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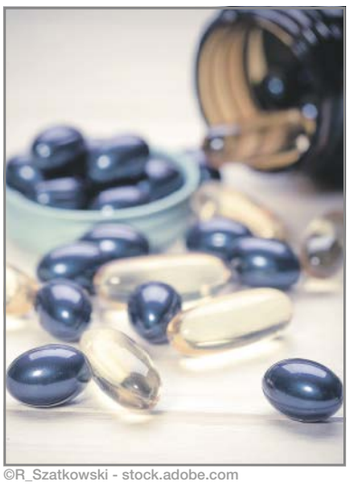

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The Chemical Labor Productivity Challenge

Unlocking Europe's Productivity Potential for Future Growth

A labor productivity crisis is looming, with Europe at its epicenter. For 15 years, European chemical companies have invested up to 7% of their annual revenues in new plants, equipment and technologies — yet labor productivity has plateaued. Productivity will become an even bigger challenge as demand increases and a retirement wave coincides with flat student enrollment in key fields. Companies can act now to crack the labor productivity conundrum.

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The chemical industry faces acute labor shortages because the talent pool is shrinking, but the industry remains heavily reliant on manual work. The underlying issue is that labor productivity (calculated as revenue per full-time equivalent or FTE) is stagnant, according to a recent report published by Accenture. Globally, revenue per FTE has improved by less than 1% per year during the last 15 years. In Europe, labor productivity growth per year has been a bit higher (1.6%), but still lower than the 2.4% average annual inflation rate (fig. 1).

> *"Technology alone does not automatically lead to greater labor productivity."*

If this trend continues, chemical companies will lack the talent needed for growth. With demand for sustainability-related products predicted to soar by about 70% by 2028, this opportunity is too big to miss.

Large Investments, Small Improvements

So far, organizations' efforts to boost productivity haven't had the desired effect. During the last 15 years, European companies have invested up to 7% of their annual revenues in new plants, better equipment, digital technologies and continuous improvement. However, productivity has remained disappointingly low.

In contrast, at a global level, several other asset-intensive industries have achieved up to six times greater improvements in labor productivity in that same period (fig. 2).

Demographic Shifts Create a Perfect Storm

Labor productivity is set to become an even bigger challenge, especially in Europe, as two pressing issues converge.

One is a looming retirement wave, as 31% of employees at European chemical companies are aged 50 or older and due to retire within the next decade. The problem is particularly acute in Germany, where 38% of the overall workforce is aged 50 or older.

The second issue is that student enrollment in key disciplines such as engineering and IT has plateaued, while demand for these skills continues to rise. This mismatch will create greater competition for a shrinking talent pool.

Technology Isn't a Silver Bullet

Other asset-intensive industries have demonstrated that capital expenditures can be converted into up to six times greater labor productivity, so what do chemical companies need to do differently to achieve the same or even better results?

The reality is, even though European chemical companies have invested up to 7% of their annual revenues in new technologies and equipment, approaches to labor have remained largely unchanged. Consequently, new plants operate like older ones, with minimal improvements in automation and efficiency.

The key lesson is that technology alone does not automatically lead to greater labor productivity. In parallel, companies need to adjust work processes, methods, roles, recruitment and training strategies to adapt to technology advancements.

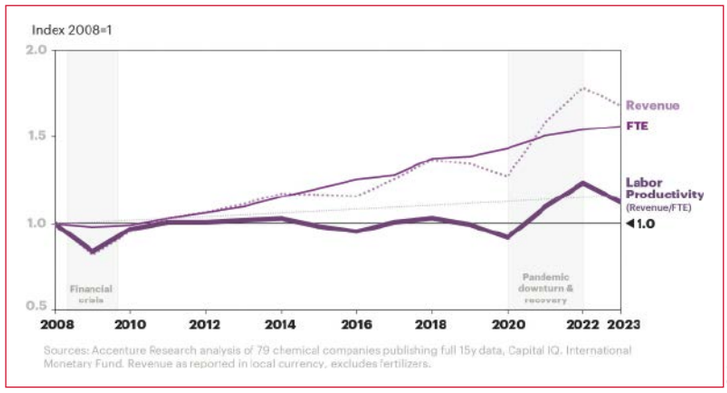

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Fig. 1: Global labor productivity for chemical companies during the last 15 years.

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Fig. 2: Global labor productivity CAGR 2008–2023 across asset-intensive industries.

How to Crack the Labor Productivity Conundrum

The good news is that chemical companies already have the technology they need to increase labor productivity and address talent challenges. They can make substantial productivity improvements by reinventing roles and reshaping the workforce across three dimensions:

1. Restructuring work to increase labor productivity

When chemical companies build new facilities, they often replicate existing plant designs and organization charts. And when they invest in digital programs, they typically do not reinvent or restructure roles. Without adjusting work processes, methods and roles, new technologies spark only small, incremental improvements, and companies miss out on larger productivity gains.

As an example, imagine that a company has invested in a technology that can automate 20% of a role. If the work isn't reorganized, the people in the role will do something else with the time gained. But if the company combines roles, it can free one FTE position for every five workers. And that really adds up. If companies can save a few hours for each person across several thousands of roles, they will achieve considerable savings and reduce the need to replace employees as they retire, easing pressure on recruitment.

■ **2. (Re-)Building the expertise to continuously reorganize work**

Executives can't approach reinvention as a contained effort undertaken every few years. Change is constant, so reinvention never ends. Executives need to build the capability to continuously adapt and reinvent as technology advances and creates new possibilities. This includes putting in place people with the capabilities to reorganize work on a role-by-role level, build new teams and unlock labor productivity potential. Implemented successfully, these kinds of changes can convert time savings from automation into reductions in the number of FTEs required to run each plant or function.

"Companies must not underestimate the magnitude of change required."

■ **3. Investing in dedicated training and knowledge capture and transfer**

Chemical companies need detailed plans focused on: identifying required skills and building them via training; capturing knowledge from retiring employees; and conveying that knowledge to new employees or those taking on new roles. Ultimately, the aim is to shift away from transactional, manual labor toward work focused on analysis, design and execution.

Companies must not underestimate the magnitude of change required. Since labor productivity opportunities affect all business divisions, functions and roles, almost every employee will require some level of training or skilling. To address this need, companies must dramatically expand training programs and transfer knowledge from employees nearing retirement.

A Critical Turning Point

The rapid pace of technological advancements presents a new world of possibilities, but many companies struggle to effectively implement these changes. As chemical companies explore future advancements in technologies—including automation, AI and now generative AI—they must continue to reshape roles, skills and organizational structures to fully benefit from them.

"A labor productivity crisis is looming."

The bottom line is that realizing labor productivity potential will be decisive for business continuity and future growth. It's time for chemical companies to seriously address labor productivity, tackling it from the board-level down. By doing so, they will be well-positioned to address talent challenges and drive growth in the transition to a low-carbon economy.

Bernd Elser, Senior Managing Director, Global Chemicals & Natural Resources Lead, Accenture, Frankfurt am Main, Germany

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Chemical Logistics Study 2024

Act Now to Be Prepared when Business Picks up Again!

It seems that the current tense economic situation in the chemical industry has come at an inopportune time — major challenges with a great need for action are currently being amplified by cost pressure and an overall economical downturn. But right now it is important to set the course for a successful restart after overcoming the current dip!

This is the summary of our findings from the 2024 Supply Chain and Logistics Chemical Study of Solventure, Aimms and Miebach, which deals with current key trends and challenges, the use of digitalization and AI, as well as how to plan in the European chemical industry.

What are the current trends and challenges in the chemical industry? This starting question has been broken down into a selection of possible trends and their significance from the participants' point of view.

Cost Pressure more Important than CO_2 Neutrality

Unsurprisingly, the participants of the 2024 Supply Chain and Logistics Chemical study rated "Increasing cost pressure on warehousing and transportation," that means the cost pressure currently being felt everywhere, as currently the most important. This also reflects our view of the current perception in the market, with one cost-cutting program after another against the backdrop of dramatic slumps in sales on the one hand and hyperinflation in terms of energy and personnel costs on the other. However, "Transparency through enhanced communication and close dialogue" was rated almost as important and significant as the current cost pressure, followed by the "Diversification of supply chains in order to be able to operate flexibly with all modes of transport." But the most surprising result has been that the "Industry ambitions to become carbon neutral" are currently only considered to play a subordinate role. Contrary to all public statements, this is considered to be the least important trend.

Industry not Well Equipped to Meet Current Challenges

Only regarding the topic of "Transparency through enhanced communication and close dialogue" around 50% respond that they are very well or well prepared, while around 1/3 each responded that they are well prepared for "Increasing cost pressure on warehousing and transportation" and "to align chemical supply chain logistics to customer- and product specifics and not to proceed according to one supply chain fits all." The maturity level "Working on it," i.e., companies are facing up to the issues without already having an answer ready, receives the most approval with regard to all the challenges mentioned. And some also have to admit that they are inadequately prepared or not prepared at all for one challenge or another.

Digitalization and the Use of AI Hardly Widespread Yet

Digitalization and the use of AI are the hottest topics at the moment and (almost) everyone is talking about them. But what about the actual spread of digitalization and AI applications in supply chain management and logistics? We asked and received sobering answers.

None of the participants in the study have a supply chain digital twin to date or are at least planning to implement one in 2024. The results regarding the use of a digital twin for warehousing and the use of control towers are almost identical. Robot process automation, big data analytics and predictive analytics have their first users, with others planning to follow in 2024 or 2025. And 2/3 of the participants are planning to use AI for inventory optimization from 2025 onwards — it remains to be seen whether this will actually be implemented to this extend.

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Strategic, Tactical and Operational Planning

The third part of the study looks at how companies in the chemical industry plan at a strategic, tactical and operational level, who is involved and which instruments are used.

Strategic planning takes place every 2-3 years or on demand, only a few plan annually, e.g., in the area of production footprint or last mile distribution. However, many companies also responded that they only plan on demand. For the majority of participants, the internal organization is responsible for carrying out such planning, but >40% also use internal (16%) or external consultancies (25%). Excel is still the dominant planning tool, as is ERP for tactical and operational planning tasks. Specific professional software is rarely found.

To summarize, the study shows a significant demand to develop a more professional approach in supply chain & logistics planning and using digitalization and AI in the chemical industry, but the industry has currently to deal with limited resources and budget constraints. We will be more then interested if this situation will change once the business will pick up again.

Klaus-Peter Jung, Partner and Head of Industry for the Chemical Industry, Beverages and Logistics Service Providers, Miebach Group, Frankfurt am Main, Germany

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Advanced Biotechnology Series

Biotechnology is a broad, interdisciplinary field of science, combining biological sciences and relevant engineering disciplines, that is becoming increasingly important as it benefits the environment and society as a whole. Recent years have seen substantial advances in all areas of biotechnology, resulting in the emergence of brand new fields.

To reflect this progress, Sang Yup Lee (KAIST, South Korea), Jens Nielsen (Chalmers University, Sweden), and Gregory Stephanopoulos (MIT, USA) have joined forces as the editors of the Advanced Biotechnology book series. It covers all pertinent aspects of the field and each volume is prepared by eminent scientists who are experts on the topic in question.

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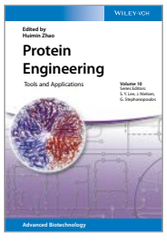

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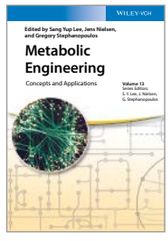

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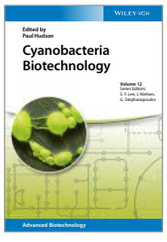

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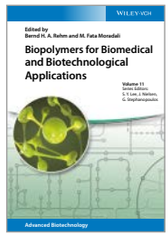

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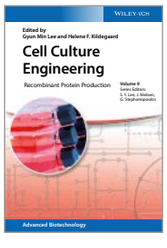

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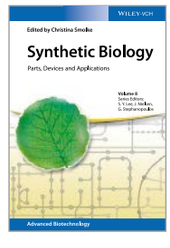

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Cambridge is part of the ‚Golden Triangle'. The region belongs to the top 25 clusters in the world.

Biotech Clusters in Europe

Some Biotech Conglomerates Stand Out due to their Concentration of Knowledge, Innovation Activity and Financing

Whether Cambridge, Leiden, Heidelberg or Paris — many European countries have biotechnology clusters in which scientific expertise meets a well-developed infrastructure, committed entrepreneurship and attractive financing opportunities. The drugs of tomorrow often emerge from such knowledge conglomerates. But what characterizes the outstanding biotech hubs on the European continent? A subjective look at the best.

The discussion on the online platform Reddit is symptomatic for the structure of the biotech industry. A user from the USA asks which are the most important biotech hubs in Europe. The feedback overwhelms him: "Seems like the Europeans are giving a ton of different answers. Would you guys say the biotech industry is just distributed more evenly across the continent compared to the US? It seems very different compared to here." In fact, while Europe has numerous biotech hubs, only one or at most two centers stand out in the USA: Boston/Cambridge and the San Francisco Bay Area.

Network, Funding, Patents, Jobs

But what characterizes a successful, strong cluster? US Commercial real estate investor Brad Thomas says: "There is a unique desire among life science entities to cluster together in campus ecosystems in order to drive productivity and collaboration, to recruit and retain top talent, to attract strategic capital, and to ensure best-in-class, 24/7 operations of their mission-critical real estate."

Ralf Huss, Managing Director of the Bavarian BioM Biotech Cluster Development company, goes into more detail: "The outstanding thing (...) is a network based on excellent science and also partly applied research (at least in selected key areas), efficient technology transfer in translation centers with the possibilities of accelerated incubation, a sustainable industrial environment consisting of start-ups, successful SMEs and, if possible, globally active pharmaceutical and biotech companies. In addition, there is a supportive policy at local, regional and national level with a close relationship to European decision-makers. Such a cluster is a strong partner for global and strategic investors, which is an important driver for further growth."

The differences between a strong cluster and a less good one depend above all on the criteria used as a basis. According to the US trade journal "Gen—Genetic Engineering and Biotechnology News", this definitely includes funding from state healthcare systems and venture capital (VC) investors, patents, lab space and the number of jobs.

For its part, the Boston Consulting Group (BCG), together with the Institute for Deep Tech Innovation (DEEP) and the Berlin educational institution ESMT, designed a so-called Biotech Innovation Hub Index (BIHI, see interview) to help evaluate and compare the effectiveness of biotech innovation hubs. A key finding of the study entitled "Biotech Innovation Hubs in Germany—Divided and Conquered?" is that while European hubs excel in terms of the quality of academic research, they otherwise lag behind those in the USA. A key issue here is the lack of transferability of academic research into successful biotech companies in the German biotech sector. This shortfall can be attributed to several factors, with fragmentation playing a significant role. In addition, German biotech centers in particular lack effective collaboration.

"While European hubs excel in terms of the quality of academic research, they otherwise lag behind those in the USA."

However, BioM Managing Director Huss considers this view to be "somewhat one-dimensional". If you apply classic KPIs for biotechnology companies, such as the number of new drugs or candidates in clinical trials, the financial volume of takeovers or even IPOs, this impression undoubtedly arises. However, the German clusters, and in particular Heidelberg, Berlin and Munich, are "certainly the most innovative centers, even in comparison with the USA". This is demonstrated not only by the number of "German" Nobel Prizes in this field, but also by the trend towards deeptech and techbio companies in the national clusters.

Huss also points to the increasing interest of strategic partners in gaining access to innovations in Europe and Germany. More and more large global pharmaceutical and technology companies are establishing their research locations in Europe and Germany with long-term investments. In his opinion,

it is only a matter of time before financial investors also follow this trend and "recognize the sustainable value creation of modern biotechnology in Germany and Europe."

European Biotech Clusters in Concrete Terms

Let us take a look at some important European biotech clusters and their characteristics. A selection that is inevitably also subjective:

Oxford/Cambridge/London

The region of London, Oxford, Cambridge and England's greater southeast is also known as the 'Golden Triangle'. It is made up of the most life science companies in one place and has been named as one of the top 25 clusters in the world. Back in 2019, the magazine "Management Today" asked: "Can Cambridge become the world's leading biotech cluster?"

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The cluster is a network of renowned research centers, healthcare providers and medical charities in a compact region that claims to be home to four of the world's top ten universities for healthcare. Furthermore, it has five out of seven of the UK's academic health science centers and is home to leading medical research institutes including the Wellcome Trust, the Medical Research Council, Cancer Research UK, and the national Cell Therapy Catapult, focusing on stem cell research and industrialization.

As part of the Golden Triangle, Cambridge alone is described as Europe's largest biotechnology cluster, consisting of more than 30 science and technology parks within ten miles of the city. According to the marketing firm Cambridge& the region attracted over £700 million in private investment in 2020 and counted 440 life sciences companies based in or around the city last year. Between them, they employed 14,000 people and generated £4.2 billion in revenue, an increase of 56% over the previous two years.

The venture investor Cambridge Innovation Capital points out, that the demand for Golden Triangle lab space surges with highest annual volume since 2015. Incidentally, the German biotech company BioNTech has leased around 79,000 sq ft at the Cambridge Biomedical Campus.

Stockholm

"Stockholm-Uppsala life science sector has a reputation of being not only Scandinavia's leading cluster, but also one of the world's most productive

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hubs for health care advancement and life science know-how. On average, 15 to 20 new life science companies were formed in the region each year during the last decade. The cluster organization Stockholm Science City (SSCI) points out that Stockholm was ranked number 1 by the EU Commission's "Regional Innovation Scoreboard," 2022, with life sciences as an important industry there.

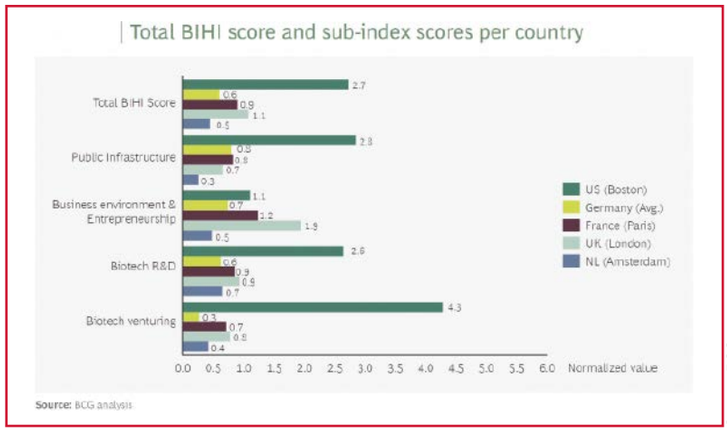
Here are 50% of all life sciences employees in Sweden, around 1,000 life sciences companies where all sectors in the industry are represented. In addition, there are five universities with significant life science activities, three university hospitals, and essential authorities such as the Medical Products Agency and the Public Health Agency.

An example where the focus is on life science besides real estate and urban development is Hagastaden. As of SSCI, one of the neighborhoods main attractions is "proximity, proximity, proximity." In Hagastaden is the Karolinska Institutet, Karolinska University Hospital, St Erik's Eye Hospital, and within walking distance of KTH and Stockholm University. Close ties between government, industry, and academia shall facilitate the development of ideas into commercially viable products. On top there is the basic principle in Sweden that the individual researcher owns the result of his or her research—which can be a considerable motivation.

Leiden/Amsterdam

The Leiden Bio Science Park (LBSP) was established in 1984 in the Leeuwenhoek area and comprises 411 companies. LBSP claims to have taken a strong, global position and evolved into the Netherlands' largest life sciences/health cluster, connecting talent, researchers and entrepreneurs. The district and its community include more than 21,000 innovators and 22.500 students.

Leiden, on the other hand, is part of the Amsterdam biotech region, around 36 kilometers away. The Amsterdam Life Sciences District in the southeast of the city comprises multiple start-ups, global medical companies, and universities. The cluster organization underlines Amsterdam´s global leading role in cancer research and artificial intelligence (AI), as well as its extensive base of clinical research. The city is home to two academic hospitals, united under the umbrella of Amsterdam UMC, plus the Netherlands Cancer Institute (NKI), Sanquin and the Academic Centre for Dentistry (ACTA). Furthermore, several industry players have relocated to Amsterdam after the European Medicines Agency (EMA) moved here from London in 2019.



Source: BCG

Fig. 1: Total BIHI score and sub-index scores per country

Paris

Paris concentrates most of the French biotech industry. Some call it even Europe's biggest bio cluster. Medicen, the local cluster organization, says, it has around 500 members—350 small and mid-sized enterprises, structured in the main areas of biotech, medtech and e-health. In total the cluster organization counts 150 biotech companies.

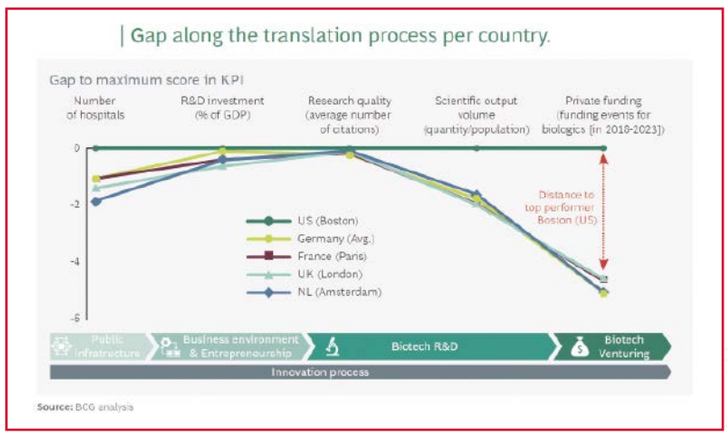
As of Labiotech, Paris was clearly lagging behind compared to the UK until the end of the 20th century. In the meantimemeantime, the city not only caught up but outpaced the UK in many aspects. The biotech platform took its own approach to site evaluation by setting the selection criteria of €1 million raised capital respectively revenues and the grade of proprietary technology. Accordingly, Paris is leading the way in Europe with 47 biotech companies matching these criteria.

The news site also has an explanation why only few people know about Paris´s position as the biggest bio cluster of Europe. One of the reasons is the performance of the politics respectively the cluster management. Labiotech: "Medicen, the cluster of the region, has been recognized as one of the worst in France."

Basel

The Swiss city of Basel is not only home to well-known pharmaceutical companies such as Roche and Novartis, but also hosts numerous biotech companies. According to the local life sciences marketing company, the location has around 800 companies and 28,000 employees and covers the entire value chain from research and development to production and marketing.

Labiotech.eu had already included Basel in its list of European biotech hubs with the most interesting companies in 2018. The region has developed into a "hotspot for pharma and biotech." For example, the biopharmaceutical company Actelion, which was acquired by the US group Johnson & Johnson for almost $30 billion, is "one of the largest companies in European biotech history."



Source: BCG

Fig. 2: Gap along the translation process per country

The proximity of Big Pharma, the presence of flagship companies and a large number of small and medium-sized biotech companies such as Basilea, Allecra, Santhera Pharmaceuticals and Polyphor make the region an incubator for success stories. The proximity to prominent life sciences research at the universities and research institutes as well as the proximity to clinical research at the university hospitals in Basel are also considered essential for innovation.

Berlin

The Berlin-Brandenburg region also counts itself among the leading locations when it comes to health and innovation. The region is particularly strong in its concentration and networking of science, clinics and industry. According to the cluster management, more than 670 companies from the biotechnology, pharmaceutical and medical technology sectors benefit from the scientific environment, the clinical research landscape and the proximity to decision-makers from politics and the healthcare sector. The biotech sector alone accounts for 281 companies with almost 7,200 employees

The consulting firm BCG says: "More specifically, Berlin stands out for its strength in the category business environment and entrepreneurship (…) driven by the considerably higher number of companies funded by angel investors."

Heidelberg

BioRN describes itself as the innovation cluster of the Rhine-Main-Neckar region around Heidelberg, "one of Germany's strongest biotech hubs". The non-profit network counts more than 140 members, including universities, research institutions and technology parks. Ten global pharmaceutical companies have R&D sites or are active in the BioRN network. The ecosystem is completed by a range of small and medium-sized enterprises as well as local government organizations and interest groups.

BCG points out that "Heidelberg is renowned for its strong scientific output and prestigeprestige, but has only a small lead compared to Munich and Berlin in terms of scientific output quantity and quality. The city's reputation and achievements in scientific research contribute significantly to its standing in the biotech community, although this rarely translates into commercial success."

Munich

According to its Managing Director Ralf Huss, the Bavarian biotech cluster BioM in Munich-Martinsried has been a national and European leader since it was founded more than 25 years ago. The starting point was and is a supportive policy with the provision of financial resources and an infrastructure with numerous innovation and start-up centers. The innovations and start-up ideas mainly come from the two universities of excellence, the Technical University (TUM) and the Ludwig-Maximilians University (LMU). In recent years, there has not only been a growth in biopharmaceutical companies, but also an increasing number of technology companies settling here.

The state's current biotech report lists 527 companies with 58,000 employees throughout Bavaria. In addition to Munich, Regensburg and Nuremberg-Erlangen are also important locations in Bavaria. In the opinion of BCG "Munich emerges as a leader in biotech venturing within Germany. The city's ecosystem is particularly favorable to the growth and development of biotech start-ups. This is remarkable because the overall start-up activity is clearly behind Berlin."

Germany Not in the Top League

However, the positive characteristics of the German locations cannot hide the fact that they do not play in the top league in international comparison. Looking at all three German locations, BCG states: "Collectively, these findings suggest that the Berlin, Heidelberg, and Munich hubs exhibit strong complementarity. However, Germany does not capitalize on these synergistic potentials. Indeed, the combined BIHI of these three hubs is 30% lower than Paris's score and 45% lower than London's."

The consulting firm concludes: "The results of this study call for a wake-up call, particularly for Europe, and more specifically for Germany. The findings are stark: Europe's performance in biotech innovation is suboptimal, with Germany displaying particularly concerning outcomes. This requires a reevaluation and reinvention of Germany's approach to collaboration and innovation in the biotech sector."

Thorsten Schüller, CHEManager

„No Clear Pathway to Commercialization"

The Competitiveness of German Biotech Locations

The Boston Consulting Group (BCG) has evaluated the effectiveness of biotech innovation centers in Europe and the USA. Thorsten Schüller asked Bianca Adolphs, Principal at BCG, to explain what is lacking in Germany in particular.

CHEManager: Ms. Adolphs, what are the characteristics of a strong biotech cluster?

Bianca Adolphs: Biotech hubs, as we call regional clusters, are epicenters of scientific and tech-nological development, which facilitate the exchange of resources like knowledge, data, talent, and funding among firms, universities, and institutions within a geographic area. The resulting ecosystems create a positive feedback loop and foster innovation. The Biotech Innovation Hub Index (BIHI) can provide a tangible representation of this concept.

How is the BIHI determined?

B, Adolphs: We assess regions along four dimensions: Public infrastructure, Business environment & Entrepreneurship, Biotech Research & Development and Biotech venturing. Each of these dimensions can be broken down into four to six measurable characteristics, e.g., number of graduates and hospitals for public infrastructure, number of start-ups for the business environ-ment, or how often scientific publications were cited as a proxy for biotech R&D. We find that bio-tech clusters thrive in areas with seamless collaboration between universities and the industry, when universities are fostering an entrepreneurial culture, and in areas with a strong venture capital and start-up ecosystem.

Why can't biotech hubs in Germany match the innovative power and strength of other Euro-pean or even US locations?

B. Adolphs: As we observe the metrics throughout the innovation process, we see that European countries score relatively similar to the US in the early stages. However, in terms of sheer scien-tific output volume and especially for private biotech venture funding, there is an increasing gap between Germany and broader Europe, including the UK compared to the US. Germany's biotech innovation landscape is highly decentralized and fragmented, with multiple biotech hubs and uni-versity clusters lacking scale and efficient expertise sharing, thus limiting their potential com-pared to the more cohesive ecosystems in the US, France, and the UK.

In your study you point out that Germany's sub-par performance could also stem from the traditional reluctance among scientists and physicians to engage with the business side of their discoveries. Why is that?

B. Adolphs: Within the German university system, structured incentives and encouragement to translate scientific outcomes into business ideas is often lacking, with a cultural emphasis on research for research's sake and no clear pathway to commercialization. In contrast, US biotech hubs intrinsically incorporate business acumen into scientific education and build up infrastruc-ture to support scientists along the journey. This includes mentorship programs and access to venture accelerators/incubators that allow scientists to spend time working on translating re-search into marketable innovation. Technology transfer at universities is often less bureaucratic and more supportive for scientists, leveraging strong industry connections to succeed. This results in numerous successful ventures within university departments and positive role models, which German scientists often lack.

Biotech investors in the US are known to be much more willing to take risks and invest larger sums of money than investors in Europe. What needs to happen to close this gap?

B. Adolphs: Higher venture capital investments and a risk-taking culture are not unique to bio-tech but apply broadly. To strengthen biotech hubs in Germany, aspects of innovation funding could be tackled: redirecting government funding to later stages of the innovation process, sup-porting science-to-business translation programs in initial grants, or considering incentives for private investors to co-fund innovation. Moreover, cross-hub collaboration in Germany's decen-tralized innovation system could standardize processes and benefit from joint expertise and ex-perience with commercialization. Creating innovation nuclei can be a starting point.

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Bianca Adolphs, Principal, Boston Consulting Group

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Bioindustry Dynamics

Exploring Innovations, Expansions, and Strategic Shifts

Driven by increased demand in biologic-based drugs, biologic drug substance manufacturing continues to be an active area of investment by contract development and manufacturing organizations/contract manufacturing organizations (CDMOs/CMOs), including several multi-billion large-scale biomanufacturing projects. What companies are expanding, and where do these expansions stand?

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Patricia Van Arnum, DCAT

Large-Scale Biomanufacturing Expansions Underway

Samsung Biologics. Samsung Biologics is proceeding with a multi-billion-dollar-plus investment to expand its biomanufacturing capacity, which includes the addition of a new biomanufacturing plant in South Korea. The expansion includes the addition of a fifth biomanufacturing plant and the expansion of its Bio Campus II, along with the establishment of a new stand-alone antibody-drug conjugate (ADC) facility in Songdo, South Korea. Plant 5, with a capacity of 180,000 L and spanning an area of 96,000 m², is slated for completion in April 2025, contributing to a significant increase in the company's overall biomanufacturing capacity, which will reach a total of 784,000 L upon Plant 5's completion.

The investment for Plant 5 amounts to KRW 1.9 trillion (~$1.46 billion). For the development of Bio Campus II, which will entail four plants (Plants 5–8) and an open innovation center, Samsung Biologics plans to allocate KRW 7.5 trillion (~$6 billion). Capacity expansion involves the construction of Bio Campus II, featuring four plants, each with a 180,000 L capacity. Combined with the company's Bio Campus I, the company aims to offer total capacity exceeding 1.3 million L by 2032.

Fujifilm Diosynth Biotechnologies. Fujifilm Diosynth Biotechnologies is proceeding with a multi-billion-dollar investment to expand large-scale cell-culture bulk drug substance and flexible single-use cell culture capacity, along with the addition of commercial-scale drug-product and finished goods capacity.

The company is proceeding with a $1.6-billion expansion of its large-scale cell-culture capacity at its site in Hillerød, Denmark. With mechanical completion achieved in January 2024, the first drug-substance expansion is set to come online later this year (2024). A new drug-product facility in Denmark is expected to be operational by early 2025, following a successful filling line test run in February 2024. The second drug-substance expansion is slated for online activation in 2026.

Earlier this year (April 2024), the company announced an additional investment of $1.2 billion in its large-scale cell culture biomanufacturing facility in Holly Springs, North Carolina, bringing the total investment in

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the facility to over $3.2 billion. The new investment will add 8 x 20,000 L mammalian cell-culture bioreactors by 2028, to the already planned 8 x 20,000 L bioreactors for bulk drug substances as part of the initial investment. The company was already investing $2 billion in its Holly Springs facility with the planned addition of large-scale cell-culture drug-substance suites in 2025.

In August (2024), Fujifilm Diosynth Biotechnologies opened a microbial fermentation manufacturing facility in Billingham, UK. The new facility triples existing microbial production throughput with the addition of a new production line equipped with 2 X 4,000 L fermenters, a primary separations suite, and a modular purification suite with an investment of over £100 million ($131 million). In addition, the company signaled in 2021, the company's intent to establish a flexible cell-culture facility at its Billingham site. A significant project scope change focused on applying modular principles, allowing lanes to mix 2,000 L and 5,000 L bioreactors. The facility is set to be operational by 2026.

Lonza. Lonza is making a large investment through its pending $1.2-billion acquisition of a large-scale biologics manufacturing site in Vacaville, California, from Roche's Genentech. Lonza plans to invest an additional CHF 500 million ($554 million) to upgrade the facility and enhance capabilities for producing mammalian biologic therapies. The products currently manufactured at the site by Roche will be supplied by Lonza, with committed volumes over the medium term and phasing out over time as the site transitions to serve alternative customers. The Vacaville facility currently has a total bioreactor capacity of approximately 330,000 L. Upon deal closing, approximately 750 Genentech employees at the Vacaville facility will be offered employment by Lonza. The transaction is expected to close in the fourth quarter 2024, subject to customary closing conditions. Upon closing, the Vacaville site will be integrated into Lonza's Biologics Division, joining a network of existing mammalian manufacturing sites in Visp, Switzerland; Slough, the UK; Tuas, Singapore; Portsmouth, New Hampshire; and Porriño, Spain.

Lotte Biologics. In July (2024), Lotte Biologics broke ground on its inaugural plant at its Songdo Bio Campus in Incheon International City, South Korea, the first plant of a $3.4 billion biocampus that the company is establishing. The company plans to build three biomanufacturing plants at its new biocampus in South Korea by 2030 that will provide total production capacity of 360,000 L, with each plant having 120,00 liters of production capacity. Lotte Biologics entered the CDMO market with the acquisition of a commercial scale biomanufacturing facility in Syracuse, New York, from Bristol-Myers Squibb in January 2023.

Other Biomanufacturing Expansions

AGC Biologics. In June (2024), AGC Biologics completed a new $200 million biomanufacturing building at its Copenhagen, Denmark, campus. The building doubles the site's single-use bioreactor capacity for mammalian services and allows the company to produce 150 more batches of drug product each year. The expansion adds 19,000 m^2 of space in a building that houses a manufacturing floor, expanded quality control and process development lab space, utilities to support all operations, and a dedicated warehouse to serve the entire AGC Biologics Copenhagen campus.

In addition, in January (2024), AGC Biologics announced an investment of JPY 50 billion ($350 million) to construct a new biomanufacturing facility at its Yokohama Technical Center in Japan. The new facility will offer preclinical through commercial services for mammalian-based protein biologics, cell therapies, and mRNA. The site will house multiple 2,000-liter single-use bioreactors and several 4,000 L or larger reactors for mammalian cell-culture products. The facility is expected to be operational in 2026. The company currently operates one site in the region, in Chiba, Japan, which provides mammalian expression and microbial fermentation services.

MilliporeSigma. MilliporeSigma, the life science business of Merck KGaA, is investing more than €300 million ($326 million) for biomanufacturing support through a new bioprocessing production center in Daejeon, South Korea, to provide products such as dry-powder cell-culture media, process liquids, pre-GMP small-scale manufacturing, and sterile sampling systems. Covering an area of 43,000 m^2, the facility will include production capacities, a distribution center, and an automated warehouse. The investment is expected to create approximately 300 additional jobs by the end of 2028.

Wacker Biotech. In June (2024), Wacker Biotech, a CDMO of biologics and a subsidiary of Wacker Chemie AG, opened an mRNA Competence Center at its biotech site in Halle (Saale), Germany, with an investment of over €100 million ($107 million). The new facility enables the large-scale production of active ingredients based on messenger ribonucleic acid (mRNA). Four new production lines have more than tripled the site's capacity. Some of the new capacity will be made available to the German government as part of its pandemic-preparedness plan to supply Germany with vaccines as and when required.

Just Evotec Biologics. Just-Evotec Biologics, a subsidiary of Evotec, is investing in a new facility for continuous biomanufacturing in Toulouse, France. The facility applies the company's J.POD design featuring a single-use continuous cell-culture manufacturing platform set inside production-on-demand modules within a ballroom manufacturing space. In this way, it replicates the design of the company's J.POD facility in Redmond, Washington.

"Samsung Biologics is proceeding with a multi-billion-dollar-plus investment to expand its biomanufacturing capacity"

The investment of approximately €150 million ($163 million) was announced in April 2021, and the company broke ground in September 2022. Last October (2023), the building shell was completed, and the autonomous cleanroom POD installation occurred at the beginning of this year (2024). The facility is set to be operational by the second half of 2024 and will contain two continuous cell-culture manufacturing streams. J.POD Toulouse will manufacture both clinical and commercial material and will have capacity to produce up to 2000 kg of antibody per year.

Aurigene Pharmaceutical Services. In June (2024), Aurigene Pharmaceutical Services, a Dr. Reddy's Laboratories' company, opened a biologics facility spread across 70,000 sq ft in Hyderabad, India. The facility provides process and analytical development and small-scale manufacturing of antibodies and other recombinant proteins for preclinical and early-phase clinical requirements. The process and analytical development laboratories are now operational while the commissioning of manufacturing capacity will be completed later in 2024.

Enzene Biosciences. Enzene Biosciences, a Pune, India-based CDMO, is adding a new facility for continuous biomanufacturing in the US via its US entity, Enzene Inc. The company is building a new GMP manufacturing facility in New Jersey, built around the company's proprietary EnzeneX technology. The company has successfully identified, leased, and set up this inaugural manufacturing plant. The facility is 54,000 sq ft and will be launched in three phases, with the Phase I launch date slated for the third quarter of 2024. The full expansion will also include a drug-product manufacturing suite with formulation and small-volume filling equipment. The facility will also include a quality control lab, development lab, warehouse, freezer rooms, and a cell-bank store.

Aragen Life Sciences. Aragen Life Sciences, a CDMO of small molecules and biologics, is proceeding with a biomanufacturing expansion by investing $30 million for a cell-culture biomanufacturing facility in Bengaluru (Banagalore), India. The process development laboratory has been operational since December 2023. The first manufacturing suite is scheduled to be operational by December 2024.

Note: investment amounts and currency conversions are as of time of news announcement.

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Defining New Rules

The Evolution of the CDMO Industry

Contract development and manufacturing organizations (CDMOs) have been on the rise in the last decade. Historically, CDMOs operated on a business model which predominantly focused on serving as external service providers for manufacturing pharmaceuticals. This model included the addition of capacity by the acquisition of manufacturing facilities from (bio)pharma companies or own capital investments. However, CDMOs have increasingly become innovation leaders and cover more areas of the pharma business, not just manufacturing, opening up additional revenue streams.

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This change of focus has been accompanied by a change in the M&A landscape in the market. Some CDMOs are expanding their services and swapping their "contracts" for "partnerships", evolving the term "CDMO" into "PDMO." By getting closer to their partners, CDMOs can move past some of the pressure and offer consultative support or innovation to develop products in new ways.

The evolution of the CDMO sector is propelled by rising manufacturing standards, the advent of groundbreaking therapies, and a shift towards personalized medicine. CHEManager asked executives and industry experts from a broad range of CDMOs to share their views on how their companies are dealing with this changing economic environment and the resulting opportunities and challenges. We proposed to discuss the following aspects:

- (How) have the rules of the CDMO market changed since the pandemic of 2020/21?
- What do you consider the most important growth drivers for CDMOs?
- What is your company's strategy to grow the market share in the CDMO industry?

Read the insightful answers of the experts here.

A Secure and Resilient Supply Chain is Crucial

Gavin Murdoch, VP Commercial Strategy, Abzena

"The Covid-19 pandemic has been a catalyst for change in the contract development and manufacturing organizations (CDMOs) landscape."

The Covid-19 pandemic has been a catalyst for change in the contract development and manufacturing organizations (CDMOs) landscape. It has underscored the critical importance of a secure and resilient supply chain, making us realize the necessity for having secondary and local suppliers to ensure the availability of essential materials and services. It has also focused onshoring activities and investment in captive capacity.

There is an increased emphasis on dual sourcing and onshoring. Companies are now prioritizing having backup suppliers and local partnerships to mitigate risks associated with geopolitical uncertainties and supply chain disruptions. The BioSecure Act has further accentuated the need for transparency and security in sourcing, making it crucial to know the origin of materials and ensuring they are not reliant on single points of failure.

The market complexity has also proliferated in therapeutic areas such as cell and gene therapy, ADCs, and complex biologics. The demand for specialized expertise across these fields means no single company can master all domains, thus driving the partnering internal capabilities with outsourcing from discovery to commercialization.

Abzena is not just reacting to these market changes but strategically positioning itself to capitalize on them. Our approach focuses on fully integrating offerings, from discovery and development to clinical support and commercial production. We also offer drop in service offerings to bridge gaps in internal bench strength to accelerate pipelines. By ensuring our clients have a seamless, end-to-end supply chain, we reduce the risk of disruptions caused by multiple failure nodes.

We are also investing in capabilities and capacity, particularly in high-demand areas like ADCs, bioconjugates and complex biologics. Furthermore, we are exploring innovative business models that foster closer collaborations with clients, transforming our R&D operations into virtual extensions of their teams. Resilience, flexibility, and strategic partnerships define the new CDMO rules. Abzena is adapting to these changes and leading this transformation.

A Pipeline Full of New Opportunities

Tom Sellig, CEO, Adare Pharma Solutions

"Companies that invest wisely and remain adaptable can stay ahead of the curve and seize emerging market opportunities."

The CDMO landscape is rapidly evolving, and companies that invest wisely and remain adaptable can stay ahead of the curve and seize emerging market opportunities. The significant biotech funding in so far in 2024 illustrates that we're in a favorable environment for innovation and development, providing more opportunities for CDMOs.

Technological advancements are a crucial growth driver. Companies like Adare with robust technology solutions are in high demand. We continuously evaluate new technologies to enhance the development and manufacturing journey for our customers. While this process requires substantial time and resources, we believe it's worth the effort to discover innovations that benefit our clients.

High potency compounds continue to play an important role in the pharmaceutical landscape, driven largely by the oncology sector. Approximately 40%-50% of the drugs in development are cancer drugs, and of those 75% are high potency. This underscores the vital importance to CDMOs of possessing both expertise and infrastructure in handling highly potent compounds, an area where Adare excels.

Pediatrics is another growing market segment, with a heightened awareness among sponsors of the need for tailored formulations to accommodate pediatric patients. As a result, pediatric formulations are now seen as essential component of a dedicated strategy to maximize a product's potential.

Additionally, there is a growing trend of reshoring pharmaceutical work to the US, which presents significant growth opportunities for US-based CDMOs.

In summary, these factors collectively drive substantial growth for the CDMO industry, which we've seen at Adare. Our development pipeline is full of new opportunities. We've experienced record proposal volumes this year and anticipate continued growth from both new and existing products. The dynamic CDMO landscape clearly offers sustainable growth opportunities for both Adare and the industry at large.

CDMOs Must Have a Clear Vision and Strategic Growth Plan

Neil Jones, Chief Commercial Officer, Aenova

"Both well-established pharmaceutical companies and emerging biopharma companies are turning to CDMOs for strategic partnerships."

The importance of contract development and manufacturing organizations (CDMOs) in the global pharmaceutical supply chain is growing rapidly. As the demand for new and innovative therapies increases, both well-established pharmaceutical companies and emerging biopharma companies are turning to CDMOs for strategic partnerships. These partnerships enhance the drug development and manufacturing process by making it faster, more efficient, flexible, and timely. The significance of CDMOs is evident in the market growth, which reached €206 billion in 2023 and is expected to expand to €293 billion by 2028, with a CAGR of over 7%.

To further grow our market share in this industry, we focus on three simple key aspects:

First, vision and strategy: A CDMO must have a clear vision and strategic growth plan. This involves investing in production capacity for rapid scalability and faster time-to-market, as well as being an innovative and flexible partner. CDMOs need to anticipate and support future customer needs with the latest technologies, such as improving the bioavailability of APIs or accelerating the time-to-market for new chemical entities (NCEs).

Second, customer-centric approach: Placing the customer — and consequently the patient — at the center of all activities is crucial. CDMOs have a significant responsibility in the development and manufacture of products that improve the health and well-being of people worldwide. This requires operational excellence to ensure the highest quality and reliable delivery every day. Additionally, it involves a collaborative mindset to address business challenges alongside customers through continuous communication.

Finally, prioritization and execution: Recognizing market position and setting clear priorities is essential for CDMOs. For Aenova, this means strengthening our presence by expanding growth platforms, enhancing operational excellence, and developing growth drivers, including extending development services and technologies for innovative medicines.

Without Sustainability in Your Vision, You Probably Will Fail

Torsten Wöhr, CCO, Bachem

"Currently, most CDMOs that have invested in a specific platform like to stay with it."

The CDMO market is very dynamic at the moment, and I think companies need to reflect this. Currently, most CDMOs that have invested in a specific platform like to stay with it. Especially in the peptide and oligonucleotide manufacturing business, one of the protectors of the niche is the capital you need to invest. There is a high entry barrier. I think this often provides a false sense of security. For example, we are currently an enabler in the market. You might think that is a comfortable position, but that should not be misunderstood as a position of strength. It is very important to stay humble. If there is huge demand not covered by supply, it is a matter of time until that gap is closed.

So, I think you need to reinvest some of the money you make to stay at the forefront with research and innovation; this is our trailblazing concept. You start 3-4 different processes based on different technologies in parallel, and you decide at certain milestones which ones you are going to eliminate, and which one you carry forward. Not every CMDO does this, that they put their own money in these platform questions. But I think that is key, also when it comes to future challenges. We have customers that say: "We have a CO_2 emission target by 2035, and you are part of it!"

So, I believe if you do not have sustainability in your vision, you probably will fail. All CDMOs have to react there as well.

Enhancing Supply Chain Flexibility and Resilience

Ashu Tandon, Chief Commercial Officer, Aragen

"We are very well positioned to manage future disruptions, ensuring seamless operations, even in uncertain times."

The pandemic reshaped the CDMO market, making diversity of supplier base a necessity and an important variable in the supplier selection process. In light of ongoing geopolitical tensions, customers are now looking again at options beyond China in their supply chain. This even extends to the back-end supply chains of CDMOs and reducing dependency on China and other overseas markets. In response, at Aragen, we've prioritized enhancing our supply chain flexibility and resilience, investing in capacities and adopting advanced digital tools, including AI and ML, to optimize efficiency and reduce errors. As a case in point, we've been working very hard to develop a local supplier base within India, including within 250 km radius of our labs to ensure continuity of materials. Additionally, imports of raw materials have reduced from around 60% of our total spend to about 20% in the last 3-5 years. As a consequence of these strategic investments, we are now very well positioned to manage future disruptions, ensuring seamless operations, even in uncertain times.

Aragen's growth strategy focuses on three key areas: investing in advanced facilities, expanding capacity and capabilities, and providing innovative solutions to meet customer requirements. We have been making strategic investments across all lines of our business. We recently strengthened our drug product service offerings by adding clinical manufacturing capacity that will allow us to provide integrated drug substance, drug product and related analytical services. While in our biologics manufacturing plant in Bangalore, we can now undertake non-GMP production for batches up to 50 L. And, by the end of the year, we will add further GMP manufacturing capacity that can deliver manufacturing batches at the 200 L to 2 KL scale. We have added large-scale biomanufacturing capacity at our campus in California. We are also strengthening capabilities in newer areas like oligonucleotides, peptides, and antibody drug conjugates (ADCs). Finally, we have also committed to an investment plan of around $250 million over the next five years — to expand both R&D and manufacturing facilities across the business.

Fostering Long-Term Collaborations

David McErlane, Group President of Biologics; and Aris Gennadios, Group President, Pharma and Consumer Health, Catalent

The CDMO market has adapted to the changes brought about by the pandemic by becoming more agile and flexible, to be able to rapidly respond to changes in market conditions, and more focused on high-growth areas such as biologics and cell and gene therapies. We have also seen more investment in digital technologies.

The Covid-19 pandemic highlighted the need for integrated and robust supply chains. Improved supply chain resilience that provides reliability and traceability can support the timely delivery of therapies to patients. A well-planned, integrated supply chain for critical raw materials and components becomes critical when high-value, individualized therapies such as cell therapies need to be manufactured and delivered in a time-sensitive manner.

There has been an increase in strategic partnerships between pharmaceutical companies and CDMOs. These collaborations are often more integrated, involving earlier stages of development and greater sharing of information to streamline the drug development process.

The emerging biopharma sector continues to drive innovation, and as a result, Catalent has seen a rise in demand for integrated services that streamline the drug development process from development to launch. As a critical partner to these companies, a CDMO's ability to offer comprehensive solutions not only accelerates timelines, but also ensures the successful commercialization of groundbreaking therapies.

We have also seen an increase in outsourcing driven by the need for flexibility, efficiency, and access to specialized infrastructure and expertise required to bring novel treatments to market. With global and industry volatility, many customers value the capacity and flexibility CDMOs bring to rapidly scale and adjust output quickly in response to changes in demand.

Of course, it has remained essential for CDMOs to provide reliable quality and maintain trust-based relationships with customers. In an increasingly competitive market, Catalent's commitment to excellence and transparency has become a cornerstone of our partnerships. By consistently delivering on our promises, we foster long-term collaborations that drive mutual success.

Create Access Equity for Biological Assets

Russel Miller, Vice President Global Sales & Marketing, Enzene

"Our expansion into the US market is a key element of our growth strategy."

Enzene's strategy to grow market share in the CDMO industry is anchored in our innovative fully connected continuous manufacturing process, EnzeneX. Through this technology, we aim to make biologics manufacturing more accessible and affordable for small and emerging biotechs, as well as animal health companies. We understand the challenges these companies face in achieving cost-effective production, and EnzeneX addresses these needs by ensuring high yields and quality outcomes — essential for the success of complex biomolecules like fusion proteins and bispecific/trispecific antibodies.

Our expansion into the US market is a key element of our growth strategy. The upcoming launch of the 54,000 sq. ft. facility in New Jersey, equipped with 500 L bioreactors and additional capacity planned beyond phase 1, will enhance our ability to serve the US market, bringing our continuous manufacturing processes closer to our clients and supporting both clinical and commercial manufacturing needs.

Our intention is to create access equity for biological assets whether human or animal and in any phase of development, by providing cost-effective local manufacturing. With the growing concerns over the uncertainty of the BioSecure act, a lot of biotechs are looking for alternatives and preferring US manufacturing, and the new site will create access equity by providing state-of-the-art, cost-effective continuous manufacturing to small and mid-size companies.

We constantly strive to improve our processes and are working on EnzeneX 2.0. This upgraded version of our technology is being designed to enhance various aspects of the manufacturing process, aligning with industry demands for greater functionality. Additionally, we are developing new cell lines capable of achieving 8-9 g/L yields, with the goal of breaking the $40/g cost barrier.

Lastly, both at our Indian site and in the US, we're expanding our services by launching a discovery arm, offering fully integrated services from discovery to commercialization.

Focus on Being in Close Contact with Partners

Frank Wegener, CEO, ESIM Chemicals

"Growth is driven via the willingness of the big players to allocate projects to a CDMO."

Actually, the rules have changed somehow. There has been a period up to the end of 2022, where customers have been very conscious about potential supply chain disruptions, focusing their operations on Europe or the US. This gave a push to all CDMOs. The consolidation of European CDMOs moved forward, especially on the back of rising energy prices and labor costs, the positive tailwind only lasted a short period of time. All companies, around the globe, are in the meantime considerably more digital and big parts of the work with the customer is done online.

Technical excellence, best-in-class service, agility. What does this mean: The growth is driven via the willingness of the big players to allocate projects to a CDMO. We therefore focus on being in close contact with our partners and trying to understand their most important needs for the specific project, which can vary a lot. It might be a fast implementation, an improvement of the process, flexibility in campaign volumes, … .

To focus on our core competences and further improve them in all areas of working together with our partners. We as ESIM are known for best-in-class operational excellence to further improve the processes and therefore the cost situation, on for example raw material usage, for our customers. Keeping the focus on further educating our workforce in operational excellence and best practice of project management. Together with a clear strategy, being one of only a few companies fully focusing on CDMO without a big line product business next to it, this will bring the tailwind for growing further the market share in the rather small world of CDMO industry.

Shift from Manufacturer to Technology Leader

Ludwig de Mot, CEO, EuroAPI

"CDMOs are addressing a broader range of therapeutic areas for chronic diseases such as obesity, diabetes and cardiovascular conditions."

In a diverse CDMO environment, EuroAPI is in a unique position to take advantage of market trends. The first of these is the shift from providing manufacturing services to becoming technology leaders. At EuroAPI, we partner a wide range of organizations, from biotech to big pharma companies, to address their needs for innovative molecules such as peptides and oligonucleotides, now growing at +10% CAGR. With the boom in precision medicine, we act as an enabler for targeted therapies notably in the domains of rare diseases, the central nervous system, oncology, and immunology. For example, we signed a partnership with the French biotech SQY Therapeutics for an antisense oligonucleotide to treat a genetic disease. We are also seeing increased demand for highly sophisticated peptides, oligonucleotides and conjugates. Among the 14 new contracts signed during the first half-year, EuroAPI contracted a new peptide-PMO conjugate project, making nearly 80 CDMO projects in our portfolio.

In a second major trend, CDMOs are addressing a broader range of therapeutic areas for chronic diseases such as obesity, diabetes and cardiovascular conditions. Although until recently the peptide market was less attractive than the oligonucleotide market, the trend has changed since last year due to strong acceleration driven by GLP-1 agonist drugs. The market now needs much larger-scale capacities for both peptides and oligonucleotides, so we are investing €17 million in these products.

Small molecules still have a key role to play but they are growing increasingly complex and more active. As a result they require a larger number of synthesis steps, and more sophisticated control of API physical quality and particle size. So to further complement its internal assets, EuroAPI has partnered with Basel-based SpiroChem to ensure the continuity of API development, and has invested in state-of-the-art high-potency GMP facilities, especially to produce sophisticated payloads for booming antibody-drug conjugates.

Prioritizing Strategic Partnerships

Kenneth N. Drew, Vice President, Flamma USA, Flamma

"The pressing question for many in the pharmaceutical industry is how to manage supply chain dependence on China."

The pressing question for many in the pharmaceutical industry is how to manage supply chain dependence on China. The global nature of the pharma marketplace makes this a complex issue. While finding a new supplier might seem straightforward, the reality is challenging.

Selecting a CDMO that has facilities in Europe as well as China can be challenging but can provide a stable supply chain. Having facilities in Europe provides an internal backup to China thus giving the innovator company the peace of mind they desire.

Most, if not all, innovator companies are scrambling today to find alternative sources for their small molecules. Due to various issues in our world (war, inflation, sluggish biotech stock markets, high interest rates, political uncertainty in the USA), many companies were in a holding pattern until recently. Now the race is on to locate a CDMO that can provide manufacturing services. This is causing CDMOs to make difficult decisions as to whom to service creating a highly competitive environment where locating a reliable CDMO partner has become critical.

Core customers deserve priority, but CDMOs also aim to expand their customer base. Many CMC leaders had previously warned their executives to address these issues yet they delayed decisions and have now placed CMC and procurement teams in a difficult position. High-quality CDMOs are now overwhelmed with CDAs, RFIs, and RFPs from innovators who have waited to act and the competition for capacity is fierce.

Innovators should build relationships with CDMOs that have diverse geographic footprints. This approach mitigates risks with supply chain disruptions in China but also ensures a more resilient and flexible production network. The companies that wait for China to have even more issues than the BioSecure Act, will be on the outside looking in. Prioritizing strategic partnerships can help secure stable supply.

Increasing Complexity in Clinical Pipelines

Gordon Bates, President, Small Molecules Division, Lonza

"Managing shortened development timelines for drug molecules will continue to be a top priority for drug developers."

Small molecules still make up the majority of the pharmaceutical market, with small and emerging biopharma companies increasingly driving the growth and innovation of small molecule-based therapies. Increasing complexity is evident in clinical pipelines, which demands both deep scientific expertise and strong process development and manufacturing innovation to resolve technical challenges. Much of this needed expertise resides with CDMOs, who, over many years, have gained unparalleled experience through exposure to thousands of molecules and are now harnessing this heritage with digital innovations to support drug developers' quest to bring innovative new therapies to market ever quicker.

Managing shortened development timelines for drug molecules will continue to be a top priority for drug developers. We observed that API synthesis has been becoming increasingly complex and lengthy — often requiring more than 20 synthetic steps — and limiting developers' speed-to-clinic.

To address this trend, our expert teams developed and implemented an AI-driven solution for route scouting that delivers route designs and associated robustness assessment of raw material supply chains.

Following the launch of this new AI-based route scouting service, drug developers are now provided with insights for optimal route design, leading to accelerated speed-to-clinic with confidence in an efficient and scalable API manufacturing process and supply chain.

CDMO Market Is Poised for Growth

Christoph Schaffrath, Head of Marketing & Sales, Lanxess

"Many Western countries have spoken out in favor of restoring local and Western supply and value chains to become independent of China."

Supply chains from China were disrupted during and after the pandemic. Due to monopolies on various drugs in China, there were shortages of various drugs in Western regions. The recent downturn in trade through the Suez Canal has once again proven the vulnerability of globalized supply relationships. As a result, many Western countries have spoken out in favor of restoring local and Western supply and value chains to become independent of China.

In meeting this challenge, Saltigo, a subsidiary of Lanxess, can provide customers with efficient support. Saltigo is a globally operating company specializing in custom manufacturing for the fine chemicals, crop protection, and pharmaceutical industries. The production of pharmaceuticals and especially active pharmaceutical ingredients, so called APIs, can be very complex. In particular, the complex intermediates require various technologies, such as hydrogenation, fluorination, nitration, etc. Ideally, these complex value chains should be served from a single source.

Saltigo is one of the world´s leading custom manufacturers with a very extensive technology portfolio, decades of experience and a large production network and the ideal partner for the CDMO market. As a true one-stop shop, we offer a comprehensive suite of services, from process development and regulatory support to in-house logistics and global sourcing. In addition, our company has a strong focus on sustainability and offers product carbon footprint optimized 'net zero' processes as a significant added value. Safeguarding the security of supply for our customers is an essential part of Saltigo's DNA.

Overall, the CDMO market is poised for growth, driven by the need for more secure, sustainable, and technologically advanced pharmaceutical manufacturing solutions. Companies like Saltigo, with their extensive technology portfolio and focus on sustainability, are well-positioned to capitalize on these trends.

Going Beyond Providing Just Services

Prasad Raje, CEO, LGM Pharma

"CDMOs capable of supporting all activities of drug development are becoming more desirable with customers seeking expertise in each area."

CDMOs were significantly disrupted along with the broader pharmaceutical industry. They faced similar challenges related to supply chains, talent retention, and acquisition. The demand for Covid-related medicines increased tremendously, but CDMOs proved their agility and adaptability by successfully meeting this demand.

Well-managed CDMOs with robust infrastructure, strong problem-solving abilities and diversity of service segments have been able to bear the shock of disruption as well as the recent pull-back in biotech funding. A general trend is emerging where CDMOs are going beyond providing just services, especially among diverse service segments capable of supporting R&D through to clinical trial material (CTM) and commercial manufacturing. They are forming partnerships with customers that resemble pseudo-funding arrangements, and in return getting returns when products are commercialized. While this business model is not entirely new, its prevalence is increasing.

CDMOs capable of supporting all activities of drug development are becoming more desirable with customers seeking expertise in each area. In other words, growth will come from being "best in class" rather than merely offering services. The ability to quickly capitalize on emerging opportunities is crucial for organizations. One classic example from 2023/24 is around the rise of GLP/GIP.

Since last year, LGM Pharma has continued to invest in infrastructure and talent. As biotech funding returns to its 'normalcy' we will be poised to address our customers' drug development challenges in the most efficient way. Our fundamental principle for success has not changed: being best in class for all our service offerings. Also, we are continuing to partner with our customers in various different business models when we see that interests and expertise can be aligned.

The Value of External Expertise

Federico Pollano, Senior Vice President Business Development & Client Program Management, Rentschler

"Growth is significantly fueled by a robust pipeline of next-generation therapeutics developed by innovative companies that do not possess their own production capabilities."

The international CDMO sector is experiencing substantial growth, driven by rising demand across therapeutic areas such as oncology, autoimmune, neurological diseases, infections, and rare diseases. According to Frost & Sullivan, the BioCDMO market is projected to grow at a compound annual growth rate of 14.3% from 2023 to 2029. Specifically, protein and antibody therapeutics are expected to grow at over 8%, while advanced therapies, including cell and gene therapies, are anticipated to surge by approximately 33%.

This growth is significantly fueled by a robust pipeline of next-generation therapeutics developed by innovative companies that do not possess their own production capabilities. These companies represent 70% of the R&D pipeline and increasingly depend on CDMOs for manufacturing support. Additionally, Big Pharma is increasingly outsourcing late-stage product candidates and market products to CDMOs, recognizing the value of external expertise.

At Rentschler Biopharma, we support clients from Phase I development through to commercial production for the market. Our recent contribution to successful FDA approvals — contributing to four out of 17 biopharmaceuticals approved in 2023 — showcases our ability to deliver integrated services, including world-class consulting, regulatory support, process development, technology transfer, and cGMP manufacturing.

We are also deeply engaged in the field of advanced therapies, which demands specialized expertise and cutting-edge technology platforms. Our objective is to assist clients in navigating the complex regulatory landscape and securing essential funding, thereby facilitating the advancement of innovative therapies.

In summary, the expansion of therapeutic areas, the rise of advanced modalities, and the growing reliance on CDMOs by both innovative and established companies are key drivers of growth in the sector.

Innovators Are Looking Increasingly at Agility in Execution

Davuluri Saharsh Rao, Vice-Chairman and Managing Director, Neuland Labs

"CDMOs are strengthening their position as integral partners, creating strategic, and agile collaboration with innovators."

The pandemic has reshaped the CDMO market significantly. Innovators are looking increasingly at agility in execution even as supply chain security becomes an important factor. While there is a bias toward one-stop shops, there is also a recognition that companies with specialized focus areas can deliver superior results through effective integration, whether at the innovator's end or at one of the CDMOs. Developments during the pandemic have opened the possibilities of much faster and efficient clinical development aided also by the advances in machine learning. This has led to a supply constraint, especially in the more specialized modalities like peptides, oligonucleotides and ADCs. Overall, innovators are looking at specialists who can be agile while simultaneously investing in capacity for greater control. CDMOs are strengthening their position as integral partners, creating strategic, and agile collaboration with innovators.

While capacity is essential to drive growth, a CDMO's capability and track record in meeting client requirements is also crucial. At the same time, staying ahead of the curve by investing in new capabilities and offering options to innovators will ensure that a CDMO will grow.

Neuland Labs differentiates itself through enhanced collaboration and agility in execution. The primary catalyst of our success has been our steadfast commitment to high quality standards. We plan to invest in new areas, offering our clients the opportunity to engage with us on more projects and provide innovative solutions to their existing challenges. Specifically, we are expanding our capacity and deepening our expertise in Peptides, with a new manufacturing plant catering to peptides.

Driving Growth through Collaborative Innovation

Tom Wilson, Pfizer CentreOne Global Head of Business Development, Pfizer

"The most important growth drivers for CDMOs include innovation, quality, and strategic partnerships."

Pfizer CentreOne is a global CDMO, leveraging Pfizer's scientific and technical expertise. We offer contract development and manufacturing services for oral solids, sterile injectables, small molecules, biologics, and regulatory services. The most important growth drivers for CDMOs include innovation, quality, and strategic partnerships and at Pfizer CentreOne we leverage these drivers to grow market share in the CDMO industry

We prioritize quality and reliability from development to commercialization, understanding that for the patient, time is life. Supply chain reliability and management are significant challenges today. However, Pfizer's extensive upstream relationships with suppliers of raw materials, active ingredients, biological drug substances, and componentry provide a competitive edge. These pre-approved, audited, and evaluated relationships allow us to bypass lengthy approval processes and deliver timely solutions, showcasing Pfizer's robust quality systems.

Manufacturing at Pfizer focuses on cost, quality, and customer service. Our upstream relationships enhance quality and customer service, reducing costs. Pfizer CentreOne utilizes the same workspaces globally for both Pfizer products and CDMO services, ensuring consistency and high standards. This means client partners benefit from state-of-the-art facilities and rigorous maintenance.

Pfizer's commitment to innovation merges our scientific expertise with that of our client partners, fostering groundbreaking outcomes. By leveraging Pfizer's scientific capabilities on behalf of other companies, Pfizer CentreOne differentiates itself in the CDMO industry and drives growth through collaborative innovation. This strategic integration of quality systems, innovative science, and efficient supply chain management positions Pfizer CentreOne as a leader in the CDMO market, delivering exceptional value to its clients.

Redefined Expectations on Drug Development Timelines

Rohtash Kumar, Senior Vice President, Chief Technology Officer, Veranova

"With an increasing focus on fast-to-clinic strategies, CDMOs require expertise and technologies to meet speed, flexibility, and safety demands."

Rapid development and scale-up of Covid-19 vaccines redefined the industry's expectations on drug development timelines. With an increasing focus on fast-to-clinic strategies, CDMOs require expertise and technologies to meet speed, flexibility, and safety demands. These strategies must accelerate development without negatively impacting safety, efficacy, and regulatory compliance.

Global supply chain vulnerabilities, particularly in the reliance on offshore manufacturing for essential supplies, were also exposed. In response, the industry has enhanced supply chain security, prioritized onshore manufacturing, and valued robust tech transfer, driving more pharmaceutical companies to partner with local, experienced CDMOs for a competitive edge.

Increasing demand for complex APIs highlighted the need to adapt to evolving trends. Leveraging artificial intelligence (AI) tools allows CDMOs to enhance drug development and manufacturing, yielding positive outcomes from enhanced supply chain logistics. Growing emphasis on patient-centricity in drug discovery and development has given rise to targeted therapeutics that deliver stronger efficacy at lower doses, spurring innovations in novel modalities, including drug-conjugate linkers and new delivery routes.

At Veranova, our core values — people, patients, and innovation — guide our market approach. People are our greatest asset, so we've focused on building a talented and diverse workforce by strengthening our senior leadership team and appointing a new advisory board.

Our commitment to patients has driven investments in capabilities to handle emerging therapies. The demand for more efficacious, patient-centered treatments has led Veranova to expand our capabilities in complex and highly potent APIs, and drug-conjugate linkers. This includes a mid-scale API expansion at our Edinburgh, UK facility, and a $30 million investment in our Devens, MA site. Innovation is central to our growth.

Veranova continuously strives to improve, exemplified by our collaboration with Phorum.AI, which is focused on enhancing our pharmaceutical manufacturing processes with AI to accelerate time to market for our clients. These strategic moves strengthen our position in the CDMO industry and help our partners deliver life-changing therapeutics to patients.

From Transactional to Collaborative Partnerships

Thomas Otto and Peter Soelkner, Managing Directors, Vetter

T. Otto: Since the pandemic, partnerships between biopharma companies and CDMOs transformed from transactional to collaborative. Fill and finish partners are heavily integrated into the drug development process from preclinical through to commercialization and long-term market supply. This has prompted a rising demand for CDMO services resulting in projected growth of the global market from $222.5 billion in 2023 to $249.96 billion in 2024, according to recent reports. The pandemic shone a light on the need for continuing production capabilities that don't inhibit quality, making the need for external support crucial for drug owners. Now, we're witnessing a rise in both small batch and blockbuster drug development as companies explore solutions for rare diseases while producing the most heavily relied-upon drugs. This is just one more area where CDMO expertise is valued for its unique infrastructure, specialized focus, and enhanced capacities.

P. Soelkner: In formulating our strategy for growing market share, we rely on lessons learned throughout our history as an independent, family-owned solution provider. The strategy comes down to several elements which we prioritize to meet our customers' needs. First, we invest proactively in the infrastructure, capacity, and technology needed to support new therapies and consequently customer demands which continue to arise. Simultaneously, we remain committed to the tried-and-true medications that will go on to serve a purpose in the market, and rather than replacing, we expand to leave room for what works and what's new. We place an equal focus on investing in our talented workforce who make it possible to provide the expertise our customers rely on. We are now represented by 6,600 global employees, over 1,000 of which are dedicated to quality tasks. Lastly, we prioritize a responsible role in the value chain. As a trusted globally-operating outsource partner, our actions reflect upon our customers. Therefore, we prioritize sustainable business practices that allow drug owners to feel confident in us as a critical extension of their teams.

A Need for Greater Variation of Manufacturing Assets

Chad Telgenhof, Chief Commercial Officer, Sterling Pharma Solutions

"Increasingly stringent regulatory requirements are making it more challenging for innovators to meet compliance standards on their own."

The current market growth for CDMOs is fueled by the continued focus of pharmaceutical companies on their core competencies of R&D and marketing, leading to the outsourcing of process development and manufacturing.

However, the role of CDMOs and the demands being put upon them are evolving. As pipelines and drugs in development change, with the rising demands for biologics and other new modalities — as well as niche and orphan drugs — customers are requiring specialized, diverse, flexible and scalable capabilities.

For small molecule APIs, lower volume demands are coming with increased molecular complexity, a greater number of processing steps and the likelihood of challenging, and often hazardous, chemical transformations. This means there is a need for greater variation of manufacturing assets to handle the necessary reagents and reaction conditions, as well as a broad range of vessel capacity to efficiently process potential swings in volumetric needs.

Another key factor is the expansion of pharma companies into emerging markets, and the need for local manufacturing capabilities. CDMOs offer cost-effective solutions through their economy of scale and flexibility for these situations, and larger CDMOs with wider manufacturing networks can assist in the security of supply chains by providing secondary sources of materials under the same quality framework, as well as back filling synthetic steps in processes.

Increasingly stringent regulatory requirements are making it more challenging for innovators to meet compliance standards on their own. As global regulations around drug development, manufacturing, and quality control become more complex and rigorous, companies are turning to CDMOs for their expertise in navigating these regulations efficiently. CDMOs have access to advanced technologies, supported by robust quality systems, and a deep understanding of global regulatory requirements, enabling them to deliver compliant solutions that meet the highest standards.

India's CDMO Market Is Growing Significantly

Alex Del Priore, Senior Vice President, Manufacturing Services, Syngene

"Today, the quality of science is perhaps the biggest differentiator for an outsourcing partner."

The Covid-19 pandemic has reshaped the CDMO market, notably altering outsourcing trends and global supply chains. Geopolitical shifts have prompted pharmaceutical companies to diversify their supply chains, reducing reliance on single-country sourcing, particularly from China. This shift benefits CDMOs like Syngene, as companies seek high-quality research and manufacturing solutions that India offers that are also cost-effective. As the world's second-largest holder of USFDA-approved facilities, India provides a skilled workforce and advanced technological capabilities. Today, the quality of science is perhaps the biggest differentiator for an outsourcing partner. In this respect, Syngene's sharp focus on innovation as well as our ability to provide science and scientific teams at scale really sets us apart.

The CDMO market in India is experiencing significant growth primarily driven by three factors: continued investment in biotechnology increasing the capacity, skills and experience available to outsourcers; the need to increase the resilience of supply chains through diversification; and geopolitical factors which are driving companies to seek new providers, particularly shifting away from China. As biotech funding rises, especially in the US, there is a surge in outsourcing activities, creating opportunities for CDMOs. Companies are looking beyond China for suppliers, opening growth avenues for CDMOs in regions like India. We are seeing companies setting up pilot projects across a broad range of services and often placing them with a select short list of suppliers. Their plan is to run these comparative pilots through the year and use this as a way of selecting future partners. Syngene's ability to deliver end-to-end solutions, its investment in cutting-edge technologies and its strong track record in quality assurance has positioned us well to capture the opportunities that are currently emerging.

We have also invested in expanding our capacity and infrastructure. Syngene sees biologics as a key driver of its future growth and has all the building blocks in place to become a major player in the biologics space.

The Future of the CDMO Industry Is Exciting

Greg Behar, CEO, Recipharm

"Demographic shifts, such as the aging global population and the growth of emerging markets, are expanding our customers' markets."

At Recipharm, we are witnessing significant growth in key areas, particularly in the demand for complex pharmaceutical products, such as advanced therapy medicinal products (ATMPs) in our ReciBioPharm business unit. This growth trajectory is closely tied to broader economic factors like interest rate trends, which impact funding availability. Additionally, there is a notable rise in demand for injectable sterile biopharmaceuticals, such as GLP-1 products and the development of highly potent drugs, highlighting the crucial role Recipharm plays in meeting these needs.

As more customers outsource production stages, we must strategically expand our capacity to deliver the required products efficiently and cost-effectively, and form genuine partnerships with our customers. From early-stage development, where we provide analytical support, to tech transfer and full-scale manufacturing, Recipharm is committed to being a reliable partner throughout the product lifecycle.

The geopolitical climate underscores the importance of supply chain security, a lesson emphasized during the Covid-19 pandemic. Prioritizing the robustness of our supply chains ensures that we continue to deliver the critical products our customers and patients rely on.

Demographic shifts, such as the aging global population and the growth of emerging markets, are expanding our customers' markets. To respond effectively, we must operate with efficiency and flexibility, anticipating the evolving needs of these markets.

Innovation remains central to our strategy. We are dedicated to leveraging cutting-edge technologies, such as artificial intelligence, to accelerate tech transfers, streamline production and enhance regulatory support.

The future of the CDMO industry is exciting. With strong customer relationships, a focus on innovation and a diverse portfolio, Recipharm is poised to fully leverage these growth opportunities and achieve success in the years ahead.

Speed Is Now a Crucial Factor in Judging CDMOs

Jordi Robinson, Chief Commercial Officer, Navin Molecular

"The reliance on a smaller supplier base leads to a partnership relationship model, rather than the more 'transactional' approaches of the past."

Since the accelerated development of vaccines in response to the Covid-19 pandemic, many pharma companies have been reviewing how development timelines for new drugs can be shortened. This has led to pressure being put on suppliers to provide extremely competitive lead times for projects, and especially for early-phase programs, where speed has always been critical. Speed is now a crucial factor in judging CDMOs, and has been used as a metric in customers' rationales for reducing the number of suppliers they work with.

The reasons for this are twofold: firstly, if a company is selecting a supplier principally on the basis of the timeline they offer, this can only happen if the two other key factors of cost and provision of a technically-sound proposal are closely matched across all suppliers; and secondly, if the customer is only working with a smaller number of suppliers, it follows that they need to be able to offer a wider range of services and technologies to fulfil the wide range of customer's needs.

Although this may appear that the customers are getting everything they want, there are also benefits for the CDMO in this scenario. The reliance on a smaller supplier base leads to a partnership relationship model, rather than the more 'transactional' approaches of the past. Despite the increased pressure for competitiveness, the likelihood of a long-term, and mutually beneficial relationship will result is increased, as each party is dependent on the continued performance and success of the other for the relationship to prosper. This leads to the potential of continued work for the CDMO, whether it be through access to new projects coming through the pipeline, or the continued supply as molecules progress through the development cycle. The result is that even if it appears that the supplier is working under ever-increasing pressure, those that are more agile and flexible can have longer-term benefits from this approach.

Unlocking the Future

Insights into Biologics and Pharmaceutical Manufacturing

Bill Humphries, CEO of Alcami, a global player in the pharmaceutical and biotechnology sectors, sits down for an exclusive interview with Christene Smith from CHEManager International. In this conversation, Humphries unveils his ambitious plans and vision for the future, offering a unique perspective on the dynamic trends currently shaping the market. Steering Alcami's growth trajectory, Humphries shares insights into the company's commitment to excellence and innovation. From the development of cutting-edge pharmaceutical solutions to the navigation of global market complexities, Alcami, under Humphries' leadership, is poised to redefine the industry's landscape. This enlightening conversation explores Alcami's strategic direction, accomplishments, and the challenges that lie ahead.

CHEManager International: Since taking over as CEO in June last year, you have led Alcami through the acquisition of Pacific Pharmaceutical Services (PPS) and initiated partnerships with other companies. Could you elaborate on how these activities enhance Alcami's offerings?

Bill Humphries: Our acquisitions and partnerships are strategic and intentional, based on both opportunity and careful planning. Our company has six campuses right now, and prior to the PPS acquisition, the furthest West we went was St. Louis, and so there's an entire ecosystem on the West Coast that may or may not know the Alcami name because they don't get to interact with us regionally as much as others do, say in the Carolinas or in the Northeast. The acquisition of PPS allowed us to plant an Alcami flag on the West Coast. This not only broadens our geographical reach but also allows us to serve a new base of clients who may not have known Alcami.

PPS tended to work with organizations with more pre-clinical assets, and so introduced us to early-stage clients who we hadn't worked with before, as we'd mainly focused on clinical and commercial. That's created an opportunity for us to share the other services we offer with these new clients, from storage and pharma services to lab services and drug product manufacturing.

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In January 2023, Alcami was acquired by Global Healthcare Opportunities (GHO) Capital Partners and The Vistria Group. Has this change in ownership influenced the strategic and operational direction of Alcami?

B. Humphries: The acquisition hasn't changed us, but rather enhanced us. With Madison Dearborn's exit and Ampersand's stay, we've gained the support of one of the world's preeminent healthcare private equity firms. Joining forces with GHO and Vistria has brought us incredible sponsors, board members, and collaborators.

GHO, with its deep bench in life sciences, and Vistria, a newer entrant into healthcare services, have both proven their depth and value. One of the best outcomes of this partnership is Pat Walsh, our former CEO, staying on as chairman of the board. His leadership has been instrumental in navigating our company forward.

With the combined strengths of Ampersand, GHO, and Vistria, we've become stronger. GHO's transatlantic thesis is particularly beneficial as we look to grow beyond our US-only business. With the acquisition of PPS, we've expanded across the United States and are now thinking more globally. We have plenty of organic growth ahead, but this partnership equips us well for inorganic growth too.

Which market sectors do you address and how is Alcami positioned in these markets in terms of portfolio range and core competences?

B. Humphries: We provide three primary services: drug product, laboratory services, and pharma storage services.

In drug product, we offer formulation development, tech transfer, manufacturing, and packaging for sterile fill finish and oral solid dose. We have facilities in Charleston, South Carolina, Research Triangle Park, North Carolina and Wilmington, North Carolina where we manufacture everything from vials to prefilled syringes and capsules to tablets. We cater to both big pharma and smaller biotech companies with a focus on clinical to commercial programs.

Our laboratory services cover almost all capabilities with the exception of NMR, although we are in talks with a client about potentially offering it in the future. We have labs in Wilmington, Research Triangle Park, Charleston, and St. Louis, offering services from release and stability testing to method development and validation for both small molecules and biologics.

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Bill Humphries, CEO, Alcami

Our pharma storage services handle everything from room temperature to ultra-cold storage, including aliquoting/fractioning to delivery and pickup. We also offer validation and calibration services.

These primary services create a synergistic flywheel, allowing us to manage a client's product from manufacture to storage. Our project managers work by client, not by service offering, ensuring continuity for clients.

Do you think that the consolidation of the CDMO market will continue or even accelerate? What do you identify as the underlying drivers of this consolidation phase?

B. Humphries: I have two perspectives. Firstly, companies like Novo Nordisk and Lilly strategically acquire to ensure capacity, like Novo buying Catalent and Lilly buying the Nexus site. This trend might not continue unless there's a new wide-reaching molecule, similar to Botox or GLP-1s .

Secondly, private equity or strategic CDMOs will continue to be opportunistic, looking for assets that fill

their needs or provide growth potential. While it may not be rapid, I believe firms will continue to strategically build their portfolios with the best in breed.

The outsourcing trend in the industry has been prominent. Do you expect this to continue, and will the reshoring of critical substances or intermediates play a significant role in capacity build-up in Europe or the US?

B. Humphries: So, on outsourcing, look, I think that's going to continue, Pharma companies are managing their head count and deployment of capital. They will discern which services to own and which to outsource, driving outsourcing decisions that benefit their molecules, companies, and patients.

Reshoring has potential to be a tailwind for the industry, with shifts like the Biosecure Act. Companies like Phlow, under Eric Edwards' leadership, are thinking about how to ensure we have a stockpile of important medicines to serve our own citizens here in the United States.

I foresee a migration from WuXi to US-based CDMOs, with companies like Civica aiming to gain more control for the American population. This reshoring trend is about controlling our own destiny and being able to treat our own citizens.

Alcami has a long history in biologics manufacturing. Could you discuss Alcami's current biologics production capacity and any future expansion plans?

B. Humphries: We have two locations for biologics drug product manufacturing: Charleston, South Carolina and Research Triangle Park, North Carolina. In Charleston, we have two lines, one legacy lyophilization (Lyo) line and a newly commissioned dual Lyo automated isolator filling line. These lines can also handle liquid vials, offering flexibility for clients.

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Alcami's advanced pharma storage and services facility in Garner, NC, USA

In Research Triangle Park, we have four isolator filling lines. One is a prefilled syringe line, which we've recently qualified for larger batch sizes. Prefilled syringes are becoming increasingly important. The second line is a traditional liquid vial line. The other two are Lyo vial lines that are under commissioning and set to be operational in 2024.

We continue to listen to our clients' needs as we build for the future. We believe large molecules are here to stay, though small molecules are not going away. Some of these will require different deliveries, like different vial sizes or cartridges, or different types of assembly for prefilled syringes. We're always listening to our clients and considering their needs in our future investments.

How crucial are the pharmaceutical storage capacities and services that Alcami provides to its overall operations?

B. Humphries: Our pharma storage facilities, mirroring the biotech triangle of Boston, San Francisco, and Research Triangle Park, are crucial to our business. However, the services we provide there, such as aliquoting, provides a value-add to our customers and expands our lab services reach.

Cold storage is becoming increasingly vital, especially with the growth of large molecules. By offering additional services and storage, we can keep the molecule within our ecosystem. This minimizes the chance for quality issues and allows us to fully serve the client's needs.

Having storage capacity together with our other services is paramount to our success.

In terms of customer needs, where do you see market trends that Alcami aims to support and benefit from?

B. Humphries: We're focusing on large molecules growth, considering how we serve this trend with our current and future lines, and our center of excellence in Research Triangle Park, for large molecule biologics characterization and testing. We continue to invest in sterile fill finish, lyophilization, and other deliveries to capitalize on this trend.

Cold storage is another area where we see a growing need. We're ensuring that our storage facilities offer this and have room to expand these services. We offer a courier service as we feel that having the ability to transport samples or products to and from sponsors or clients to our testing facilities, particularly in Wilmington and Research Triangle Park, is crucial.

The services we provide as part of our pharma storage and services business, notably aliquoting, clinical trial supplies, and labeling, are key. We anticipate that clinical trials and the need for sampling will continue. The demand for cold storage, and even ambient storage, is only increasing. This all ties back to our focus and belief in the continued growth of large molecules-based products.

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Uncovering Potential

Addressing Customer Needs with Innovative and Sustainable Solutions

Arxada was created in 2021 following the carve-out and sale of Lonza Specialty Ingredients to private equity firms Bain Capital and Cinven. The Swiss specialty chemicals company achieved sales of CHF 2 billion in 2023 in its two businesses, Microbial Control Solutions (MCS) and Nutrition, Care & Environmental (NCE), which focus on multiple end-markets such as Human Health & Nutrition, Home & Personal Care, Paints & Coatings and Wood Protection. Michael Reubold spoke with Olivier Lambrechts, executive leadership team member and president NCE at Arxada, about the plans and vision for the future, and current CDMO market trends.

CHEManager: After the businesses were carved out from Lonza and Arxada was established in 2021, how has independence transformed the company since?

Olivier Lambrechts: In our first year, we focused heavily on building Arxada as an independent company, focusing on establishment as a player in the chemical industry and setting up best practices to serve our customers in an agile and flexible way. We also made two key acquisitions, Troy Corporation and Enviro Tech, which allowed us to offer customers an even broader portfolio of microbial control solutions and performance additives. We expanded our global supply chain capabilities, improving operations, supplying ability and other efficiencies that benefit our customers.

What do the company's owners, Bain Capital and Cinven, expect from you in terms of further development?

O. Lambrechts: Bain Capital and Cinven are investors with a long-term commitment to Arxada's success. The expectation is for our business to focus on growth through sustainable innovations. In our Microbial Control business, these innovations will allow us to lead a transition towards more sustainable products that meet or exceed regulatory changes and global macrotrends towards more eco-friendly microbial control. For our NCE business, it means building upon our strong CDMO capabilities and using them to provide low carbon footprint solutions to our customers. Sustainability is key for our owners. In fact, Arxada's financing includes a sustainability-linked bond, the first of its kind. This founding principle guides us as we plan and invest in our sustainability strategy and help our customers adapt to meet their own sustainability goals.

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Olivier Lambrechts, President Nutrition, Care & Environmental (NCE), Arxada

Arxada's roots go back more than 120 years. Having such a heritage of innovation and technology, what would you define as your key differentiators in the CDMO market today?

O. Lambrechts: Our more than 100-year history is most visible at our manufacturing site located in Visp, Switzerland. The Visp site is extremely well invested and offers an unparalleled level of vertical integration into chemical building blocks that no other company can provide. We have on-site production of ethylene and acetylene through an efficient and compact acetylene generating unit. Additionally, we can produce other base building blocks including complex and sophisticated molecules such as ketenes and diketenes as well as hydrogen cyanide. The latter is unique in the Western world given the complexity of producing and safely handling these molecules.

This vertical integration combined with our multipurpose assets enables us to provide a flexibility to our customers that no one else can offer. Depending on customer needs, Arxada has the capability to: 1) tailor towards more cost competitive solutions through a leaner supply chain 2); protect from supply chain disruptions by foregoing the need to source molecules from overseas; 3) provide low carbon footprint solutions through the usage of green electricity and feedstock combined with mass balancing through our vertically integrated assets. For some customers, it's a combination of all three value propositions!

How have the rules of the CDMO market changed based on the lessons learnt in the pandemic years of 2020/21? Have customer requirements like cost, quality, trust, supply reliability, time to market or sustainability shifted?

O. Lambrechts: We absolutely see a strong interest from our customers to increase supply reliability. This was driven by the supply disruptions during Covid and more recently by the Red Sea issues. We anticipate it will only be exacerbated by increasing geopolitical tensions. Sustainability is equally gaining in importance not only by public pressure, but by regulations. We notice that customers appreciate a partner like Arxada who enables them to bring demonstrable sustainability claims that are grounded in scientific reality.

In 2021 Arxada acquired two companies — Troy and Enviro Tech. What have they added to the NCE division in particular in terms of chemistries and technologies?

O. Lambrechts: As previously mentioned, the acquisitions of Troy and Enviro Tech were strategic moves aimed at expanding our market reach and technology portfolio in microbial control. Recognizing that microbes are omnipresent wherever there's water, our solutions span a wide array of industries, from paints and coatings to personal care and healthcare. Troy gave us access to new markets, particularly in paints and coatings, where our microbial control technologies could be applied. Enviro Tech introduced a new technology that we could scale across various industries. These acquisitions underscore Arxada's unique position in the market, being one of the few companies on our scale capable of serving multiple industries with a broad range of technologies. Our NCE division's capabilities provide opportunities to leverage manufacturing assets and explore other companywide synergies between the two business units.

What role within the company does the NCE business play today in terms of revenues and growth potential?

O. Lambrechts: NCE represents roughly a third of Arxada's revenues and is an essential contributor to the company's overall growth strategy. Arxada sees the combination of both divisions as highly relevant to provide a robust platform for growth grounded in global macrotrends. In the case of MCS, it is protecting the world from the harmful impacts of ever-evolving microbes. In the case of NCE, we are looking to provide supply reliability in a more sustainable manner through low carbon footprint solutions, renewables and battery materials.

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Arxada's Kourim site in the Czech Republic is dedicated to biotech projects.

Do you have plans to further develop your technology toolbox, capabilities or capacities and/or participate in the consolidation of the CDMO sector?

O. Lambrechts: Based on our current project portfolio, we have a growth strategy lined up for the Visp site which involves expansion of chemical capabilities and capacity additions. While we do not rule out further consolidation, our primary focus is on delivering the solutions our customers need today and building on our strong backbone in Visp for chemical specialties and biotech projects at our Kourim site in the Czech Republic.

In which customer markets do you expect the biggest growth in the years to come? What are the main growth drivers and how do you support growth in these areas?

O. Lambrechts: We expect significant growth in nutritional ingredients as well as battery materials . The main growth drivers are increased global population and consumer trends for more sustainable nutrition as well as a growing demand for renewable energy—and associated need to store that energy—on the other hand.

Do you expect the outsourcing trend, that started in the pharma sector to continue and gain momentum also in other areas important for the NCE business?

O. Lambrechts: Indeed, we observe that our customers are increasingly focusing on leveraging their core capabilities and proximity to the end markets to innovate, market and sell their solutions while relying on Arxada as a partner to quickly scale up and reliably manufacture their products. This partnership enables them to be agile, asset-light and benefit from working with a partner enjoying the benefit of 100+ years of experience to deal with the manufacturing of complex and not always easy to handle chemistries.

Many corporations have announced ambitious net-zero goals, some even excelling the net-zero targets of nations' governments. What is Arxada's approach to support customers in reducing their carbon footprint?

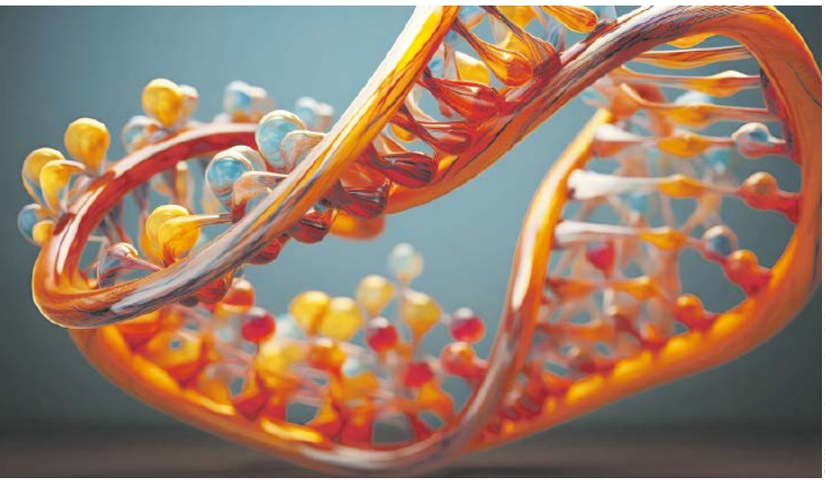
O. Lambrechts: Arxada helps customers reduce their carbon footprint by the unique combination of three things. First, the deep vertical integration enables Arxada to directly use green feedstock for its acetylene generating unit as well as other core production assets. Second, through its location in Switzerland, Arxada can enjoy easy access to green energy. Finally, our sourcing team is highly experienced in identifying and working with partners to offer low-carbon footprint materials where we cannot directly produce the molecules in-house. Combined, this is Arxada's unique value proposition.

■ www.arxada.com

Minicircle DNA

A Promising Tool for Gene Delivery and Therapeutic Applications

The minicircle has emerged as a next generation gene vector and as a promising tool in the field of gene delivery and therapeutic applications. This overview aims to cover the characteristics, production methods, and potential applications of minicircle DNA.



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Gene therapy holds great promise for the treatment of various genetic disorders and diseases. However, the success of gene therapy largely depends on the efficient and safe delivery of therapeutic genes into target cells. Traditional, non-viral gene delivery vectors, such as plasmid DNA (pDNA), often suffer from limitations such as immunogenicity, limited cargo capacity, potential undesired integration into the host genome, and carry unwanted gene motifs like antibiotic resistance genes.

A promising approach to overcome the few drawbacks of pDNA are minicircles. These are supercoiled circular double-stranded DNA molecules that lack bacterial backbone sequences, resulting in a smaller size compared to conventional pDNA. Like plasmids. They can be designed to contain specific regulatory elements, such as tissue-specific promoters or enhancers, to enhance gene expression in desired cell types. Minicircles are structurally identical to plasmids as they are supercoiled covalently closed (ccc), resulting in an extremely small but at the same time highly efficient topology, superior to open circular or linear forms (Figure 1). However, the notable smaller size allows for increased cargo capacity, improved stability, and reduced immunogenicity. In contrast to small e.g., so called nano plasmids, no selection process is used in their production and, of course, no sequence element as such is included.

Minicircle Production

PlasmidFactory uses an exclusive proprietary patented technology to produce non-synthetic minicircle DNA. A plasmid containing the gene of interest (GOI) serves as the starting material. The GOI is inserted into the so-called parental plasmid, followed by intramolecular recombination. The resulting minicircle DNA contains almost exclusively the GOI and its regulatory sequence motifs as well as a short (<150 bp) residual sequence region (SCAR). Superfluous bacterial backbone sequences are completely removed.

Minicircle vs Plasmid DNA

When comparing a minicircle with the corresponding conventional plasmid, carrying the same gene cassette, e.g. the reporter gene GFP, minicircles show enhanced gene expression in all cell lines tested. This improvement is not only mediated by increased intracellular DNA copy numbers after gene transfer using minicircles but also by a higher number of GFP-positive cells after minicircle gene transfer as revealed by FACS analysis. The effect is also visible when comparing the equimolar ratio between plasmid and minicircle DNA. Altogether, this enhanced gene transfer rates after transfection with minicircle DNA lead to enhanced transgene mRNA transcription compared to the results obtained with conventional pDNA.

Minicircles carrying other reporter genes such as luciferase, and lacZ are regularly produced in high yield and reproducible quality, thus they are kept constantly in stock. They already have been used for gene transfer, e.g. via lipofection or electroporation into various mammalian cell lines.

Applications of Minicircle DNA

1. Gene therapy, gene editing

In vivo gene editing often requires multiple editing elements. The increased cargo capacity of minicircles allows for the co-delivery of multiple components, enhancing the efficiency and versatility of gene editing approaches. For example, minicircle-based delivery of CRISPR-Cas9 elements enables precise modifications of the target genome to modulate specific cellular processes and in general holds great potential for other gene therapy applications due to its improved safety profile and increased cargo capacity. Additionally, cargo sequences exceeding 22 kbp can be integrated into the minicircle.

"The ability to design minicircles with specific antigenic sequences and immunomodulatory elements makes them an attractive platform for vaccine development."

2. Gene therapy, RNAi

The natural mechanism of RNA interference (RNAi) offers new strategies to silence gene expression in target cells using for examples short interfere RNAs (siRNAs) and fight e.g., neurodegenerative diseases such as Parkinson disease.

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Marco Schmeer, PlasmidFactory

However, although being quite effective in reducing gene expression, the use of siRNAs is limited by its rather short half-life in the target cell which is not favourable to treat chronic diseases. Thus, constructing a delivery system that enables prolonged expression that is not affected by immune inhibition remains one of the major challenges in this context. While plasmids tend to be resistant to electroporation into exosome (which is essential for brain-targeted delivery), adeno-associated viruses (AAVs) cause issues with the host immune system. Using minicircles can overcome both these shortcomings due to their small size and the lack of bacterial backbone sequences.

Based on this, scientists developed short hairpin RNA (shRNA)-minicircles that have the potential to reduce silence alpha-synuclein expression, a small protein cluster playing a critical role in Parkinson's disease development. These findings offer hope for long-term treatment strategies in chronic, neurodegenerative diseases.

3. Vaccine development

The ability to design minicircles with specific antigenic sequences and immunomodulatory elements makes them an attractive platform for vaccine development. Such minicircle-based vaccines have shown promise in inducing robust immune responses against infectious diseases and cancer.

4. Production of viral vectors: AAV

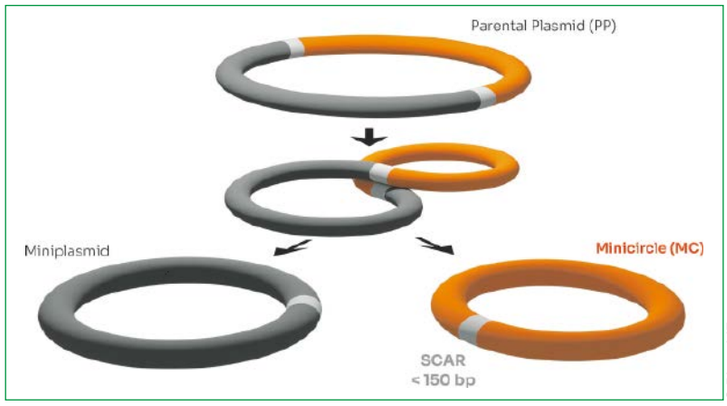
In the production of AAV vectors, plasmids are often used as starting materials. These plasmids contain information on the packaging of therapeutic genes in the virus particles. However, bacterial resistance genes contained in the plasmids can potentially be trans-

ferred into the AAV capsid as well. This so-called retro-packaging can lead to contamination and impair the therapeutic application.

Rsearchers from PlasmidFactory, the Medical University of Hannover (MHH), the Centre for Molecular Medicine Cologne (ZMMK) and the Kornea Laboratory of the University of Erlangen have established an innovative workflow based on minicircle DNA. The use of the minimalistic DNA vector instead of conventional plasmids avoids retro-packaging of bacterial sequences and greatly improves the purity and quality of the viral vector.

"… minicircle DNA provides several advantages over traditional plasmids and overcomes current shortcomings in the field of gene and cell therapy."

Moreover, this strategy enables the production of AAV vectors without bacterial resistance genes and hence, already meets future regulatory requirements for therapeutically usable viral vectors—making Minicircle DNA a promising alternative for AAV production.



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Parental plasmid transformed into minicircles and miniplasmids.

5. Cellular therapies: CAR-T cells

The field of oncology has seen an expansion in immunotherapies with the introduction of CAR (chimeric antigen receptor) T-cell therapies. These therapies target antigens expressed on tumour cells with CAR-modified T-cells recognising and destroying them. However, current manufacturing methods using plasmid transfection have low efficiency due to a certain DNA toxicity, while viral vector-based transfection poses safety risks and regulatory challenges. The low gene transfer rates and high T-cell toxicity often require repeated expansion cycles to maintain modified T-cells, which is time-consuming, expensive, and may lead to T-cell depletion.

Minicircle DNA shows a significantly reduced DNA toxicity and immunogenicity, making CAR-T cell production much more efficient. In combination with transposon systems e.g. like Sleeping Beauty or PiggyBac, it allows for non-viral gene transfer with a close-to-random integration profile. This significantly improves the safety profile of the resulting CAR-T cells. This also holds true for reprogramming of comparably sensitive stem cells.

Conclusion and Outlook

Altogether, minicircle DNA provides several advantages over traditional plasmids and overcomes current shortcomings in the field of gene and cell therapy.

The small size and reduced immunogenicity are only two examples that in turn are associated to further advantages. With these unique characteristics, it combines safety, efficacy, and regulatory compliance, making it an attractive alternative to traditional gene delivery vectors and an indispensable tool for advancing gene therapies and personalized medicine.

To also be able to provide plasmid and minicircle DNA for direct human application, PlasmidFactory has established the worldwide first GMP facility especially equipped for the (large scale) production of minicircle DNA as well as pDNA. In this facility, single-use equipment is exploited, including single-use fermenters to produce GMP-certified DNA in milligram to gram scale. The first production run will be finished by the end of the year. DNA produced in this facility will meet the stringent requirements for therapeutic products for human application.

Future research and development will further expand the application area of minicircle DNA and explore its full potential for therapeutical use.

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Flowchemistry — The Right Tool for CDMOs

Continuous Operation Coupled with a Small Footprint and Full Automation Enable Dedicated Production

Small and medium-sized enterprises (SMEs) face specific challenges, particularly due to the complex and highly regulated environment in the chemical and pharmaceutical industries. In the pharmaceutical sector, strict regulatory requirements for the approval of new products result in high costs and long development times. In addition, companies must constantly adapt to changing regulations such as REACh in Europe as well as GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice). This inevitably leads to high resource requirements for the company's own employees.

As a result, many manufacturing SMEs are unable to focus on their core competencies such as research and development, marketing and sales of their products. Consequently, these companies are increasingly turning to so-called CDMOs (contract development and manufacturing organizations) for outsourcing their production. These companies are specialized in contract research and manufacturing of chemical and pharmaceutical products in compliance with all regulatory requirements. They also provide access to expert knowledge, state-of-the-art technology, scalability and production

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Fig. 1: Lab scale setup with a 30 mL reactor, two dosing units, sensors (mass flow, temperature, pressure) and connection to heating and cooling units.

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flexibility. Through this collaboration, SMEs can reduce their time to market, strengthen their own innovative power and at the same time reduce production costs and risks.

CDMOs Need to Rethink

CDMOs are also facing enormous challenges, especially on the European market, as they have to compete with the often-cheaper competitors from the Indian or Asian market. In order to remain competitive, these companies must invest in future-proof technologies and skilled workers and be able to master the complex global supply chains. These are becoming increasingly disrupted, especially in the current geopolitical uncertainties, making it more difficult for SMEs and CDMOs to obtain the necessary raw materials and intermediate products. This increases costs and delays production. These boundary conditions are now slowly leading to a rethink on the part of companies to produce certain intermediate products on the domestic market. However, the technologies used to date cannot be used to ensure that this is competitive. Historically, almost all chemical syntheses still take place in classic discontinuous vessel operation (batch operation). This method of operating chemical reactions has many advantages but has the major disadvantage that in many cases it is already fully optimized. Any further increase in efficiency requires a high input of resources and investment for a relatively small gain in efficiency. This necessitates a rethink and the use of a different mode of operation and technology.

Flow Chemistry — a "New" Technology?

As a relatively new technology, flow chemistry addresses precisely these disadvantages of the optimized batch process. The chemical syntheses take place in continuous operation, for example in a flow-through pipe. Another feature of this technology is the small reaction volume (factor 1,000 compared to batch) of these reactors with dimensions on a millimeter scale. This combination leads to better control and reproducibility as well as higher reaction rates than in classic batch operation, as the reaction conditions such as temperatures can be increased due to precise control of these parameters. Thus, different process windows than in classical batch can be obtained and chemical reactions which normally need several hours can be processed within minutes at higher yields and selectivity. As an example, a millistructured reactor with a volume of 300 mL can process within an annual operation of 8,000 h already around 50 metric tons. Depending on the reaction time also 100 metric tons are possible to process in such a small reactor. While combining this technology with automation and the usage of real-time online and inline monitoring of the individual reaction parameters the product quality can be always ensured. This approach can already be used in the development of new products in lab scale for optimizing reactions according to their requirements e.g. yield, selectivity, etc. The reactor volumes hereby range between 0.5 mL and 50 mL. Subsequently, the results obtained can be directly applied to production-scale reactors through a seamless scale-up concept and in addition, this technology can be scaled up e.g. up to 20,000 tons per year easily by parallelizing the reactor channels similar like tube bundle or plate-type heat exchanger. The small volume of the reactors enhances safety, as only a small amount of hazardous material is processed under reaction conditions in the reactors, allowing potentially hazardous reactions to be better controlled. This reduces the risk of accidents and explosions. Particularly in Europe, where chemical companies are struggling to find space for new plants, flow chemistry can play to another strength: the need for a small footprint. A small footprint in a chemical plant is important because it saves space and therefore costs, especially in expensive industrial areas. It also minimizes material and energy consumption, resulting in lower operating costs and increased efficiency. A smaller footprint also reduces the plant's environmental impact, helps meet environmental regulations and facilitates future expansion or adaptation to new technologies. The above 100 ton plant requires only 4–6 m² of floor space for the dosing, reactor and automation sections.

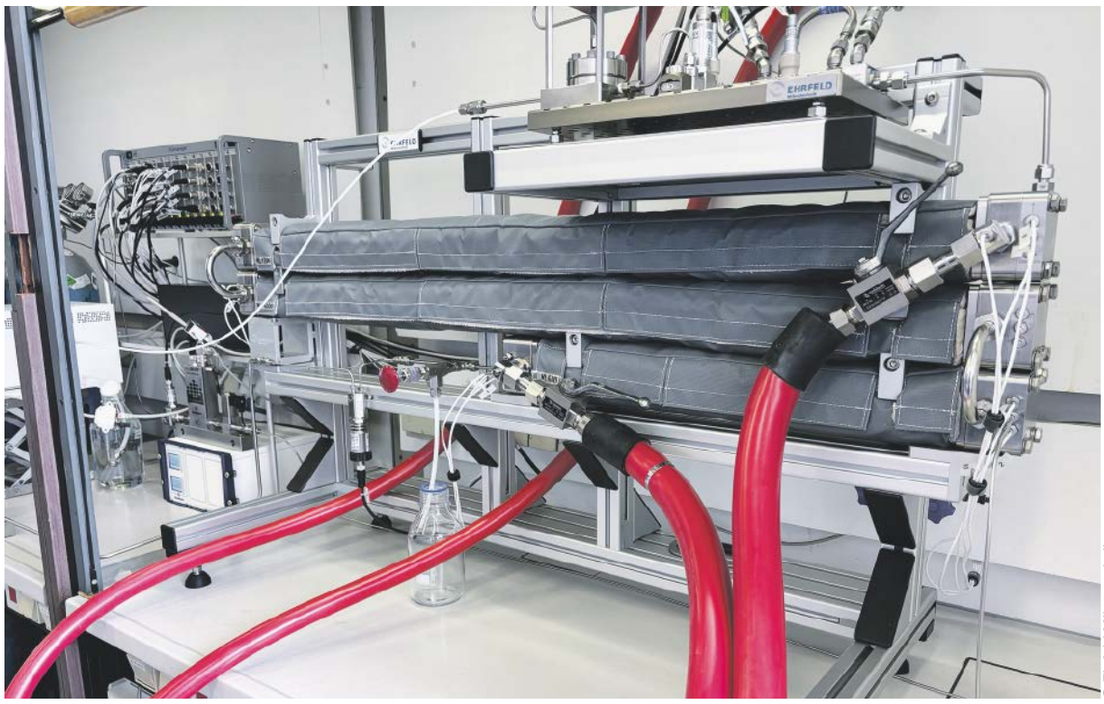

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Fig. 2: Small production scale setup (up to 100 metric tons per year) with a 300 mL reactor, dosing units, sensors and automation unit (LabManager).

Flowchemistry — Intermediates and Development on Demand

The benefits of this technology are particularly evident in the production of intermediates for CDMOs. Toxic or explosive raw materials are often used for these intermediates and the syntheses present a high safety risk. In many cases, the products themselves do not pose a safety risk, which simplifies storage. The otherwise high regulatory requirements for the manufacture of these products can be significantly reduced through the use of flow chemistry, as the reactive reaction volume is simply small and corresponds to a normal volume in the research department. In addition to the production of intermediates, this technology can also be used in research and development at CDMOs. Due to the small reaction volume and short reaction times (a few minutes), a large number of different process parameters can be tested in a very short time, allowing the reaction to be rapidly screened and quickly optimized in a resource-conserving manner. This enables the use of efficient and scalable reactor technology and minimizes the use of raw materials right from the development stage of new products. Thanks to their versatile reactor design, flow chemistry reactors can be adapted to a wide range of chemical reactions, from simple syntheses to complex multi-step processes. This flexibility allows CDMOs to tailor their processes to the specific needs of each customer.

For CDMOs, the adoption of flow chemistry can provide a competitive advantage by improving efficiency, safety and quality, while reducing costs and development times. As the pharmaceutical industry increasingly demands fast, flexible and sustainable manufacturing solutions, CDMOs that integrate flow chemistry into their offerings will be well positioned to meet these needs and drive innovation in drug development and manufacturing.

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Flow Chemistry in Drug Discovery

Exploring the Benefits and Considerations for Synthesis

Flow chemistry enables safe, precise and efficient synthesis of compounds that can be scaled from pilot projects to manufacturing. Automated flow systems can quickly synthesize a wide range of compounds, making it ideal for generating libraries for early stages of drug discovery. This article delves into the key considerations when using continuous or segmented flow chemistry approaches.

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Flow chemistry is when reactants are continuously pumped into a flow reactor with efficient mixing, and the product is collected. However, the development of automated flow systems is now allowing segmented flow regimes, using careful coordination of smaller aliquots of reactants to create smaller quantities of products. It is therefore important to carefully consider the appropriate flow regime to match your aims and experimental needs.

Flow Chemistry: Continuous Flow

Continuous flow describes chemical reactions occurring in flow reactor systems with cylindrical geometries, where reactants are continually introduced and mixed radially, effectively functioning as a series of 'plugs' —or slugs—flowing through the system. Figure 1 highlights this phenomenon, where each coherent plug has a given length (dx) and volume (dV), traveling in the longitudinal direction of the reactor. The 'ideal' plug flow model assumes a steady state, no mixing between plugs, a constant density, and that only one reaction occurs.

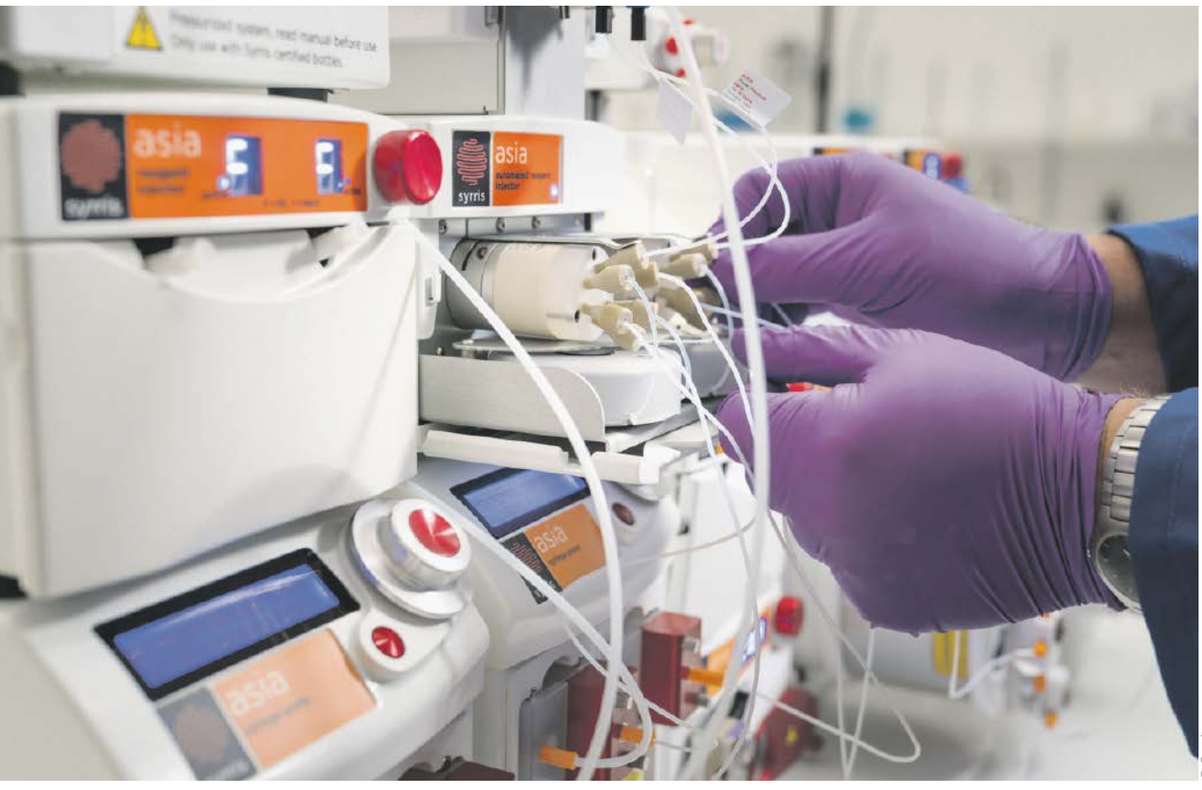
Flow Chemistry: Segmented Flow

Segmented flow is characterized by individual slugs of liquids or gases separated by a carrier fluid (fig. 2). Each discrete slug (Δx) has a defined volumes (ΔV) and the carrier fluid—which can be either liquid or gas—is usually the same solvent used for the reaction to reduce solubility issues. This approach creates discrete 'segments' that allow screening of reaction conditions or the generation compound libraries.

Optimizing Reactions

Traditional batch methods for optimizing reaction conditions can be time consuming and expensive. Modern flow chemistry systems with reagent injection modules—such as the modular Asia Flow Chemistry System [Syrris] controlled by advanced Asia Manager Software [Syrris]—provide a fully automated, walk-away alternative, allowing both continuous and segmented flow applications to save time and resources.

Compared to batch processes, continuous flow regimes enable faster, easier exploration of reaction parameters like time, temperature and reaction stoichiometry. However, continuous flow still requires the system to return to a steady state between experiments—as well as additional thorough cleaning to avoid cross contamination—demanding time and materials. Segmented flow, on the other hand, allows multiple reactions to be conducted sequentially using a single flow reactor setup, as the carrier solvent serves as a wash fluid to clean the reactor between experiments. The combination of reagent injection modules and advanced software makes it possible to efficiently explore both continuous reaction parameters and discontinuous variables, such as reagents and catalysts.



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Library Generation

Automated flow chemistry systems can be integrated with process analytical technologies and computational chemistry to synthesize chemical libraries with minimum human intervention. Segmented flow regimes particularly excel in compound synthesis and library generation, and systems equipped with a reagent injection module and liquid handling capabilities can help to quickly evaluate various reactants for compound synthesis. These injectors can introduce reactant segments more quickly than the typical reaction—or residence—time, allowing multiple reaction segments to prog-

"Automated flow systems can quickly synthesize a wide range of compounds."

ress through the system concurrently. This reduces the synthesis time for the desired compounds and enhances overall process efficiency. Segment volumes can also be adjusted to enhance processes, offering maximum efficiency for a range of applications, including the generation of analytical data for reaction optimization and production of screening libraries.

Automation and Software

Automated segmented flow is more efficient and accurate than traditional manual methods. For example, introducing the correct volume aliquot with a manual reagent injector is highly dependent on flow rates, so requires calculating the exact time to switch the injection loop in and out of line. This is often done using a stopwatch and injecting manually, leading to potential errors and inefficiency. Automated reagent injectors help to ensure that this process is consistent and reproducible, as well as accelerating the time to results.

In addition, it is important to track each segment to verify convergence at the correct junctions. When multiple reactants are introduced into a flow system, the segments must converge at the mixing junction for the reaction to occur, as shown in fig. 3. Advanced automation—such as Asia Manager—can accurately track segments to ensure proper convergence at the appropriate location. The injection of known solutions of compounds or dyes—followed by quantitative analysis after automated sample collection—can be used to assess convergence within a flow system.

Minimizing Dispersion and Diffusion

It is crucial to minimize dispersion and diffusion within the system when conducting a flow chemistry experiment. Dispersion is minimal relative to the size of the slug in continuous flow reactions, so its impact is generally minor. In contrast, some dispersion—primarily in the longitudinal direction—can occur in segmented flow regimes using a miscible carrier solvent. In many cases, the reaction and carrier slugs mix, leading to the blurred regions at the front and back of the reaction slug. This creates a solute concentration gradient, which can impact reaction rates and residence times for concentration-dependent reactions. To eliminate this issue, an immiscible carrier solvent that prevents dispersion can be used, such as fluorinated solvents that have proven effective under organic reactions conditions.

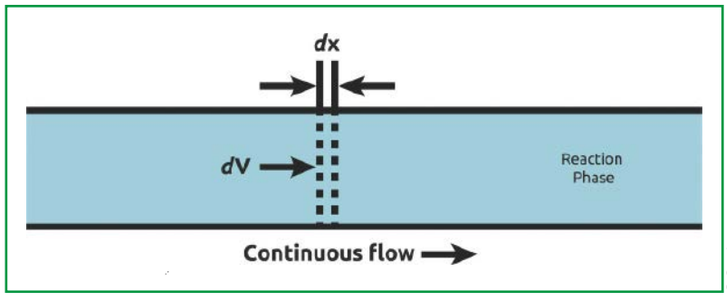

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Fig. 1: Plug flow reactor model for a continuous flow regime.

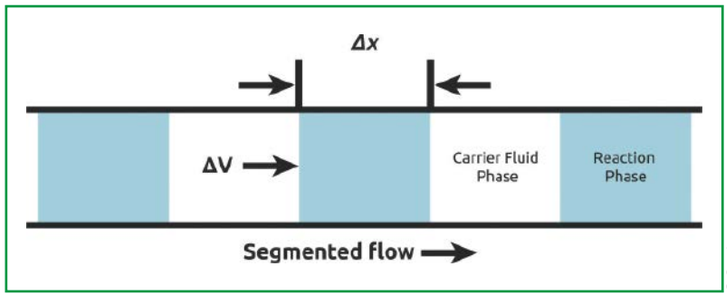

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Fig. 2: Segmented flow reactor model for a continuous flow regime.

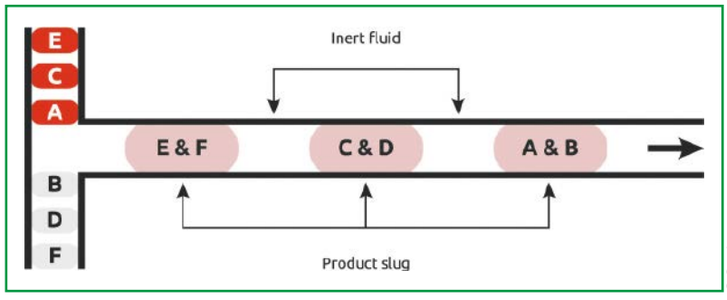

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Fig. 3: Use of segmented flow to generate a library of compounds.

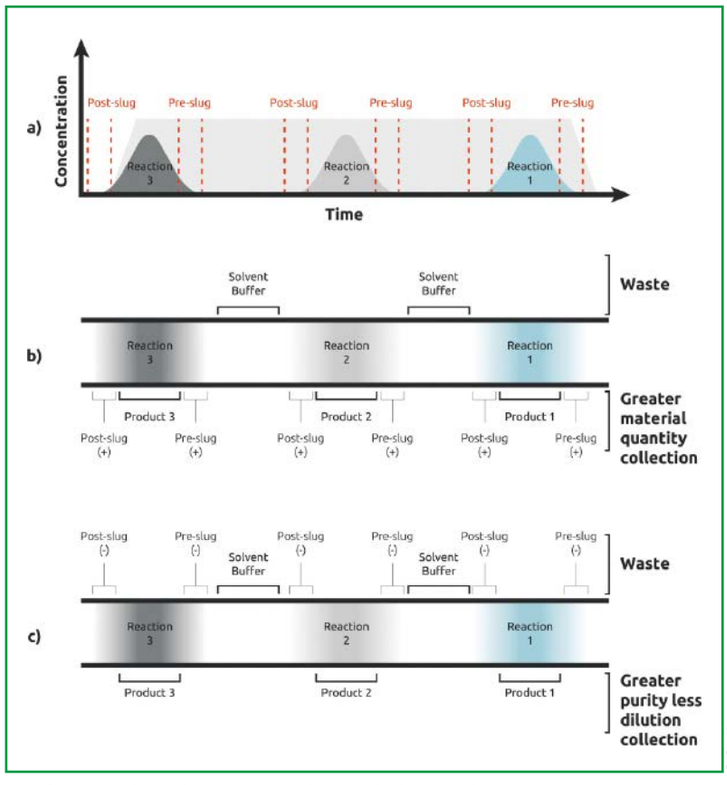

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Fig. 4: Application of pre- and post-slugs to the reaction collection.

Dispersion is more likely to occur when using a miscible carrier in combination with small segment volumes and longer residence times. Small samples undergoing significant dispersion will fail to achieve steady state conditions, so a smaller volume flow reactor should be used for these sample types. Increasing segment volume can help to minimize dispersion, as larger segments improve convergence, and typically achieve a steady state condition that provides the desired reaction concentration. Various pre- and post-slug values can also be employed to capture the steady state sample. When these values are zero, the total input volume is collected. Alternatively, additional volume can be added to either the front or the rear of the slug—to increase recovery—or subtracted to achieve greater purity and/or less dilution.

"Compared to batch processes, continuous flow regimes enable faster, easier exploration of reaction parameters."

Conclusion

It is important to select the most appropriate flow chemistry regime and equipment based on the goals of the application. For segmented flow, automated flow systems and sophisticated software are necessary for accurate segment tracking and effective convergence, helping to ensure optimal results. By carefully selecting these tools, researchers can significantly improve the effectiveness and efficiency of their flow chemistry processes.

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References for this article can be requested from the authors.

Pharma's Digital Transformation

Lessons Learned from ISPE's Pharma 4.0 Baseline Guide

Pharma 4.0 is the term coined by the International Society for Pharmaceutical Engineering (ISPE) that describes the Industry 4.0 shift towards advanced technology. It includes artificial intelligence (AI) and machine learning (ML), cloud computing, and the Internet of Things (IoT). At the peak of Pharma 4.0, ISPE envisions organizations using the full power of digital technology to provide safe, fast, and effective solutions for the problems we are facing today. In December last year, ISPE published its Pharma 4.0 Baseline Guide which addresses the evolving Pharma 4.0 landscape and the integration of new technologies. In this interview, Michelangelo Canzoneri, Josef Trapl, Wolfgang Winter, Christian Woelbeling, and Thomas Zimmer — all members of ISPE's Pharma 4.0 guide core team — explain the transformational challenges and critical success factors of the digital Pharma 4.0 journey.

CHEManager: Can you briefly summarize what Pharma 4.0 is all about?

Thomas Zimmer: Digitalization opens up the possibility of processing extremely large volumes of data in the shortest possible time. This presents users with major challenges in terms of preparedness for digitalized applications. That is why Pharma 4.0 is NOT an IT project, but an 'industrial approach' that encompasses all areas of a company or user. The magic word is 'holistic view' of all elements and enablers, as shown in the so-called 'Operating Model Pharma 4.0'. This concerns resources, organization and processes, information technology and — very importantly — corporate culture. Enablers are digital maturity and data integrity by design.

Originating historically from Industry 4.0 approaches, Pharma 4.0 aims to transfer the principles of Industry 4.0 to the pharmaceutical industry, in particular to the codes and terms typical of the industry and the strict regulation of processes, products and technical standards that are unique to this industry.

Pharma 4.0 therefore describes the prerequisites for a successful digital transformation, regardless of size and area of application.

Christian Wölbeling: Pharma 4.0 addresses holistically all stakeholders in the pharma industry and this includes also the regulatory bodies like EMA and FDA based on the international guidelines of International Council of Harmonization (ICH). The Pharmaceutical Quality System Guideline ICH Q10 is building the basis for the link to the Industry 4.0 basic elements.


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> *"Pharma 4.0 takes a systematic, holistic approach to digital transformation across the pharmaceutical supply chain."*
>
> Michelangelo Canzoneri, Merck Germany

So, what key needs guide companies on the way to Pharma 4.0?

Wolfgang Winter: Many organizations are realizing that they struggle to unlock the potential of their data assets and that their approaches for solving problems across the business are not scaling — they find that the different silos are disjointed. This creates unexpected failures and bottlenecks in drug and process development, scale-up, manufacturing and the supply chain. Companies are desperate to drastically increase their operational excellence. The holistic control strategy approach of Pharma 4.0 addresses this.

Michelangelo Canzoneri: The journey towards Pharma 4.0 is driven by several pressing business needs and challenges that pharma companies face in today's rapidly evolving landscape. These forces are encouraging companies to embrace digital technologies and enhance their operations to stay competitive, efficient, and compliant. Below are key business needs and challenges guiding pharma companies toward Pharma 4.0 adoption:

- *Operational efficiency, cost reduction and business resilience*, including automation and digitalization as well as streamlined processes
- *Faster time-to-market* through digital tools and data analytics
- *Quality and compliance* is enhanced through real-time monitoring and secure data management
- *Patient-centricity and personalized medicine*, that is, digital tools help to refine and expand personalized treatment options
- *Sustainability and environmental responsibility* are supported through greener manufacturing and the adjustment to regulatory standards.

The challenges are:

- *Legacy systems and infrastructure*, which includes outdated technology and high cost of upgrading
- *Regulatory complexity* through stringent and evolving regulations as well as validation of digital processes
- *Data management and utilization,* like data silos and data security
- *Workforce development and change management*, that is, lack of digital expertise and cultural resistance
- *Supply chain complexity*, including globalization and complexity of supply chains as well as risk management
- *Collaborative ecosystem* is more important than ever

By addressing these business needs and overcoming these challenges, pharma companies are positioning themselves for success in the Pharma 4.0 era. This transformation will enhance operational efficiency, uphold high standards of compliance, and drive innovation in a highly competitive and regulated market, ultimately benefiting patients and society as a whole.

What are the benefits that Pharma 4.0 can offer the pharmaceutical industry?

Josef Trapl: Pharma 4.0 is revolutionizing the pharmaceutical industry by integrating advanced technologies such as the Internet of Things (IoT), Module Type Package (MTP), Asset Administration Shell (AAS)/digital twins, artificial intelligence (AI), and blockchain into drug development, technology transfer, manufacturing and supply chains.

First, it enhances efficiency and productivity by enabling real-time monitoring and automation of processes, reducing human error, and optimizing resource utilization. MTP technology allows for modular and flexible production, enabling rapid adaptation to changing demands and reducing downtime. The use of digital twins, virtual replicas of physical systems, allows for predictive maintenance, process optimization, and simulation of production scenarios, leading to more informed decision-making. AAS further standardizes and integrates digital data, ensuring seamless communication and interoperability across systems.


© Memo3

> *"A science- and knowledge-driven holistic control strategy drives true quality at all levels."*
>
> Josef Trapl, Memo3

A science- and knowledge-driven holistic control strategy drives true quality at all levels, leading to improvements in diagnostic and therapy efficacy, process efficiency, and drug availability. As companies progress from a pre-digital state to predictive plants — where complex interactions are anticipated based on real-time analytics — they are moving toward the adaptive plants of the future. These adaptive plants operate in a self-optimizing, autonomous manner, embodying the essence of Pharma 4.0. Additionally, Pharma 4.0 significantly improves product quality and safety, with advanced data analytics allowing for more precise control over manufacturing conditions and better prediction of potential issues. The data-driven approach ensures that decisions are backed by robust evidence, leading to more consistent outcomes and streamlined operations. The integration of track-and-trace systems boosts supply chain transparency and security, effectively combating counterfeiting and ensuring that only genuine products reach the market.

Furthermore, Pharma 4.0 fosters a patient-centric and data driven model, tailoring treatments and therapies to individual needs through personalized medicine, ultimately improving patient outcomes. Finally, it facilitates regulatory compliance by ensuring that all processes are fully documented and traceable, simplifying audits and accelerating the approval process for new drugs. In summary, Pharma 4.0 represents a comprehensive transformation that drives innovation, reduces costs, and enhances patient safety across the pharmaceutical industry.

M. Canzoneri: A successful roadmap for the digital transformation of a pharmaceutical company on the journey to Pharma 4.0 typically involves several key stages, each building on the previous one.

This roadmap is designed to directly address the business needs and challenges outlined earlier, ensuring that technology adoption aligns with strategic goals, organizational culture, and regulatory requirements.

- *Assessment and vision setting (phase 1)*: business objectives alignment, current state assessment, and define future state vision
- *Strategy development (phase 2)*: comprehensive digital transformation strategy, technology selection and investment planning, and regulatory and compliance planning
- *Pilot programs and early wins (phase 3)*: select pilot projects, deploy pilot solutions, and measure and communicate success
- *Scaling and integration (phase 4)*: expand successful pilots, end-to-end integration, and workforce transformation
- *Continuous improvement and innovation (phase 5)*: performance monitoring and optimization, sustainability and patient-centric innovations, and stay aligned with regulatory changes
- *Future-ready adaptability (phase 6)*: agility in response to market changes and innovation ecosystem
- *Governance and risk management (phase 7)*: governance framework and risk management

This roadmap provides a structured approach that balances technology adoption with organizational change, ensuring that digital transformation efforts align with business objectives, regulatory requirements, and long-term sustainability goals.

Implementing digital technologies and initiating successful digitalization projects is a challenging process — especially in the pharmaceutical sector. What do you see as the biggest challenge(s)?

W. Winter: Since the first CHEManager interview on this topic, we witnessed an impressive number of Pharma 4.0 digital transformation projects across the industry. These initiatives began with informal grass-roots activities such as presentations, workshops, hackathons, plug-fests, proof-of-concept projects. Research institutes and universities have been instrumental in pushing the scientific and technical boundaries, exploring areas like process analytical control, mechanistic modeling, robotics, machine learning and more. In the meantime, the regulatory agencies explicitly encourage the industry to rethink traditional approaches to discovery, development pilot scale, and manufacturing. This led to pilot or lighthouse implementations at new manufacturing sites. Some of these projects have even been recognized in prestigious awards like ISPE's FOYA — Facility of the Year — awards.

However, implementing digital technologies and initiating successful digitalization projects in the pharmaceutical sector remains a challenging process. Despite the progress, getting buy-in at the C-level and overcoming compliance-related concerns are still the biggest roadblocks. Businesses driven by shareholder value often prioritize short-term wins over long-term investments, making it difficult to sustain momentum in digital transformation initiatives. Digital transformation is not a sprint; it is an ultra-marathon, requiring patience, persistence, and a long-term vision.


© Agilent

> *"The encouraging news for Pharma 4.0: there are already approved continuous manufacturing sites in many regions of the globe!"*
>
> Wolfgang Winter, Agilent Technologies

J. Trapl: Navigating the stringent regulatory environment is another major challenge. Pharmaceuticals are highly regulated, and ensuring that new digital tools comply with rigorous standards set by agencies like the FDA or EMA, while still fostering innovation, is a delicate balance. Additionally, data integration and interoperability pose significant difficulties. The industry relies on vast amounts of data from diverse sources, and integrating this data into cohesive digital systems that allow for real-time analysis and decision-making is complex, particularly when dealing with legacy systems.

Change management and cultural resistance within organizations add another layer of difficulty. The pharmaceutical industry has traditionally been conservative, with a strong emphasis on proven processes and risk aversion. Introducing digital technologies requires a shift in mindset, and achieving this cultural shift can be challenging, especially when there is a lack of digital literacy or fear of job displacement due to automation.

Cybersecurity concerns also loom large as digitalization progresses. Protecting sensitive data, including intellectual property and patient information, from cyber threats is crucial, and implementing robust cybersecurity measures while ensuring seamless digital transformation adds to the complexity.

What could a roadmap for the digital transformation of a company look like?

T. Zimmer: There are several ways to approach digital transformation: pilot projects, so-called 'light house projects' or more systematic approaches that cover one or more functional areas or even a cross-functional business process, like product transfer, production/quality or upstream and downstream supply chain. The preparations are im-

portant: a clear business objective, a clear idea of the benefits to be achieved, a clear idea of the operational capabilities for data, processes, capable project staff, sustained support from the client and budget owner combined with regular checks on progress including bug-tracking and all performance indicators. There are numerous ISPE guidances, the individual elements of good engineering practice, good project management, advanced pharmaceutical quality, to name but a few, which can be used as support here.

W. Winter: Let me add that a pre-requisite to successful digital transformation is a certain professionalism and maturity in terms of skills, processes and quality system in a company. I do not remember the exact source of the quote, but if you digitalize a bad process, you just have a digitalized bad process that does not advance your digital maturity and operational excellence at all.

How will the new Baseline Guide Pharma 4.0 developed by ISPE support pharmaceutical companies in their digital transformation?

C. Woelbeling: The new Baseline Guide is building a comprehensive repository for approaching the digital business transformational journey for an organization and all of its involved stakeholders. It will be the basis also for new training programs to prepare organizations for the transformation.

W. Winter: This new guide is a helpful compendium for decision makers, stakeholders and professionals on how to approach digital transformation in pharma, understand the 'why' and how to approach technology & automation requirements in light of evolving regulatory compliance. The Baseline Guide contains a large reference list of current industry use cases and implementations that already went live. The baseline guide is intended to connect the silos by building common understanding between development, manufacturing, engineering & IT, regulators, suppliers and patients.

Can Pharma 4.0 offer new business opportunities for established products?

W. Winter: Based on the Pharma 4.0 use cases evaluated for the first edition of the baseline guide, we see that existing brown-field plants selectively implementing Pharma 4.0 upgrades increase their asset utilization, decrease maintenance cost, optimize inventory and often reduce quality deviations, all leading to incremental productivity overall. These focused projects typically show the general feasibility of the approach, and create appetite for drastically higher outcomes and benefits.

M. Canzoneri: Yes, Pharma 4.0 can offer significant new business opportunities for established products by leveraging digital technologies and advanced data analytics to enhance product value, improve efficiency, and create new revenue streams.

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"Pharma 4.0 addresses holistically all stakeholders in the pharma industry and this includes also the regulatory bodies like EMA and FDA."

Christian Woelbeling, Körber Pharma Software

Below some examples on how Pharma 4.0 can unlock new opportunities for established pharmaceutical products:

- *Product lifecycle extension*: improving manufacturing efficiency and enhanced quality and compliance
- *Personalized and targeted therapies*: Patient-specific variants and targeted drug delivery systems
- *Data-driven innovation and real-world evidence*: post-market surveillance and real-world data as well as predictive maintenance and supply chain optimization
- *Patient engagement and digital health solutions*: connected devices and adherence solutions as well as patient support programs

© ISPE

"Pharma 4.0 is NOT an IT project, but an 'industrial approach' that encompasses all areas of a company or user."

Thomas Zimmer, ISPE

- *Expanded market access and new revenue models*: geographic expansion and pay-for-performance models
- *Sustainability and corporate responsibility*: eco-friendly manufacturing and circular economy initiatives
- *Innovation in distribution and supply chain*: cold chain and advanced logistics as well as blockchain for traceability
- *Regulatory and market differentiation*: regulatory innovation and competitive advantage
- *Digital twins and simulation for product improvement*: product optimization and innovative Formulation Development
- *Collaboration with healthcare providers*

Pharma 4.0 offers pharmaceutical companies a wealth of opportunities to innovate and extend the business potential of established products. By leveraging digital technologies, companies can improve manufacturing efficiency, enhance product quality, personalize treatments, and create new value-added services. These innovations can not only reinvigorate existing product lines but also open up new revenue streams, improve patient outcomes, and strengthen the company's position in a competitive and evolving market.

Will Pharma 4.0 become a new industrial revolution?

W. Winter: When you are amidst big changes, you don't realize a revolution is happening around you. I would ask this question in a different way… Industry 4.0 is an industrial revolution that changed so many things already: Ubiquitous broadband, computing power, data and knowledge changed customer experience, the way we purchase and consume, how we navigate, our preferences, how we interact with our families, colleagues, customers or competitors. To me, the question is: Which corners of the healthcare industry think they can avoid the digital transformation (revolution), why and how long?

C. Woelbeling: The revolution started already with the launch of the "FDA PAT —A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" guideline in 2004. This paradigm shift for process understanding, quality by design and process control is now enabled by the 4.0 technologies. In the early years the analytical and mechanistical process & control models were too expensive to implement and only some business cases showed up. Change management is still the key issue—both in terms of the human element and from the perspective of traditional validation concepts. The ISPE Pharma 4.0 Community of Practice (CoP) is exactly tackling these obstacles to overcome them.

How long do you think it will take for digitalization to reach the entire pharmaceutical production process? Which hurdles and where in the pharmaceutical value chain still need to be overcome on that journey?

W. Winter: I clearly see that, for the time being, we will live in a hybrid world. Different models will operate concurrently. Manufacturing sites designed, planned, built, validated and put into operation 10 or 15 years ago will continue for years on the basis of that design space. They will make only very focused, gradual investments and upgrades. New modular sites designed in the last three to five years, and which are going into operation now, often embrace Pharma 4.0 concepts at many levels and will continue down that path for the next 15, 20 years. It is not a question of either Pharma 4.0 OR 'traditional' Pharma 3.0, we will continue seeing 3.0 AND 4.0 concepts in parallel.

C. Woelbeling: The Pharma 4.0 Operating Model is designed to include continuous improvements, developments and managed changes in the interest of efficiency, cost reduction and at the end to prevent drug shortages and to ensure constant product quality by Digitalization.

The complete interview including references is available at https://bit.ly/ISPE-Pharma40

■ www.ispe.org

CHEManager INTERNATIONAL

INNOVATION PITCH

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Continuous Synthesis
End-to-End Platforms for Flow Manufacturing On-Demand

Bioinformatics
Search Engine for Protein Discovery in Biocatalysis and Pharma

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The Subscription Revolution in Flow Chemistry

End-to-End Platforms for Flow Manufacturing On-Demand by Subscription

Flownetics Engineering designs, develops, manufactures, and operates end-to-end platforms for continuous synthesis on behalf of customers. The on-demand offering covers the complete cycle from inquiry to product and includes proof-of-concept as well as process development and machine learning (ML)-supported production system. Michael Reubold and Ralf Kempf spoke with founder and CEO Sridhar Balaram. In this interview he describes his mission and motivation.

CHEManager: Mr. Balaram, you are the head of a manufacturer of machines and software for additive manufacturing. With Flownetics as a "game changer", you now want to help flow chemistry to flourish globally. How does that fit together?

Sridhar Balaram: Technically, the answer is simple. The micro-reactors for our flow manufacturing platforms are additively manufactured and a key element of the end-to-end promise to our customers. The longer story: I first came into contact with flow chemistry more than a decade ago at a trade fair. You didn't have to be a chemist to recognize the fascinating possibilities. I never lost sight of the topic and kept asking myself why the process had not achieved an industrial breakthrough. This question eventually led to the idea of founding a specialized start-up in order to revolutionize the industry as a "game changer" and virtually on a subscription basis.

Revolution is a huge word …

S. Balaram: And we use it very confidently! Not to provoke as a newcomer, but as a problem solver on behalf of customers to produce relevant raw materials, active ingredients and their intermediates — either as a factory-as-a-service at the customer's site or as a contract manufacturer in a performance-as-a-service model. We know what we can do! Our end-to-end platforms deliver what users expect from us. And customers only pay for what they get from us. The risk of moving into flow chemistry, which has been repeatedly used for years as an argument against moving away from traditional batch chemistry, is therefore completely lost.

So you are predicting the beginning of the end of batch chemistry?

S. Balaram: No. The batch process has its merits in the past and certainly has a future. But the process is also well known for its limitations and restrictions. This, in turn, makes flow manufacturing the better solution from a technical, economic and ecological point of view in countless areas of application. Industry experts speak of up to 40 percent of applications to which this could apply. I think it will be closer to 50 percent. The future will provide the answer.

> *"Customers only pay for what they get. The risk of moving into flow chemistry, which has been used for years as an argument against moving away from traditional batch chemistry, is therefore completely lost."*

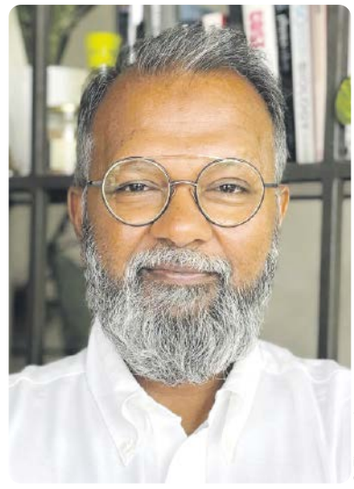
You presented the end-to-end range for the first time at this year's ACHEMA. How was the response from the market?

S. Balaram: As a start-up, we can be very satisfied with how the trade fair went. As expected, the pharmaceutical industry was strongly represented. However, we were pleasantly surprised by the many inquiries from the cosmetics sector. Something else we had not expected in this form: The fundamental aspects and advantages of the flow process were less the subject of discussion in the trade fair talks than very specific questions about our subscription models.

What do you conclude from that?

S. Balaram: On the one hand: A lack of knowledge about the advantages of flow manufacturing does not appear to be the reason for the still low market presence of the process. Secondly: Subscription models still need to be explained to customers despite, or perhaps because of, their simplicity.

> *"Limitations and restrictions of batch processes make flow manufacturing the better solution from a technical, economic and ecological point of view in countless areas of application."*



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Sridhar Balaram, Founder and CEO of Flownetics Engineering

Personal Profile

Sridhar Balaram has more than 30 years of experience in leading positions in the field of metal processing. He describes himself as a foundryman with roots in core manufacturing processes in various industries and services. He has founded and built several companies. Among others, he founded the company Intech Additive Solutions in 2012, which is today a leading manufacturer of machines and software for metal 3D printing. In April 2023, he founded Flownetics Engineering with the mission to revolutionize manufacturing in the chemical industry.

What was the most frequently asked question?

S. Balaram: Why we as a start-up are able to assume the financial and operational risk for the systems.

And what did you answer?

S. Balaram: That such an offering is only possible if a company combines all areas of excellence, in particular systems engineering, mechanical engineering, process engineering, process development, additive manufacturing, control technology and artificial intelligence or machine learning, under one roof. Otherwise, the friction losses between the individual competencies would be far too high and the coordination processes across company boundaries far too time-consuming.

> *"By combining expertise in mechanical engineering, process chemistry, 3D printing, control engineering and AI, Flownetics unlocks a unique multidisciplinary approach for its customers that optimizes every aspect of their production."*

Business Idea

Transformation in Flow

The chemical industry is still dominated by batch processing, even though the process is associated with inefficiency, high costs and considerable waste. In addition, batch processes are labor-intensive, prone to quality fluctuations and have limited scalability. The multitude of limitations are increasingly calling for more sustainable, efficient and resilient manufacturing methods.

In contrast, flow manufacturing is a revolutionary alternative as it enables continuous production that minimizes waste, improves quality control and reduces operating costs. In contrast to batch production, flow manufacturing also enables real-time monitoring and adjustment, resulting in consistent product quality and a significant reduction in production time and costs.

This is where Flownetics' mission begins. By integrating mechanical engineering, process chemistry, AI and advanced control technologies, the company offers scalable and efficient solutions that democratize access to cutting-edge manufacturing technologies. Flownetics also addresses the arguments of high initial investment, technological complexity and the need for specialists. To this end, the end-to-end solutions are offered as Factory-as-a-Service (FaaS) and Performance-as-a-Service (PaaS) models.

Factory-as-a-Service (FaaS) is a subscription model in which Flownetics installs and operates flow manufacturing solutions at the customer's site. This model enables localized production, reduces upfront costs and provides scalability. Flownetics provides continuous on-site support, including maintenance and upgrades, to ensure that production systems are state of the art. FaaS improves supply chain stability by enabling local production and reducing reliance on centralized suppliers.

Performance-as-a-Service (PaaS) is a subscription model in which Flownetics provides continuous flow manufacturing capacity. Companies outsource their production requirements to Flownetics, which manages the entire process from input material to final product based on its end-to-end platform. This model reduces capital expenditure, provides flexibility to scale production and leverages advanced technology for optimized performance and quality control.

- sales@flownetics-engg.com
- www.flownetics-engg.com

FLOWNETICS

Elevator Pitch

Milestones and Roadmap

Flownetics Engineering was founded in April 2023 after an innovative prelaunch phase. The company, based in Bengaluru (also known as Bangalore), the capital and largest city of the southern Indian state of Karnataka, is on a mission to revolutionize pharmaceutical and cosmetic chemistry by providing scalable, efficient and sustainable end-to-end flow manufacturing solutions.

By combining expertise in mechanical engineering, process chemistry, 3D printing, control engineering and artificial intelligence, Flownetics unlocks a unique multidisciplinary approach for its customers that optimizes every aspect of their production. This synergy increases process efficiency, reduces waste and ensures high-quality production that overcomes the limitations of traditional batch production.

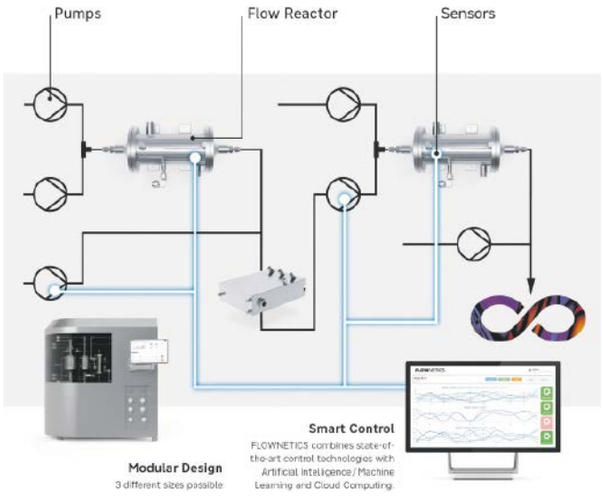
This is especially true for the business model: Flownetics' offers Factory-as-a-Service (FaaS) and Performance-as-a-Service (PaaS), two subscription models that can democratize access to advanced manufacturing technologies in the chemical industry. Most importantly, these business models lower the financial barriers and enable companies of all sizes to revolutionize the future of chemical manufacturing without large upfront investments. By promoting local production, the inherent benefits of the process and improving supply chain resilience, Flownetics lowers costs for companies and promotes environmental sustainability.

Milestones & Roadmap

2022
- Vision and research activities
- MVP presentation at Achema 2022 Frankfurt, Germany

2023
- Launch of Flownetics Engineering
- Establishment of a Flow R&D Lab in Bengaluru, India
- Integration of the Software Flow Control Suite
- Integration of the FlowScale Suite

2024
- Flownetics Operational Suite
- World premiere of the End-to-End-Platform-Subscription at Achema, Frankfurt, Germany
- Several proofs-of-concept in progress as well as scale-up/FaaS commercialization projects



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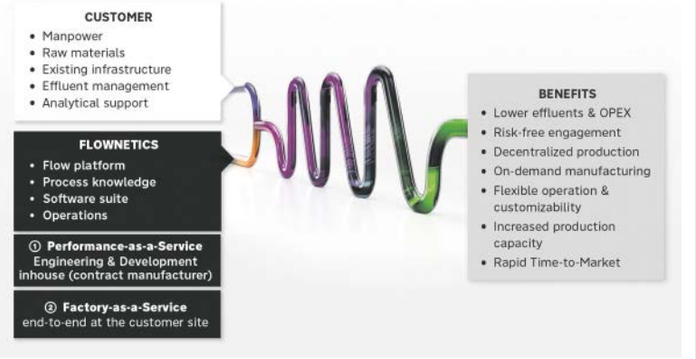
Accumulated expertise at Flownetics for mechanical and control systems engineering, process chemistry, 3D printing, and artificial intelligence opens the window for unique end-to-end platforms in the field of flow manufacturing.



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As comprehensive subscription models, Factory-as-a-Service (FaaS) and Performance-as-a-Service (PaaS) by Flownetics minimize the financial risk of high initial investments.

World's Most Comprehensive Protein Search Engine

Transforming Protein Discovery Processes for Industrial Biocatalysis and Pharma

In the rapidly evolving field of bioinformatics, the ability to access and analyze protein data is crucial for scientific advancement. While established tools have been instrumental in allowing researchers to find protein sequences, there are limitations, particularly when it comes to accessing novel data. Proteineer has developed a new search engine designed to bridge these gaps and provide a more comprehensive approach to protein discovery.


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Aron Eiermann, CTO, Proteineer


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Johannes Kabisch, CSO, Proteineer


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Joseph Heenan, CEO, Proteineer

CHEManager: What inspired you to create a new protein search engine?

Johannes Kabisch: The realization that there are huge amounts of untapped sequence data besides the most commonly used Genbank. Our vision with Proteineer became to expand the accessibility for our customers to these already existing, yet very difficult to access data. Our search engine goes beyond just sequence similarity, we also use structural similarity and search through many data sources including short read archives thus including novel proteins that have not been previously discoverable. In short, with our approach we find far more protein sequences than any other search engine.

How many proteins do you typically find in a search?

Joe Heenan: The number of proteins we identify depends on the search criteria, but it's usually over 100,000 results. While this number seems large and unmanageable for testing, it is good to have more results to filter them for preferable properties.

Once we find a protein, we predict its structure and various useful properties, such as thermostability, optimal operating temperatures, and expected expression levels in E. coli. We as well assess the structural similarity to the query protein and perform clustering. This in-depth analysis provides researchers with a comprehensive understanding of the search space and a wide variety in the selection of proteins to be tested in the laboratory.

What challenges did you face in developing and providing your services?

Aron Eiermann: One of the major challenges was scaling our processes, which require really massive computational power, to be cost-effective for a larger customer base. This was solved by collaborating with the largest computational providers like OVH, Google, Amazon and NVIDIA. Another unexpected challenge was that the customers were overwhelmed by the amount of sequence data we could provide them, which was more than is readily testable in a lab. We have tackled this by developing a software called GeneStore which allows our customers to use their expertise about their proteins to select a diverse panel they want to produce and characterize.

How does that work?

J. Kabisch: The GeneStore is our web application with which we present search results, allowing customers to explore protein properties, including structural and docking results. They can filter these results based on various properties or start new searches. It's a comprehensive tool for managing and analyzing protein data.

What are Proteineer's future plans?

A. Eiermann: We've recently built a robust docking pipeline that can also be used by biologists who are not experts in structural biology. We will integrate this into the GeneStore to allow our users to filter proteins based on their binding properties. We believe that this will enable our clients to select even better candidates for laboratory testing.

J. Heenan: We are also working on integrating language models to provide in-silico data and use our extensive training data to improve our offering.

J. Kabisch: Another exciting potential we see is the expansion of our services to support clients in obtaining freedom to operate and to help them file robust and comprehensive patent applications using the sequence space we offer.

What is your business model?

J. Heenan: We operate on a Software as a Service (SaaS) model, offering subscriptions to GeneStore. We also take on specific bioinformatics challenges on a contract basis. With our services, we support biologists by providing them with new proteins and ideas for their research and helping them to better understand their proteins.

Personal Profile

Aron Eiermann (CTO) has worked in bioinformatics (robotics and classical artificial intelligence) at TU Darmstadt for three years. He has supervised two student software development teams at TU Darmstadt, is a board member and co-founder of Freie Netze Südhessen (association for the promotion of free access to internet). Aron has experience in system integration and scaling as well as developing search algorithms for huge data sets (bigdata).

Johannes Kabisch (CSO) teaches and researches at NTNU, Norway's largest university, with so-called microbial cell factories to establish a bioeconomy. Johannes brings his knowledge of DNA sequencing and protein production to Proteineer. During his research activities in Germany (University of Greifswald and TU Darmstadt) and on an ongoing basis, he was able to build up and now contributes an extensive network to global biotechnology companies and stakeholders.

Joseph Heenan (CEO) has 15 years of experience managing and technically leading machine learning teams in a Fortune 100 company and has worked in three software start-ups with successful exits. Joe has extensive experience scaling software teams, rapid prototyping, and commercializing machine learning research and development.

Business Idea

Protein Search Engine Built by and for Biologists

Identifying new proteins can lead to breakthroughs in understanding diseases, developing new treatments, and advancing biotechnology and sustainability. This knowledge enhances drug design, personalized medicine, and the development of bioengineered products, driving innovation in health and industry.

Accelerating Protein Engineering

Proteineer's mission is to accelerate biological research via organizing and annotating the entirety of the world's publicly available genomics data. The company helps teams of biologists and bioinformaticians to discover, annotate, analyze and unify genomics data from a vast amount of different sources with unprecedented thoroughness and ease. Proteineer's APIs allow for deep integration with existing systems and processes.

Trusted by Users and Partners

GeneStore is the only offering on the market that uses spot instances and cloud compute to cost-efficiently scan and annotate the petabytes of publicly-available genome data. It provides datasets and insights to customers to help accelerate their own protein engineering and machine learning initiatives.

Through Proteineer's participation in various accelerators and research consortia it has already achieved widespread visibility.

In the competitive and rapidly evolving landscape of bioinformatics, Proteineer is in a unique niche by revolutionizing the protein discovery process.

Built by and for Biologists

Proteineer's business model is anchored in the Software as a Service (SaaS) paradigm, providing clients with subscription-based access to its GeneStore platform. This ensures that users continuously benefit from the latest advancements and updates without the need for significant upfront investment. The subscription model also fosters an ongoing relationship with clients, allowing Proteineer to offer consistent support and gather feedback for continual improvement.

- Proteineer, Dietzenbach, Germany
- www.proteineer.com

Proteineer

Elevator Pitch

Driving Biotechnological Innovations

Over the past decade, life sciences have been revolutionized by affordable DNA sequencing technologies. Since 2008, the cost of sequencing DNA has dropped dramatically, making genomic data more accessible. However, the challenge has shifted to managing and interpreting the vast amounts of raw data generated. Stored in the Sequence Read Archive (SRA), this data is a treasure trove of potential discoveries but is underutilized due to its complexity. Researchers face significant challenges in processing and analyzing this data, limiting the scope of their scientific inquiries.

Proteineer, founded in January 2022, aims to empower life science researchers to fully harness DNA sequencing data. Our Software-as-a-Service (SaaS) platform allows clients to efficiently search and analyze protein data. Resulting for most queries in more than 200,000 results. We enrich this data with modern machine learning algorithms to predict properties such as thermostability or structures.

Our primary market is the industrial biotechnology sector, responsible for producing basic and specialty chemicals, pharmaceuticals, and agricultural products, with an annual revenue exceeding €300 billion. Proteineer offers unparalleled data analysis capabilities, accelerating research and development in this robust and rapidly growing industry. Our proprietary search system allows searching for more data, giving our clients a competitive edge. This technological advantage, combined with our first-to-market status, positions Proteineer as a leader in driving biotechnological innovations and sustainable solutions across the industry.

Milestones

2022
- Q1 Founding

2022-
- Q2 First Publicly Traded Customer

2023
- Q1: Web App to display search results
- Q4: Accepted into Hessian.AI AI Startup Rising Accelerator

2024
- Q1: Start of publicly funded CO_2BioTech Project for CO_2-based bioproduction platform for cysteine, aspartate, and glycolate.
- Q3: Docking Based search

Roadmap

- 2023-Q4 In silico protein generation based on search results.

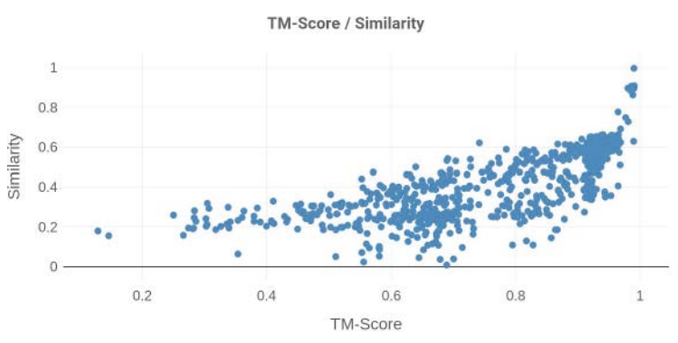

Fig. 1: The GeneStore not only searches for sequence similarity but as well for structural similarity of proteins. The plot shows how sequences with a high structure similarity, yet a low similarity on the sequence are found.

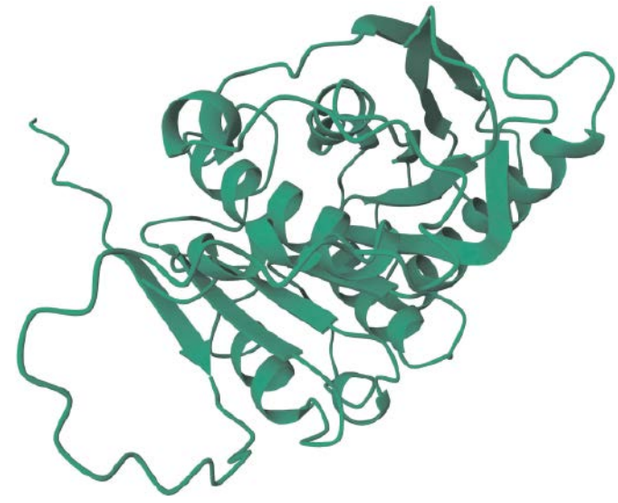

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Fig. 2: The GeneStore predicts structures for all hits, many of which cannot be found elsewhere, enabling even better cherry picking.

CPhI Milano 2024

CPhI Worldwide, taking place in Milan, Italy, on October 8–10, 2024, is dedicated to pharmaceutical developments, trends, products and services. Exhibitors include providers of contract research and synthesis services, suppliers of APIs, excipients, ingredients, intermediates and finished dosage forms, as well as producers of pharma manufacturing and packaging equipment. Additional online activities present even more possibilities to connect and do business.

■ www.cphi.com/europe

CIEX 2024

CIEX, the Chemical Innovation Conference 2024, is taking place in Indianapolis, Indiana, US, on October 23–24, 2024. Created for C-level R&D and innovation experts from the consumer, industrial and specialty chemical sectors and brings together the right people to create synergies and actively network potential partners. Attendees will hear from and discuss with industry leaders, international experts and innovative thinkers from the world of specialty chemicals.

■ www.ciex-eu.org

Food Ingredients Europe 2024

Food ingredients Europe, taking place in Frankfurt am Main, Germany, on November 19–21, 2024, has been uniting the world's leading food & beverage suppliers, buyers, R&D experts and production specialists for over 35 years. Each year, it showcases a diverse range of innovative, new ingredients & services and over its lifespan, has welcomed more than 500,000 people through its doors. The event is the market leader in helping F&B ingredient companies find the right people and solutions.

■ www.figlobal.com

Process Innovation Asia Pacific 2024

Process Innovation Asia-Pacific—Powered by Achema is a bienniale event in Singapore that will take place on November 19–21, 2024. The event provides a comprehensive platform where innovation meets challenges: harmonizing global expertise with local needs, enhancing regional ecosystems, and propelling emerging economies forward. Here, stakeholders experience innovative process technology hands-on, trade expert insights build sustainable connections within their ecosystem.

■ www.processinnovationapac.com

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