoring and control of the nutrient concentration with a novel mid-infrared spectroscopy system and a machine-learning evaluation software.

Lorenz Sykora (CTO), Anja Müller (COO) and Alexander Geißler (CEO) founded Irubis in 2017.

CHEManager: How did it all start and what was there first: the idea or the company?

Alexander Geißler: It all started with a cost-effective silicon crystal that serves as a sample carrier for mid-infrared spectroscopy. The master's thesis of our co-founder Lorenz Sykora was about this silicon crystal. This sensor component, which is up to 100 times cheaper than conventional crystals, laid the foundation for the company. The big question was for which market and for which application.

How did you find your market in the biopharmaceutical industry?

A. Geißler: We did a lot of market research, read dozens of publications and spoke to many people from different industries. After digging deeper and deeper into the various „problems" of the customers, the application has finally revealed itself to us, as several experts from the biopharma industry asked: "Why don't you use your single-use technology to monitor bioreactors?"

Why didn't other companies monitor bioreactors with spectroscopy? What makes Irubis' technology different?

A. Geißler: With existing spectroscopic methods, a time-consuming calibration of up to three months is required to monitor cell culture processes. Instead, we will initially focus on glucose control. Our analytical device Monipa requires only a starting value and then keeps this value constant based on a relative measurement.

Anja Müller: The relative measurement is achieved by our mid-infrared spectroscopy system combined with our software that evaluates the spectra, controls feeding pumps and thus creates a closed loop system for glucose. We realized a plug-and-play solution without the need of a calibration. The bioreactor is connected to our device by disposable flow-cells that contain the silicon crystal.

Where does the device name "Monipa" come from?

A. Müller: Monipa is the combination of "Monitoring" and "PAT". PAT stands for process analytical technology, a term defined by the FDA for the control of important process parameters in manufacturing of pharmaceuticals.

Which obstacles did you have to master so far during the Irubis journey?

A. Geißler: As a technology-driven company, a challenge was to find the market for our technology and to understand the customer problem down to the smallest detail in order to build a great solution through a close exchange and cooperation with the biopharma industry.

A. Müller: We are very excited to be among the winners of the H2020 EIC Accelerator Pilot as we now have the resources to expand our team and finalize our product. The biggest challenge now is to find top-level talents.

What will be the next steps to develop Monipa?

A. Müller: The next steps for Monipa are to complete a certified small series in 2021 and to share the message to all biopharma companies around the world: We have the solution for your needs! With Monipa, we deliver a plug-and-play device that enables continuous glucose control and monitoring.

Personal Profiles

Alexander Geißler (Co-founder and CEO) holds a master's degree in technology and business administration from the Technical University of Munich (2013). Before founding Irubis, he worked for 4 years for another TUM high-tech spin-off. He has vast experience in sales, marketing, and business development. He blends the needed technical and sales skills to make a high-tech company like Irubis succeed. Now he is driving all sales strategies forward and aims for the successful market launch of Monipa.

Anja Müller (Co-founder and COO) holds a master's degree in physics from the Technical University of Berlin (2016). Over the course of her studies, she acquired relevant knowledge and skills in the field of FTIR spectroscopy. During her master's studies, she has been awarded a scholarship for the Career Building Program at Femtec, where she acquired important management and leadership competencies. At Irubis she is responsible for funding and project management.

Business Idea

Single-use Flow Cell and MIR Spectroscopy

Biopharmaceuticals are produced mainly by mammalian cells in vessels, so-called bioreactors. Production and process development of biopharmaceuticals require a precise monitoring and control of key parameters such as nutrients and metabolites. Currently, nutrients and metabolites of most bioprocesses are measured by offline analytical technologies. Offline measurement means taking the samples from the bioreactor and analyze them in a separate device. This manual process needs to be performed by the lab technicians once a day and also at weekends. Thus, a continuous regulation is not possible, leading to suboptimal product yields and an increased risk of cross contamination. By online monitoring, which means a 24/7 control of the process, a higher product quality and yield can be achieved.

The high potential of mid-infrared (MIR) spectroscopy for online monitoring of glucose and lactate in mammalian cell cultures was already demonstrated in several publications. Translating this technology into bioprocessing has been an issue because of high equipment costs and low robustness of the probes used so far. Irubis developed Monipa, an innovative MIR spectrometer system that enables efficient and robust online control of glucose concentration in up to four bioreactors simultaneously. It uses a qualitative measurement method, thus eliminating the time-consuming need of generating calibration models. Monipa can be easily integrated into the bioprocess by connecting its single-use flow-cell via a loop to the bioreactor. The external flow cell results in a higher robustness than an inline alternative. Monipa allows the use of infrared spectroscopy in bioprocessing, which leads to a high product yield and product quality.

Features of Irubis' Technology:

- 24/7 online control of glucose by closed loop
- No contamination due to sterile single-use flow cells
- High robustness compared to other spectroscopic methods
- No calibration model necessary, thus very high transferability (scale-up, cell lines, media, etc.) possible

- Contact details: Irubis GmbH, Munich, Germany
www.irubis.com

IRUBIS

Elevator Pitch

Bioreactor Monitoring Made Easy

Irubis was founded in 2017 by Lorenz Sykora (CTO), Alexander Geißler (CEO) and Anja Müller (COO). The three young professionals started their business with a cost-effective silicon crystal for infrared spectroscopy. While other sample carriers for infrared spectroscopy are usually made of diamond, zinc selenide or germanium, the Irubis crystals are fabricated from silicon wafers. They therefore only cost a fraction of the price while maintaining the same high quality.

The Irubis microstructured silicon crystal is an innovative sample carrier for ATR infrared spectroscopy. ATR stands for attenuated total reflection and is the method of choice for almost all routine analyses of fluids and solids.

In 2018, the founders started building an online monitoring system for bioreactors and to test it in the biopharma environment at three big biopharma companies. In 2020, Irubis began expanding the team and completing product development.

Milestones

2017
- Winner of the Medical Valley Award
- Foundation of Irubis
- Development of a silicon crystal for infrared spectroscopy

2018
- Technological proof of concept: online monitoring of glucose with Irubis silicon crystal and mid-infrared spectrometer
- Prototype with higher sensitivity of the system

2019
- Validation of Monipa prototype at three biopharma companies

2020
- One of the winners of the H2020 EIC Accelerator Pilot
- Additional projects and validation of Monipa prototype in the biopharma industry

Roadmap

2021
- Certification of Monipa
- Market entry in Europe

2022
- US market entry

Monipa from Irubis connected via tubes to a bioreactor.

Single-use flow cell with silicon ATR crystal. It easily click-mounts to Monipa.

Revolutionizing Surface Functionalization

Single-step, Ambient, Dry Grafting of Organic Compounds and Biomolecules onto any Substrate

Molecular Plasma Group (MPG), founded in 2016, was created as a spin-off from the Luxembourg Institute of Science and Technology (LIST) and the Flemish Institute for Technology Development (VITO). Four years after its creation, the start-up is about to make a major international breakthrough. With its revolutionary cold atmospheric plasma technology, the company is able to immobilize a wide range of bio-molecules such as antibodies, DNA, proteins, peptides, etc. onto any substrate whilst keeping full bio-functionality. The main focus in the market is on major players in the field of gluing and on robotics technology integrators who can use the technology as part of their solutions in industrial production lines. But MPG's technology can also be used in the biomedical industry, e.g. to add antiviral and antibacterial agents, in the form of ultra-thin coatings.

Marc Jacobs,
Molecular Plasma Group

Régis Heyberger,
Molecular Plasma Group

CHEManager: How did it all start?

Marc Jacobs: In 2016, Luxinnovation, Luxembourg's national innovation agency, introduced me to a researcher who had started a company based on their research at the LIST. I could see that the technology was groundbreaking and that with a little help, it could take off.

At first, we had no idea where we would bring the most value and therefore which industry we should go after. In light of this, we started very broad, entering the market by reaching out to multiple industries to see which problems we could help them solve, and where we would be able to offer a unique solution. Within one year, we had initiated 50 customer-funded proofs of concept with multiple clients.

What makes the technology so unique?

Régis Heyberger: Our technology allows us to permanently bond organic molecules onto any surface and change its chemical and/or physical functionalities. Our process of surface functionalization takes place at room temperature and at extremely low energy levels, making it both environmentally sustainable and possible to work with highly sensitive molecules such as antibodies and proteins.

The reach of our technology is only limited by imagination, but the bulk of our solutions are applied in the world of adhesion. As an example, we enable Teflon, a notoriously difficult material, to be adhesively bonded onto any material with our trademarked MolecularGrip solution.

Which obstacles have you had to master so far?

M Jacobs: Since the company was founded, we have had to pivot our business model several times, however Covid-19 presented one of the most challenging obstacles, effectively shutting down all our R&D in the automobile and aeronautical industries.

That being said, it also gave us a fantastic opportunity. We started looking into the possibility of grafting antiviral molecules onto face masks and other types of PPE to protect healthcare workers and the wider population. We have now successfully concluded the proof of concept and are initiating scale-up.

What has been your most exciting project?

R. Heyberger: Our most exciting project, which even surprised us, was our proof of concept showing that we could immobilize antibodies onto a substrate in a single-step, 10-second process, 10,000 times faster than the current standard.

This proof of concept was completed in collaboration with the University of Leuven and was a key development in our technology, as it showed that complex biomolecules retain their function when bonded to a surface using our plasma technology. It also opened the door to the healthcare industry, which we had never considered as an interesting direction beforehand.

This project clearly showed us that our position as a technology platform is viable and we firmly believe that our way forward is in partnerships, with industrial companies as well as research institutes and universities.

What will be the next steps to develop?

M. Jacobs: Over the next 12 months, we will have two key focus areas. Firstly, we will be developing the antiviral functionalization of PPE and taking it to market with multiple industrial partners.

Secondly, we will be tackling the adhesion issues which are omnipresent in many industries by continuing to develop the scope and breadth of the application of our technology, both in terms of machine and solution development.

In the near future, we will be also entering the American market and we expect several strategic partnerships to come to fruition over the next 12 to 24 months.

Personal Profiles

Marc Jacobs (CEO and investor) has a master's degree in Engineering from the University of Leuven and a Sloan master's degree in Leadership and Strategy from London Business School. He is a serial entrepreneur and is widely involved in the Luxembourg start-up ecosystem. He is also a cross-cultural consultant in the Hofstede Insights Network and author of the book "Negotiate like a Local" which applies Geert Hofstede's 6D model of culture to the world of business.

Régis Heyberger (COO and shareholder) holds a Ph.D. in Cosmology from the University of Strasbourg. He has several patents in his name and is an expert in robust upscaling of innovative technologies having worked for General Motors, Sony and Plastipak. He is certified as a Six Sigma Master Black Belt expert and leads the scientific team as well as the operations of the company.

Business Idea

Key Enabling Technology

MPG's technology breaks the barriers of traditional plasma technologies by using cold atmospheric plasma as a vector to covalently bond organic molecules onto any substrate. Positioning themselves as a technology platform, MPG develops new and exciting applications with partners in multiple industries such as the aerospace, automotive and healthcare industries. They offer the unique ability to robustly scale up the solution developed on the R&D equipment to industrial level. They are also interesting to universities and research institutes who can use MPG's groundbreaking technology for research purposes with the goal of publishing in journals and developing application-related patents.

Unique in five ways:

- One-step, dry process: No time lost to solvent flash-off, drying or incubation
- Permanent: The plasma activates both the substrate and the chemistry, causing them to bond covalently to each other. The surface remains stable as the functionality has been permanently modified.
- Eco-friendly: As the process is very low in energy consumption, with no solvents and near-zero emission, it is very eco-friendly. It also typically uses 100 times less chemistry to coat a surface than conventional wet chemical methods.
- Versatile: The technology can be used with an extremely wide range of precursor molecules (from organic molecules to complex biomolecules and nanoparticles) and almost any substrate (plastic, glass, metal, elastomers, temperature sensitive materials etc.).
- Readily scalable: Any process solution developed on our lab systems can be readily scaled to a robust industrial solution.

The technology can have widespread impact in many sectors, most recently aiding the fight against Covid-19, by developing an application to treat hard-to-treat PPE materials, such as polypropylene nonwovens, with antiviral compounds to limit the spread of infection within a healthcare setting.

- Contact Details:
  Molecular Plasma Group, Foetz, Luxembourg
  www.molecularplasmagroup.com

Elevator Pitch

Uniquely Scalable

MPG was founded in 2016 in Luxembourg, a newcomer into a world of plasma that had been around for decades. MPG is however unique in its ability to use atmospheric plasma as vector to graft organic chemistry onto any surface, opening a completely new field of plasma technology. Going where no one has gone before, they develop solutions to problems which cannot be solved with traditional plasma technology. Their scope of impact is limited only by imagination as they are easily able to functionalize any surface and deposit a vast number of different precursors like primary amines, epoxies, organosilanes, antibodies and antiviral compounds. The process is near-zero emission, very low energy and uses no solvents, which makes it fit perfectly in the ideals set out in Europe's Green Deal.

Milestones

2016
- Foundation of the Company

2017
- Spin-off agreement with VITO (Flemish Institute for Technology Development)
- Creation of MPG's Belgian subsidiary

2018
- 50 successful proofs of concept sold, mostly in the field of adhesion
- Successful proof of concept for the immobilization of antibodies
- Successful application to Luxembourg's Fit 4 Start Accelerator Program in the first health tech cohort

2019
- Reached €1.5 million turnover
- Successful graduation from the Fit 4 start Accelerator Program
- Moved Belgian subsidiary into the Bio-Incubator in Leuven

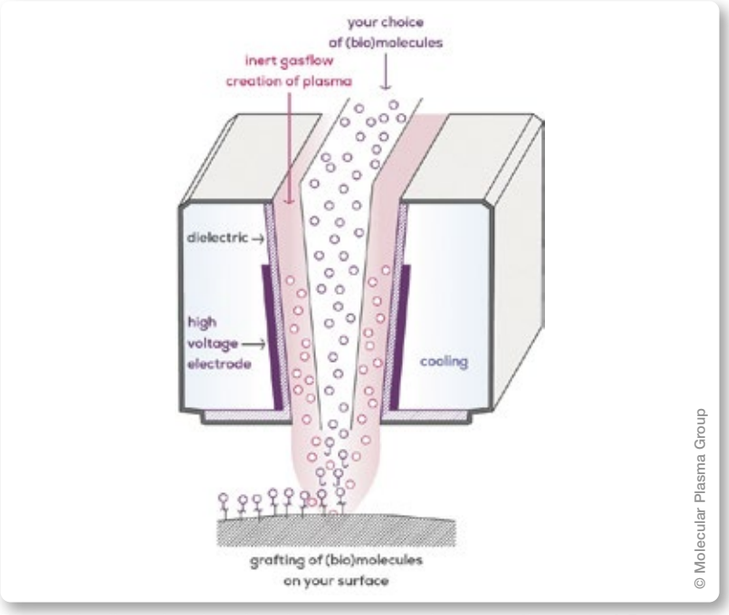
2020
- Creation of MPG UK
- Successful proof of concept for antiviral functionality
- Initiated industrialization of antiviral technology

Roadmap

2021
- Industrialization of antiviral technology
- Entry of North American market
- Initiate powder treatment technology

2022
- Move to larger premises
- Enter diagnostics market

Molecular Plasma Group's PlasmaLine 300 – R&D System.



PlasmaLine linear head enables homogeneous plasma coating up to 1.5 m width.

Evolving an Entrepreneurial Ecosystem

The Environment in which Start-ups Operate Influences their Success to a Large Degree

We are in the midst of a start-up revolution. The growth of innovation-driven start-up activity is profound and global in scope, and it is a driving force of change even in mature industries such as the chemical and pharmaceutical sector. But what has triggered this start-up boom, makes start-up communities thrive and improves collaboration in these complex environments? CHEManager asked Brad Feld and Ian Hathaway, the authors of a new book on the topic, to discuss these questions. Feld has been an early-stage investor and entrepreneur for over 30 years; he is a recognized speaker on the topics of venture capital investing and entrepreneurship. Hathaway is a leading thinker and writer in the areas of entrepreneurship and innovation, and advises start-ups in the United States and Europe.

Brad Feld

Ian Hathaway

CHEManager: The last decade has been a transformational one for entrepreneurship throughout the world. What are the reasons for this start-up boom?

Brad Feld: Today, the proliferation of digital technologies, the availability of information on entrepreneurship, and the quest for sustained economic growth have put start-ups on the map for people, governments, corporations, and other stakeholders around the world. The confluence of ubiquitous high-speed connectivity with inexpensive, powerful, and remote computing has dramatically lowered the cost of starting a digitally enabled business, allowing entrepreneurs to start new ventures in more places. The momentum and excitement behind today's entrepreneurs feel unprecedented.

Do you believe that your book 'Startup Communities: Building an Entrepreneurial Ecosystem in Your City', published in 2012, has been one reason for this shift in thinking?

B. Feld: Yes, today, we understand that communities of support and knowledge-sharing go hand in hand with other inputs and resources. The importance of collaboration and a long-term view has gained broad acceptance by entrepreneurs and start-up community builders. These principles are at the forefront of the leadership behind many start-up communities around the world.

Using the example of Boulder, Colorado, my book provided practical guidance for entrepreneurs and other stakeholders to improve the start-up community in their city. 'Startup Communities' stressed the behavioral, cultural, and practical factors that are central to a collaborative system of local entrepreneurship.

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Considering this progress made in recent years, where do we stand in terms of the start-up ecosystem?

Ian Hathaway: A great deal of start-up activity is still highly concentrated in large, global, elite cities. Governments and other actors such as large corporations and universities are not collaborating with each other or with entrepreneurs as well as they could. Too often, these actors

try to control activity or impose their view from the top down, rather than supporting an environment that is led from the bottom up, principally by entrepreneurs. We continue to see a disconnect between an entrepreneurial mindset and that of many individuals and organizations who wish to engage with and support local start-ups.

How can these problems be solved?

B. Feld: There are structural reasons for this, but we can overcome these obstacles with appropriate focus and sustained practice. We have to get all relevant parties better aligned — from founders to governments to service providers to community builders to corporations and beyond. We hope that our new book 'The Startup Community Way' will be transformational while building on top of the foundation created by 'Startup Communities' and the work done by people in start-up communities everywhere.

Financing is critical for entrepreneurs. While in some parts of the world, capital available for start-ups is plentiful, in many others, it is still lacking.

B. Feld: Right! Consider Boston versus Orlando, or London compared to Caracas. Talent and technology are ubiquitous, but tangible opportunities are not. Along with the widely recognized growth opportunity presented by entrepreneurship in the digital age, the environment in which start-ups operate influences their success to a large degree. It is the nature of these external factors — and more critically their linkages with entrepreneurs and with each other — that explains why some places can consistently produce high-impact start-ups while others struggle.

In many cities, regions, and countries, little progress has been made in cultivating the communities of support and knowledge-sharing that entrepreneurs need to thrive. The gap between success and failure is not due to an absence of available knowledge about how to improve conditions for local entrepreneurs.

So, why is this so challenging?

I. Hathaway: While the attitudes, behaviors, practices, and values at the heart of vibrant start-up communities are second nature to many entrepreneurs, they often are counterintuitive or misaligned with competing incentives, especially when the person represents an organization such as a large corporation, university, or government. These institutions, which are hierarchical organizations, operate in ways that are antithetical to start-up communities, which, like entrepreneurial companies, thrive in a network model.

> *„The importance of collaboration and a long-term view has gained broad acceptance by entrepreneurs and start-up community builders."*

B. Feld: As we started work on the new book, we compiled a list of mistakes people make around start-up communities. We found many similarities to the mistakes people make when interacting with complex adaptive systems, including applying linear systems thinking in a nonlinear world; attempting to control a start-up community; addressing problems in isolation; focusing on the parts of a start-up community rather than the interactions between them; believing that a start-up community is formulaic or replicable; and measuring the wrong things. Shifting from a linear system approach to a complex systems mindset is a powerful way to address these challenges.

Yet, there are numerous examples of successful entrepreneurship in cities or regional clusters around the globe. What do they have in common?

B. Feld: We emphasize that no two start-up communities are the same, have equivalent needs, or operate on a comparable time frame. For each example where something worked in one city, there's at least one other city where it didn't. That's the nature of these systems.

In 'Startup Communities', I introduced the idea of the Boulder Thesis as a basis for creating a start-up community in any city. The four principles of the Boulder Thesis are:

1. Entrepreneurs must lead the start-up community.
2. The leaders must have a long-term commitment.
3. The start-up community must be inclusive of anyone who wants to participate in it.
4. The start-up community must have continual activities that engage the entire entrepreneurial stack.

Does that mean that any city or region can become a start-up hot spot by applying the principles of the Boulder Thesis?

B. Feld: Boulder has a lot going for it — a well-educated workforce, a leading research university, a flurry of high-tech companies and research labs, a plethora of amenities, and the strong sense of community. For that reason, using Boulder as a model for start-up communities is criticized by some for being too idealistic. While understandable, this criticism misses the point. The lesson from Boulder is not that everything is perfect and that, if copied, a similar outcome can be achieved elsewhere. The true lesson is that Boulder's collaborative nature is what allows it to get the most out of the resources it already has in place.

Rather than be concerned about imitating Boulder, instead draw the lesson that building a critical mass of people who are helpful and collaborative will improve the odds that entrepreneurs will succeed, no matter what other resources are available today.

I. Hathaway: We have a deeply held belief that you can create a vibrant, sustainable start-up community in any city in the world, but it's hard and takes the right kind of philosophy, approach, leadership, and dedication over a long period of time.

Many entrepreneurs move to places with a vibrant start-up community like Silicon Valley - and still fail.

B. Feld: We don't think a person should have to move to Silicon Valley — or any other specific place — to become a successful entrepreneur. Instead, we want people to be empowered to pursue entrepreneurial endeavors anywhere they choose to live. Doing so may come with inevitable tradeoffs, but people who start businesses in the places they want to live are more likely to succeed than those who do not.

I. Hathaway: We believe entrepreneurship can transcend political, economic, and cultural boundaries. For us, this is especially important to address in our current geopolitical climate and in the face of the many societal challenges we face globally.

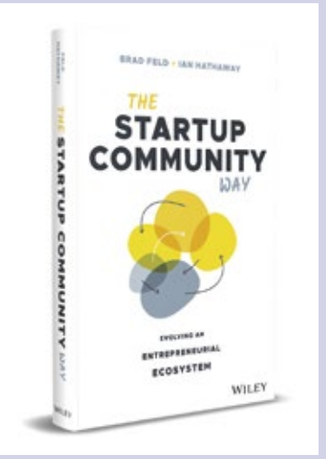
https://startupcommunityway.com/

The Startup Community Way

Evolving an Entrepreneurial Ecosystem

The 'Startup Community Way' is an explanatory guide for start-up communities. The book builds off of the success of 'Startup Communities', going more in-depth in some areas while correcting foundational mistakes in others. Being neither an update nor a second edition to 'Startup Communities' the 'Startup Community Way' benchmarks progress made, develops new areas of inquiry and exploration, makes adjustments, and takes the content in a new direction. The book's goal is to help understand how to create a long-term, vibrant, sustainable start-up community in any city in the world.

The authors collectively bring decades of experience to the practice and study of start-ups, start-up communities, and their impact on local societies and economies. They have spoken with thousands of entrepreneurs and other start-up community participants around the world and have taken both a pragmatic and researched approach to cultivate the material presented in this book.



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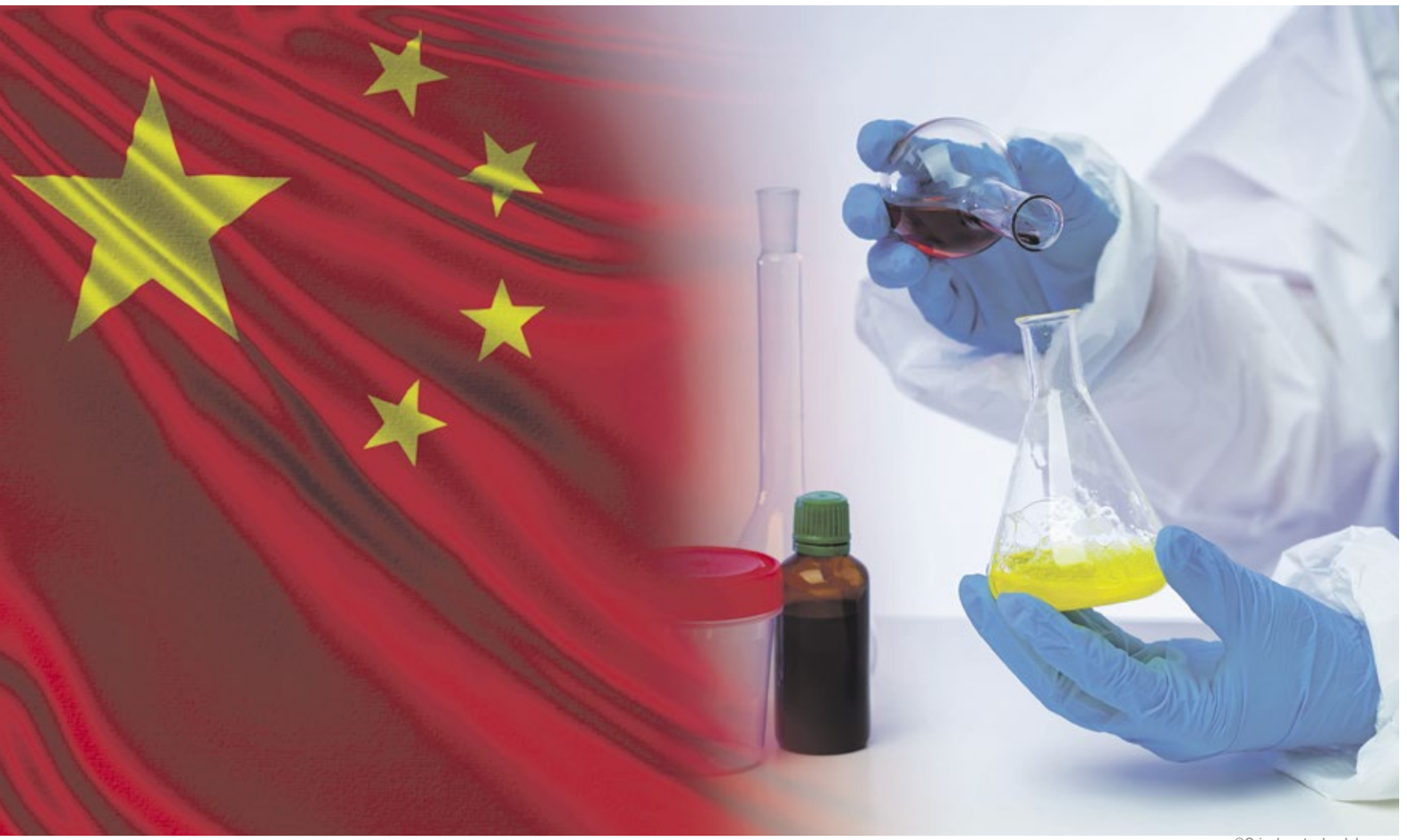

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Continuation Rather than a Change

Preview on the 14th Five-Year Plan and China`s Chemical Industry

China`s 14th Five-Year Plan (FYP) covering the period from 2021 to 2025 will only be published after its acceptance by the National People`s Congress in March 2021. However, the drafting process has long started, beginning with ministries commissioning investigations and research organizations working on reports.

Kai Pflug, Management Consulting – Chemicals, China

The development of the FYP is led by the National Development and Reform Commission (NDRC), which collects input from the ministries and other sources and uses this input to prepare a series of draft documents. Some potential focus areas of the new plan have already been mentioned in the press. The objective of this paper is to give an overview of these likely key points and discuss their impact on China`s chemical industry.

What will the 14th Five-Year Plan Be about?

According to a RIAC report, "The new plan is expected to focus on the creation of a high-income economy while prioritizing four spheres: digitalization, market accessibility, environmental improvement, and rural development." Overall, this represents only a gradual shift from the key themes of the 13th Five-Year Plan, which in 2016 I summarized by the five points of innovation, environmental protection, reducing the income gap, opening and rural-urban balance.

Indeed, the way the five-year plans are developed — in multiple stages over a period of time, with a large number of input providers — virtually guarantees that a new plan will not represent a massive deviation from the previous one, but rather a document that builds on previous achievements in a gradual way. Let us get a bit more specific about likely key themes of the 14th FYP and discuss their impact on China`s chemical industry.

Environmental Protection

The 13th FYP will likely be remembered in particular for its strong emphasis on environmental protec-

tion. The 14th FYP will continue to highlight environmental protection, building on the path outlined in the past few years. One key climate and sustainability advisor to the government, Wang Yi, has suggested replacing the energy consumption cap with a carbon emissions cap in the 14th FYP. On the other hand, in some areas there will likely be a reduction of subsidies, for example for solar and wind energy as well as for electric vehicles, as these technologies are assumed to no longer need constant support to be competitive in the marketplace.

For the chemical industry in China, this will mean that the tight supervision of the industry will not loosen up. The relocation of chemical production to chemical parks will continue, while at the same time the confirmed chemical parks will be upgraded.

In the years to 2025, even large chemical plants will have to relocate. Certain chemical segments that are regarded as highly polluting and not contributing to China`s modern economy may find it hard to find any suitable location at least in the most popular chemical parks, for example leather chemicals or some dyes.

"There will likely be a reduction of subsidies, for example for solar and wind energy and for electric vehicles."

Chemicals for which alternative production routes with different environmental impact exist may see a more strongly enforced shift to the more environmentally friendly route — for example, this may be the only route for which capacity expansions will be permitted.

On the other hand, increased environmental protection will also be a boon to many chemical segments that provide relevant materials, be it membranes or lithium salts for rechargeable batteries, polymers and coatings for wind turbines, electronic chemicals for the production of photovoltaic cells or filter materials used in exhaust cleaning.

A further push may come depending on specific goals in the FYP, for example, tighter fuel efficiency regulation for vehicles could benefit the producers of high-end plastics for automotive applications. Negative surprises are also possible — for example, a carbon cap may increase the cost of chemical production.

Innovation and Technology

Somewhat surprisingly given the background of China`s top politicians in engineering and sciences (Xi Jinping himself has a degree in chemical engineering), R&D spending is one of the few areas where China is likely to fail meeting its target outlined in the 13th FYP. In 2019, China's R&D expenditure was only 2.2% of GDP, compared to a 2020 target of 2.5%.

"The tight supervision of the chemical industry in China will not loosen up."

The 14th FYP will almost certainly at least confirm the previous target. Political developments such as the USA restricting exports of some high-tech goods to China have increased China`s desire to reduce its reliance on such imports. This will mean that leading-edge sectors of the Chinese economy will receive greater investments.

For chemicals, the electronic segment is highly relevant. It is the chemical segment for which China`s dependency on imports is the strongest. At the same time, it is the most difficult segment for local players to catch up due to its rapid pace of innovation. Local players in this segment will likely be able to benefit from generous R&D subsidies.

Other chemical areas are new materials, mostly those already listed in the 13th FYP, including engineering plastics, organosilicones, fluoro-organic compounds, membranes for water treatment etc.

It will be interesting to see to what extent modern coal chemistry will be further promoted in the 14th FYP. On the one hand, this is an area in which China has a leading global position and ample natural resources, and its promotion may also help the development of some Western provinces. On the other hand, pushing coal chemicals contradicts China`s environmental targets, as even if the technology does not cause local pollution, it certainly contributes to carbon emissions.

Self Sufficiency

Within the framework of the 14th FYP, China is expected to rely more on its domestic market than in the past. This is both a consequence of the increase of this market due to China`s massive past GDP growth, and of complications in global trade due to frictions with the USA and the effects of the coronavirus.

An early indication of this shift is the latest "Go West" plan announced in June 2020. This plan outlines a way to seek growth from China`s western regions to compensate for economic losses in the export-reliant eastern provinces. It includes a number of infrastructure projects including a Sichuan-Tibet railway, high-speed rail links, and a series of airports, reservoirs and irrigation projects. The government will also develop new energy projects, such as oil storage facilities, and encourage industrial projects to shift operations westward.

China`s objective to become more self-sufficient is highly relevant for the chemical industry, as China currently is a strong net importer. According to CPCIF president Li Shousheng, the domestic market for chemicals has been undersupplied for a long time. In 2019, the trade deficit of the whole industry was $268.3 billion. Imports of synthetic resin increased by 12.4%, polyethylene increased by 18.8%, polypropylene increased by 6.4%, polystyrene increased by 13.6%, polycarbonate increased by 12.8%, and pesticide imports increased by 14%. In particular, the import volume of high-end products such as new chemical materials and special chemicals has increased to varying degrees.

"The relocation of chemical production to chemical parks will continue."

This stands in contrast to goals increasing self-sufficiency that were published in 2016. For example, China aimed to increase self-sufficiency in the ethylene chain from 49% in 2015 to 62% in 2020, and from 67% to 92% for PP. However, for PP, the rate stood only at about 86–87% in 2019. As a consequence, the 14th FYP is likely to further promote self-sufficiency for these basic polyolefins.

The issue is not only one of insufficient capacity, but also of China not producing some chemical materials at all. According to 2018 statistics of the Ministry of Industry and Information Technology, 32% of the more than 130 key chemical materials are not produced in China and all, and for 52%, China still depends on imports, including high-end electronic chemicals, high-end functional materials, high-end polyolefins. Here, the quest for self-sufficiency is closely linked to the objective of not relying too strongly on imported technologies.

The gap is particularly obvious in fine chemicals. Again, according to Li Shousheng, the share of fine chemicals in China is only around 45%, much lower than the average level of 60% to 70% in developed countries. The top ten high-end chemical companies in the world are all foreign companies, and they all have full-chain processing and research and development capabilities from basic chemicals to high-end chemical materials. Chinese chemical companies generally lack these highly developed, extended value chains that include fine chemicals. Reducing China`s dependency on imported fine chemicals will therefore mean political support for such domestic companies.

Conclusion

So, in summary, what can the chemical industry expect from China`s 14th Five-Year Plan? As outlined above, none of the likely key thrusts of the plan represents a massive change from the 13th FYP. Rather, it is a continuation with slightly different emphasis. While with regard to environmental aspects and also mainly for R&D, the focus will be on continuation, the added emphasis will be on self-sufficiency, particularly in high-end chemicals. Recent events — particularly frictions in global trade and the coronavirus — are at least partly responsible for this.

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CIEX 2020 — Virtual Event

Taking place on October 7-8, 2020, the conference is aimed at R&D and innovation experts from the consumer, industrial and specialty chemical sectors. By bringing together all players across the value chain, the event creates a unique platform for participants to learn, exchange ideas, and collaborate. It provides participants with a fresh channel to explore cutting edge innovation in the rapidly evolving chemical industry. Connecting innovators with investors, potential customers and budget holders, it enables the delegates to share, collaborate, explore and experiment. **http://ciex-eu.org**

CPhI Festival of Pharma — Virtual Event

The CPhI Festival of Pharma, taking place on October 5-16, 2020, will feature expert speakers from the world's leading pharma companies to share their insight and expertise as part of this online content program, dedicated to the new challenges that the industry is currently facing. The online event will welcome an anticipated 20,000 pharma professionals and over 700 international exhibitors. An AI-driven matchmaking platform will use participant's profile details to suggest the most relevant matches for their business, while its secure video meeting function lets them meet potential partners face-to-face from the comfort of their own home. **www.cphi.com/festival-of-pharma**

Bio-Europe — Virtual Event

This year's BIO-Europe will be held on October 26-29, 2020. It will include on-demand early access to the company pitches, program sessions, and sponsor and showcase company content up to five weeks prior to the live event. The event is expected to bring together over 4,000 executives from more than 2,000 life sciences companies spanning an estimated 60+ countries. Without the need to travel, more delegates can participate worldwide. The program content in business development, therapeutic areas, startup innovations, digital health, and more will be available on demand beforehand as well as in live sessions during the conference. **www.informaconnect.com/bioeurope**

Chemspec Europe — Virtual Event

The digital Chemspec Europe event will take place on November 11-12, 2020 and will offer participants matchmaking facilities to conduct business meetings as well as webinars and further digital content for the exchange of knowledge and expertise. The event is the key platform for manufacturers, suppliers and distributors of fine and specialty chemicals. The product portfolio of this international exhibition covers a maximum range of fine and specialty chemicals for various industries. Excellent networking opportunities and webinars presenting the latest results of ongoing R&D projects round-off the event. **www.chemspeceurope.com**

Due to the coronavirus pandemic, events may be postponed or cancelled. We therefore cannot guarantee the validity of the dates mentioned here.

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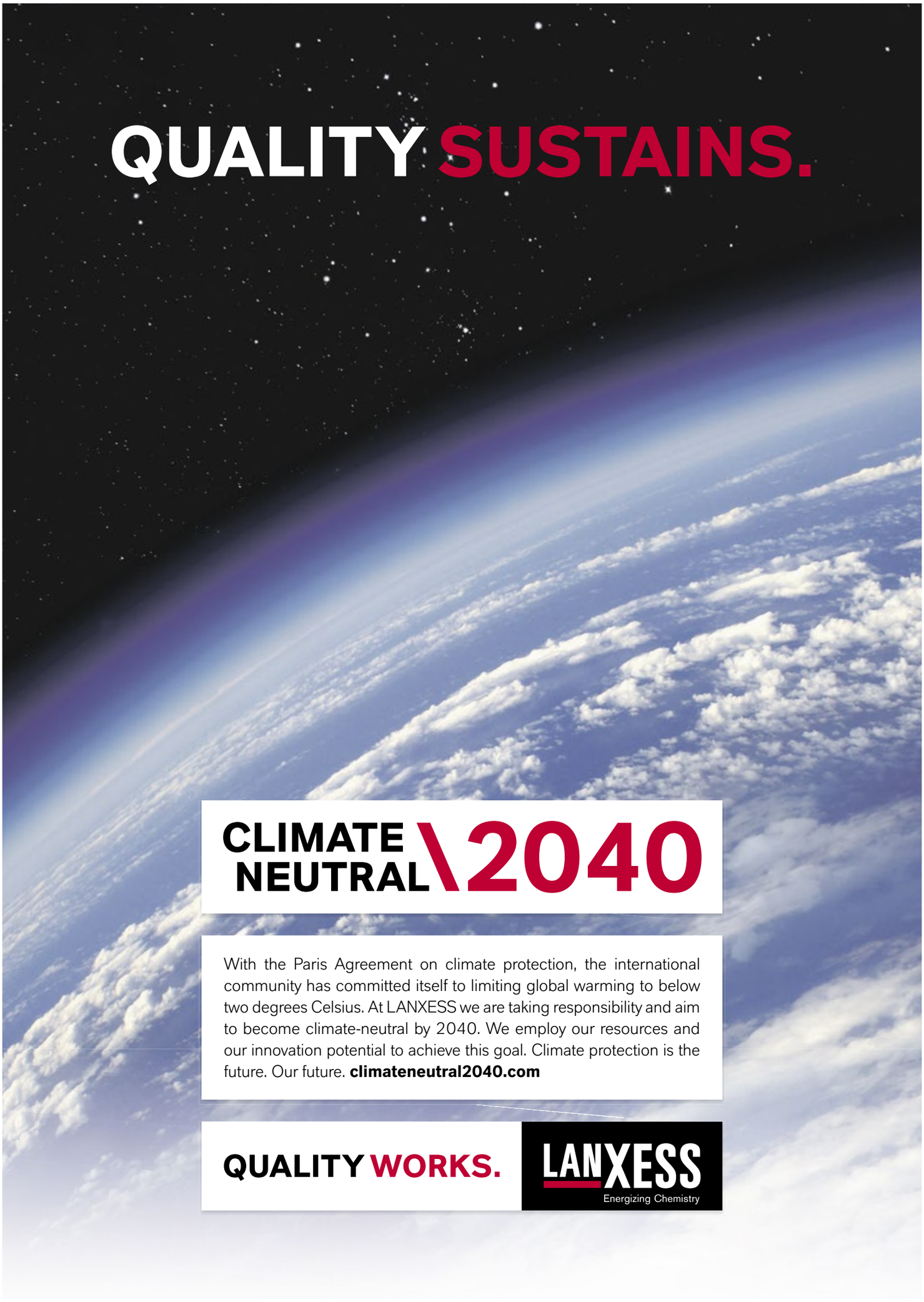
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With the Paris Agreement on climate protection, the international community has committed itself to limiting global warming to below two degrees Celsius. At LANXESS we are taking responsibility and aim to become climate-neutral by 2040. We employ our resources and our innovation potential to achieve this goal. Climate protection is the future. Our future. climateneutral2040.com
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