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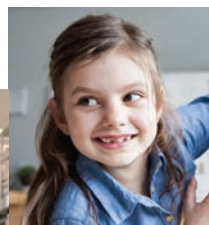
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Welcome to the Pharma Party

April is always a time of celebration for The Medicine Maker, but this year it's a bigger party than ever before

Editorial



April is a month of celebration at The Medicine Maker. Since 2015, our annual Power List has helped shine a spotlight on the pharmaceutical leaders helping to drive positive change in the industry. It's certainly a wonderful way to pay tribute to the industry's best and brightest, but we've decided that the celebration needs to be even bigger...

We recognize that, although good leaders make a huge difference in medicine making success, businesses are made up of more than the people at the helm. From lab scientists to project managers, a company is only as good as its workers. And the drug development and manufacturing wheel is only able to turn when these people have access to the right technologies, partners, and suppliers.

And so, alongside The Power List, we are delighted to present The Medicine Maker Company of the Year Awards (page 20). We asked you to vote for the top companies across six categories: Best Big Pharma, Best Biopharma Equipment Company, Best CDMO, Best API Supplier, Best Processing Equipment Company, and Biggest "Talking Point."

But the excitement doesn't stop there as we're also announcing the grand winner of our annual Innovation Awards on page 28. You'll also notice that our Power List has a new look. The updated format compiles a list of the Top 30 medicine makers across three key areas: Small Molecules (page 13), Biopharmaceuticals (page 16), and Advanced Medicine (page 18). The winners hail from every corner of the industry – biotechs to big pharma, manufacturing to philanthropy – and you'll find that our winners are playing diverse and meaningful roles in creating the medicines of tomorrow.

Once you've explored the issue, let us know what you think. Share your thoughts and messages on Twitter and LinkedIn tagging @medicine_maker. You can also share your feedback on the new, improved awards with us at maryam.mahdi@texerepublishing.com.

Maryam Mahdi
Deputy Editor



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Welcome to the Pharma Party
By Maryam Mahdi

On The Cover



Welcome to our pharma festival which includes our 2022 Power List and inaugural Company of the Year Awards!

Upfront

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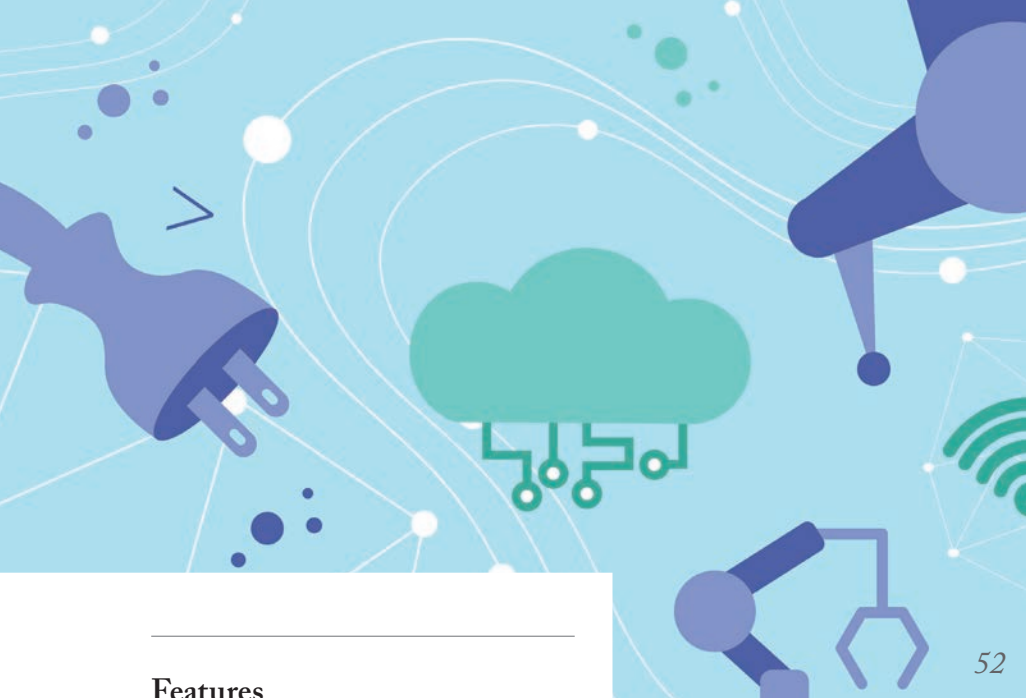


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We celebrate all areas of the pharma industry. Our famous Power List honors 30 inspiring individuals making a difference in drug development and manufacturing. The Company of the Year Awards looks at the best companies in the sector, as voted by readers. Plus, we reveal the grand winner of the 2021 Innovation Awards. It's a festival of celebration!

Best Practice

- 50 **Top Tips for mRNA Sequencing**
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mRNA is firmly in the spotlight, but what does this mean for cell and gene therapies? We ask three "champions" for their thoughts
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We speak with a medchem company and their Ukrainian partner about drug discovery disruption, and find out how a new industry agreement is creating anti-COVID-19 equity

Sitting Down With

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the Medicine Maker

ISSUE 84 - MARCH / APRIL 2022

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Distribution: The Medicine Maker (ISSN 2055-8201),
is published bi-monthly by Texere Publishing Limited, Booths
Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS,
UK. Single copy sales £15 (plus postage, cost available on
request info@themedicinemaker.com). Non-qualified annual
subscription cost is £110 plus postage

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Ukraine: Pharma's Response

Aid Ukraine or disengage from Russia? There is no consensus

Three days after the Russian military began its invasion of Ukraine, a statement from Business Leaders for Ukraine saw numerous life science CEOs call for total economic disengagement from Russia (1), until “the restoration of peace and democracy in a sovereign Ukraine.” The letter has since garnered hundreds of signatories (2).

In March, the European Federation of Pharmaceutical Industries and Associations (EFPIA) spoke up (3). Its statement expressed “solidarity with the people of Ukraine” and condemned the invasion, but did not advocate cutting ties with Russia, instead insisting on the need to “ensure that medicines reach the patients that need them in Ukraine, in the neighboring EU Member States, in Russia, and in other countries where access to medicines may be negatively impacted.” Almost every big pharma brand name – plus numerous major

middleweights – are attached to this letter. The companies’ individual statements feature expressions of emotional concern, general condemnation of “the violence,” and details of donations to Ukraine rather than any direct references to Putin or the Russian government.

But some companies have since indicated that they will reconsider how they do business in Russia. Pfizer, for example, has revised its policy to opt for “a middle way” in which it will continue operations in Russia, but hold off all domestic investments and clinical trials, and divert all profits made in Russia to aid for Ukraine (4).

In early March, Andrey Tolmachov, CEO of Kyiv drug discovery company Enamine, noted the failure of Western powers to confront Russia all the way from the 2014 annexation of Crimea to the buildup of forces on Ukraine’s borders in early 2022 (5). Mincing no words, he wrote: “...we address the whole drug discovery, biotech, and scientific community which should sound like

one voice now. If any of you have any means, any contacts and connections to influence the decision to close the Ukrainian sky it is time to use them, to convince your government, to convince NATO to finally interfere.”

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3. EFPIA, “Pharmaceutical industry response to the war in Ukraine”, *EFPIA* (2022). Available at: <https://bit.ly/efpia-ukr>
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5. A Tolmachov, “The official appeal of Enamine founder and CEO Andrey Tolmachov to the drug discovery and scientific community”, *Enamine* (2022). Available at: <https://bit.ly/andrey-t>

Show Me the Salary!

Pharma companies hit the top and bottom of a study on race and gender pay gaps in the US

The results published in the fifth annual edition of the Race and Gender Scorecard (1) gave Pfizer reason to celebrate. The big pharma company didn’t just score

the only “A Grade” among competitors in the report’s healthcare category; it came out on top of the entire pack of 57 participating American corporations. The report – authored by Natasha Lamb of Arjuna Capital and Michael Passoff of Proxy Impact – notes that women at Pfizer, on average, earn (a tiny percentage) more than men, and that Pfizer increased its score from last year’s winning figure of 93 up to 96.57.

The other six competitors in the healthcare category did not fare so well.

Healthcare insurer Cigna scored a C, and the rest – including Massachusetts’ Biogen – flunked with an F.

Reference

1. N Lamb et al., “Racial and Gender Pay Scorecard – Fifth Edition”, *Arjuna Capital/Proxy Impact* (2022). Available at: <https://bit.ly/IDpay>





IMAGE OF THE MONTH

*Fighting COVID-19 in the Himalayas*

Nepalese doctor Prasanna Karki heads up-mountain in a five-day horseback journey to a remote Himalayan village where a young woman reported a reaction after being vaccinated for COVID-19.

Credit: Pragya Timsina, Gavi (2022) <<https://bit.ly/bmly-horse>>

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Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"A voluntary pause in the flow of our medicines to Russia would be in direct violation of our foundational principle of putting patients first.

Ending delivery of medicines, including cancer or cardiovascular therapies, would cause significant patient suffering and potential loss of life, particularly among children and elderly people."

Pfizer, in an update on the company's position in Russia. The pharma giant will be funneling all profits from its Russian subsidiary into humanitarian support for Ukraine.
<<https://bit.ly/pfi-rus>>

Listen Now: The Medicine Maker x DNDi Podcast

The six episode miniseries "DNDi: Medicine Makers Without Borders" will take listeners behind the scenes of a range of projects at the Drugs for Neglected Diseases initiative

Here at The Medicine Maker, we admire the Drugs for Neglected Diseases initiative and the work they do. That's why we are extremely excited to announce that we have put together a podcast miniseries on the DNDi and its efforts to lift the burden of disease in low-and-middle-income countries.

In the series, our Associate Editor, Angus Stewart, speaks with DNDi leaders, coordinators, partners, and contributors working in the clinic, the lab, and even at the computer terminals of cutting edge tech and AI. We look at open source missions to beat mycetoma, leishmaniasis, and COVID-19, to name just a few of the diseases in DNDi's crosshairs.

To subscribe, just search for "DNDi: Medicine Makers Without Borders" on your favorite podcast service. Alternatively, go to:
<https://bit.ly/DNDi-TMM>



An Ode to Flexible Cleanroom Furniture

Why modular or mobile is the best way to go for CMOs

By Sue Springett, Commercial Manager at Teknomek

When running a CDMO, your customers will have high expectations. Of course, you'll need to be competitive on price, but you'll also need to demonstrate that you can guarantee regulatory compliance and the highest standards of manufacturing practice, including hygiene. But one size never fits all. The ability to rapidly reconfigure your cleanrooms to meet the ever-changing needs of your customers and the marketplace has to be a priority.

When planning a new cleanroom or purchasing replacement or additional furniture for your existing spaces, there are several things to consider to ensure you are making the best use of the area available and getting maximum return on the investment in your kit. If you are 100 percent sure that the requirements of your cleanroom will never change, you may wish to opt for fixed furniture. However, if you want to be able to adapt in the future, a modular approach to cleanroom furniture is the way to go.

The use of free-standing or modular furniture allows a space to be reconfigured to support developments within the business as well as the different aseptic requirements of each project. The configuration of the room can be added to or simply adapted to meet all the needs of a new project.

And when it comes to maintaining ISO



In My View

Experts from across the world share a single strongly held opinion or key idea.

14644 standards, your furniture plays a much bigger part than you may think. How furniture is designed and where it is positioned in a cleanroom can have a massive influence on air circulation – either hindering or assisting the flow – and microbe behavior. Although your HVAC system might be doing its job, a workbench or storage unit with a solid back panel immediately creates a barrier to ventilation. However, by switching from solid to perforated or slatted materials at the back of the workbench, dirt particles can disperse safely to mitigate risk. Ensuring that there is sufficient space around equipment so that air does not stagnate is something that should always be considered.

And what about your people? The single biggest risk to hygiene in laboratories is humans and the 10 g of skin we each shed every day. But humans present another risk in terms of their impact on airflow; for example, a person working in the wrong place for an extended period can cause airflow blockages and affect the hygiene of a cleanroom. And what governs where they're working? That's right, furniture.

If you are not already consulting with your cleaning team when reconfiguring your cleanroom, you are missing a trick. They are the experts and will know where challenges and risk areas lie. Seemingly innocuous shelves and edges can form potentially dangerous harborage points

for objectionable organisms which, in the right conditions, can quickly multiply. And these danger zones are even more of an issue if your furniture is not designed with effective cleaning in mind. Every piece of furniture in your cleanroom should allow for easy access by your cleaning team. When adapting to each new contract, consider mobile furniture (with lockable brakes). This will make it easier to adapt to each new contract, access all areas, and carry out deep cleans. If your furniture isn't easy to move, ensure there is sufficient space between the floor and base of units, as well as around the sides, for thorough cleaning access.

If you opt for modular or mobile furniture, it must be sufficiently robust. Does it offer the stability and firm platform you require for any new

equipment you'll be bringing in? When working with hypersensitive scales you cannot afford extreme movement from your furniture.

As the end users, your cleanroom staff could have valuable input for any new equipment or furniture. What features make the kit easy or cumbersome to use? Do they prefer to work standing up or sitting down – or would they prefer to have the option to do both? In the same way that processes and sensible workflow have an impact on efficiency, if the height of a desk or workbench is causing your team members discomfort, it could have a significant impact on productivity and potentially lead to staff absence.

Manufacturers face a multitude of challenges in order to remain competitive and profitable. Admittedly, taking a flexible approach to the furniture in

"The single biggest risk to hygiene in laboratories is humans and the 10 g of skin we each shed every day."

your cleanrooms – and thus supporting rapid reconfiguration and exceptional hygiene standards – is just one small way of staying ahead. But it could well be the one your competitor has not yet thought about!

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High Intensity Purification

How multi-column chromatography can support companies as they set their sights on intensified bioprocesses

The biopharmaceutical industry is constantly reaching new heights. Driving the sector's continued success is investment in a diverse array of products and processes. From biosimilars to viral vectors to bispecific antibodies, companies are pursuing various drug modalities. But as companies continue to explore the potential of these new therapeutic avenues, they are also focused on process intensification to increase productivity—and that demands closer scrutiny of equipment choices in all bioprocessing steps.

Here, Anthony Grabski, Global Technical Leader of multi-column chromatography (MCC) instruments and applications for Tosoh Bioscience, and Emily Schirmer, Senior Director, Process Development, Catalent Biologics explain why Tosoh's upcoming MCC product launches – Octave® BIO and ProGMP™ Systems – can help companies achieve their bioprocessing goals.

How are bioprocessing needs changing in the industry?

Schirmer: From large pharma companies to contract manufacturers, there are several trends that are changing the industry landscape. We are seeing the addition of larger volume bioreactors,

a trend towards optimized cell line development, and increased use of process intensification and continuous processing methods to drive higher productivity. These technologies and product development approaches have enabled a significant increase in the amount of material that can be generated upstream. This increase in upstream material means there is a need for efficient downstream purification methods – to avoid bottlenecks and reduce manufacturing footprints.

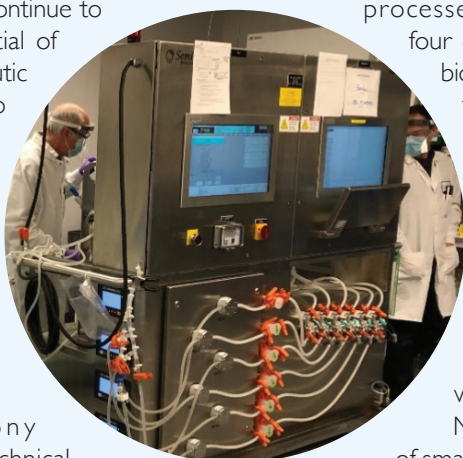
What role can MCC play?

Grabski: MCC fits the growing industry trend of switching from batch to continuous processes and meets the four design principles for biofacilities of the future:

fast, flexible, small, and sustainable.

Companies no longer want or need to deal with the large stainless steel equipment, and buffer and resin volumes associated with batch processes.

MCC relies on a series of small columns instead of one large column, reducing the total resin volume required by as much as 90 percent. The various operations of the process protocol (loading, washing, elution, and cleaning) are carried out simultaneously in different columns under the control of individual pumps. Periodic switching of the inlet and outlet streams to downstream column positions via a valve system executes the progression of process steps in a continuous cycle. MCC also allows maximum productivity as mass transfer to the Protein A chromatography resin allows the total capacity of columns to be reached as fast as possible while maintaining high purity and recovery.



“Companies no longer want or need to deal with the large stainless steel equipment, and buffer and resin volumes associated with batch processes.”

Ultimately, MCC opens the bottlenecks that companies typically experience and provides significant economic advantages over traditional batch methods for mAb purification, including 3–10-fold increased productivity, 85–95 percent resin capacity utilization, 30–50 percent reduced buffer consumption, decreased column volume, and smaller versatile process skids.

All very impressive! But what makes MCC technology most important to me is the patients treated with the mAbs and biologic therapies manufactured using it. I hope MCC will make biological medicines more affordable and available, producing the highest quality, safest, and most effective treatments possible for those who need them.

Schirmer: Protein A can be costly – often requiring a large upfront investment to establish the downstream process. The investment required for expensive chromatography matrices is limiting for many of our partners, especially small biotechnology

companies. But this can be avoided using MCC because it reduces resin usage. As the industry looks to overcome the bottlenecks that can occur during process intensification, I believe that MCC can offer a pertinent solution.

What's the story behind Tosoh's upcoming MCC launch?

Grabski: The Octave® BIO and ProGMP™ Systems are based on MCC technology developed by Semba Biosciences. Semba's in-house research focused on developing MCC methods for Protein A capture of mAbs. After screening many commercial Protein A resins, Semba found that TOYOPEARL® AF-rProtein A HC-650F from Tosoh Bioscience had the best combination of capacity, flow properties, and resulting product purity to achieve the highest productivities when used on Semba's MCC Systems. These findings and additional superior MCC results using other TOYOPEARL resins for mAb polishing led to a strong partnership with Tosoh Bioscience – and then Tosoh's acquisition of Semba in 2021.

“As the industry looks to overcome the bottlenecks that can occur during process intensification, I believe that MCC can offer a pertinent solution.”

The new Octave® BIO works particularly well with Tosoh Bioscience's SkillPak pre-packed columns; this powerful combination offers customers a single-source solution for robust, flexible, and rapid MCC process development.

What sets these systems apart?

Grabski: The Octave® BIO and ProGMP™ Systems paired with TOYOPEARL® AF-rProtein A HC-650F resin allow flow rates of >600 cm/h and loading residence time as short as 0.25 min for Protein A adsorption of the mAb versus 4 min or more in a single column batch process. As all non-loading steps are carried out simultaneously in the other columns, there is no delay in completing each step. The entire Protein A capture is achieved with greater speed and efficiency than a single column process. Flexibility is afforded by adjusting the column number, size, and configuration to suit feed and adsorbent properties, accommodate all process steps, and satisfy run time requirements.

How are customers benefiting from the systems?

Schirmer: Catalent had been considering alternatives to traditional batch chromatography to address process

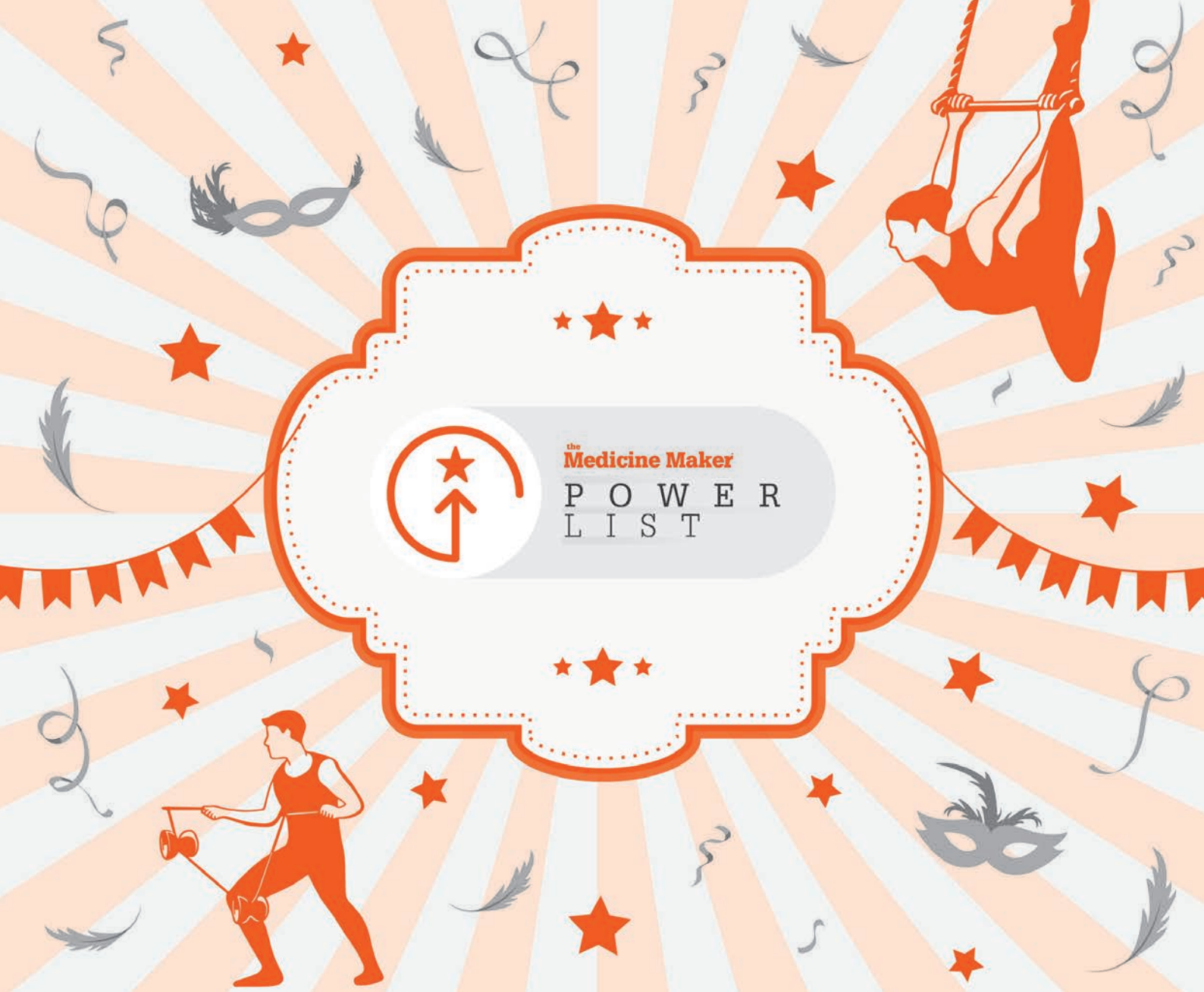
intensification upstream. And that's how our partnership with Tosoh came about.

We worked with Tosoh's MCC systems and completed several pilot and manufacturing scale runs. The results clearly illustrated the potential to make significant time and cost savings for our partners. The automation the systems provide is also beneficial to the manufacturer with respect to operator time.

How can companies learn more about MCC?

Grabski: Over the past three years, Tosoh has been investing in the support infrastructure to help educate current and future MCC users, both with virtual and in-person offerings. Tosoh Bioscience has created its MCC Center of Excellence in Madison, Wisconsin, and expanded the US headquarters in King of Prussia, Pennsylvania, to include a demonstration lab and training facility dedicated to MCC education. We are also investing in a similar set of Centers of Excellence and Application Labs at other offices worldwide. The platform is helping to educate and support the industry all the way from the lab to the field.





Presenting 2022's flag bearers of small molecule, biopharmaceutical, and advanced therapy drug development and manufacturing

The Medicine Maker team is constantly in conversation with industry experts, but whoever we speak with, whether keen start-up teams, seasoned veteran CEOs, or inspiring academics, the discussions are consistently enriching and provide insight into the inner workings of the sector. The stories we hear are a testament to the industry's continued commitment to serving patients.

The industry has faced wholly new challenges and pressures over the last few years. We are still living with COVID-19 and, in recent months as the international political climate intensified, the pharmaceutical industry's efforts to manage supply chains and ensure access to much-needed drugs and

therapies has been highlighted time and time again, all while continuing to develop new medicines.

We asked you to nominate the influential people making the most impact in the drug-making space – and we listened. Now, we invite you to join us as we celebrate the top 10 leaders in small molecules, biopharmaceuticals, and advanced therapy – 30 amazing individuals in total. Find the winners on pages 13 (Small Molecules), pages 16 (Biopharmaceuticals), and pages 18 (Advanced Therapies).

The full list can also be found online at www.themedicinemaker.com

JOHN CHIMINSKI

CHAIR AND CEO, CATALENT

In the more than 20 years Chiminski has spent at Catalent, he has overseen the company's strategy to help accelerate the small molecule development process and improve clinical outcomes. He became Chief Executive Officer in 2009.

"Throughout the COVID-19 pandemic, we learned that the industry can go fast. When faced with the biggest challenge of our lifetime, Catalent partnered with government and industry to develop vaccines that saved lives and allowed people to get their freedom back. Going forward, I would like to see the industry preserve this speed and recreate it outside of a pandemic by ensuring senior leaders are involved in decisions that can accelerate projects and contracts; making decisions quickly that balance risk alongside back up plans (such as building capacity/facilities with the flexibility to adjust designs if necessary); and having open collaborations, with more sharing partnerships and mutual risk taking."



KEVIN COOK

CEO, STERLING
PHARMA SOLUTIONS

Kevin has over 30 years' experience in the pharma industry. He started with Robinson Brothers as an assistant plant manager before progressing to senior roles at the company – and then beyond.

"I always thought that work was a physical location that you went to,



which was perhaps an old-fashioned way of thinking. The pandemic made us work differently, as we introduced remote working and witnessed the benefits of all the new technology platforms. Initially, many businesses were fearful of how well this would work, but for Sterling it has proved very successful, and we will continue to offer remote working wherever practical."



CHENG FANG

SENIOR VICE
PRESIDENT OF
RESEARCH &
DEVELOPMENT,
ANNOVIS BIO



Cheng Fang is an accomplished neuroscientist with over a decade of experience in neurodegenerative diseases. Before joining Annovis, she worked on cutting-edge projects with the world's top pharma companies. Not many people know it, but she has been to nearly as many salsa congresses as scientific conferences.

"Despite low adoption rates, telehealth was ready to roll out when the pandemic hit. The pandemic also accelerated the adoption of decentralized clinical trials. I think the industry now needs to keep up with the ongoing change, and maintain the adoption of new technologies."

PATRICK COUVREUR

EMERITUS PROFESSOR OF
PHARMACY, PARIS-SACLAY
UNIVERSITY, FRANCE

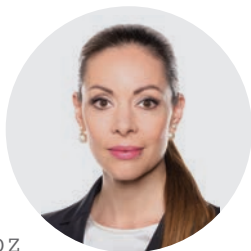
Couvreur is a member of the French Académie des Sciences and holder of the Chair of Innovations Technologiques (2009-2010) at the prestigious Collège de France. In 2009, he was appointed as a Senior Member of the Institut Universitaire de France.

"I find that the COVID-19 crisis has given researchers, financiers, and industrialists an extraordinary lesson. The mRNA vaccine represents, indeed, an extraordinary scientific and technological revolution. It is perhaps the greatest discovery of the century."

REBECCA GUNTERN

HEAD OF EUROPE, SANDOZ

Passion for success through work drives Rebecca Guntern Flückiger. As vice president of Medicines for Europe, she strongly advocates for sustainable healthcare in Europe and takes the position that access to healthcare should be a right, not a privilege.



“The value of the generics and biosimilar industry to both patients and society is often lost in

the public debate surrounding medicine prices. Policymakers must actively pursue a social agenda that recognizes the full role and value of off-patent medicines. This requires a shift in perception away from cost to contribution and value to societies and healthcare systems.”

NIGEL LANGLEY

GLOBAL TECHNOLOGY

DIRECTOR, BASF

In 2018, Langley was awarded the Industry Research Achievement Award in Excipient Technology by the IPEC Foundation. He has been a member of the Executive Committee at IPEC Americas since 2010 and is currently chair.

“One of the major breakthroughs in recent years in small molecule drug development is in novel excipients and the FDA novel excipient pilot review program that was introduced in December 2021. The FDA novel excipient pilot review program should help to reduce the regulatory risk for using novel excipients and provide the opportunity for excipient suppliers to develop new excipients that have been specifically designed to help address current and future formulation challenges.”

**EDWARD HAEGGSTROM**

CEO, NANOFORM

In 2015, Haeggström commercialized the nanoparticle engineering platform he developed with Jouko Yliruusi, acting professor at the University of Helsinki, Finland. This marked the beginning of Nanoform. When asked about what could improve the pharma industry, he responded, “The shift toward a more patient-centric approach in the design of new drugs is something that has been gaining momentum and which I am keen to see more of in the pharma industry. It is my belief that it is not only patients who stand to gain from therapies more tailored to their needs, but also a chance for pharma to grow from both a commercial and humanitarian standpoint. Wider adoption of patient-centric practices and incorporation of patients’ feedback from the early stages of drug discovery through to development has the potential to revolutionize patients’ quality of life. In today’s ever more technologically advanced world, it is easier than ever to achieve.”

**JOHANNES KHINAST**

PROFESSOR OF
PHARMACEUTICAL
ENGINEERING, GRAZ
UNIVERSITY OF TECHNOLOGY,
AND CEO, RCPE

Khinast has hundreds of publications in peer-reviewed journals and a number of patents registered under his name. He has worked with numerous pharmaceutical companies as an advisor for the implementation of novel drug formulations.

“Pharma will look back on COVID-19 as a game-changer that hopefully brought back API production to Europe. We will be better prepared to face another health crisis in the future by reacting faster and making rapidly invented drugs accessible for a large number of people around the world.”

CLAIRE THOMPSON

CEO, AGILITY LIFE SCIENCES

Thompson is a multi-award winning scientist, the CEO of Agility Life Sciences, Entrepreneur in Residence at the University of Cambridge, and a former footballer who launched and fully funds the Girls In Football Teams (GIFT) Grants, which support girls' and women's teams across the UK.

"Pharma can improve itself by using less jargon. As scientists, we are taught to use very technical language to talk about the features of what we do, not the benefits. None of this is very engaging to non-technical people, particularly the public and young people."



MARTIN VANTRIESTE

PRESIDENT AND CEO AT CIVICA RX

Under VanTrieste's leadership, Civica has expanded its membership to include more than 55 health systems representing over 1,500 hospitals across the US, and has delivered nearly 60 essential medications for hospitals, 11 of which are being used to treat COVID-19 patients. Most recently, Civica announced its plans to manufacture and distribute insulin that, once approved, will be available to people with diabetes at significantly lower prices than insulin currently on the market. The availability of affordable insulin will benefit people with diabetes who have been forced to choose between life sustaining medicines and living expenses, particularly those uninsured or underinsured who often pay the most out of pocket for their medications.



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BIOPHARMACEUTICALS



RICK A BRIGHT

CEO, PANDEMIC PREVENTION
INSTITUTE, THE ROCKEFELLER
FOUNDATION

With decades worth of experience under his belt, Bright joined the Pandemic Prevention Institute (PPI) at The Rockefeller Foundation in 2021. He leads the development of the Foundation's pandemic data-to-action platform, which, in collaboration with global partners, integrates modern technology and data analytics to lessen the threat from emerging and future infectious diseases. He has also held government positions. Prior to his current appointment, he was the deputy assistant secretary for Preparedness and Response and the director of the Biomedical Advanced Research and Development Authority (BARDA), in the US Department of Health and Human Services.



ERIC DUBE

PRESIDENT AND
CEO TRAVERE
THERAPEUTICS

Dube served as the president and head of North America at ViiV Healthcare, and spent more than 18 years working in roles of increasing leadership at GlaxoSmithKline across the US, Europe, and Japan. In his current role, Dube works to develop live-changing therapies for people living with rare diseases. He has won several awards during his career, including being named one of 100 OUTstanding LGBT+ Executives in the Financial Times.



**MICKI
HULTQUIST**

GLOBAL FRANCHISE
HEAD, ASTRAZENECA

Hultquist has spent over 25 years in drug development. Her career began at Abbott Laboratories where she worked as a biostatistician. She joined MedImmune in 2000, bringing her knowledge of biostatistics with her but transitioned into a project management role at the company in 2008.

Today, she leads the Franchise Team at AstraZeneca and is responsible for the development and commercialization of Saphnelo, a monoclonal antibody treatment for systemic lupus erythematosus. Discussing the significance of the treatment, she said, "I view Saphnelo as a massive breakthrough for patients and the lupus community. Looking forward, I'm interested in watching the evolution of AI and clinical trials."

**SABRINA
MARTUCCI
JOHNSON**

PRESIDENT AND
CEO, DARÉ BIOSCIENCE
OPERATIONS



A lifelong advocate for women's healthcare issues, Johnson founded Daré Bioscience Operations in 2015 and has served as President, CEO and a member of the board of directors since its inception and following its business combination with Cerulean Pharma in July 2017.

"We need to continue to do a better job as an industry by including women in clinical studies and understanding how disease (and treatments) manifest differently in women versus men. Doing so will improve the standard of care for everyone."

MAIK JORNITZ

PRESIDENT AND
CEO, G-CON
MANUFACTURING



Jornitz has honed his bioprocessing expertise over the last 35 years in industry. As a subject matter expert in sterilizing grade filtration, he has published over 100 scientific articles and books on both facility design and bioprocess-related issues. Alongside his current role at G-CON, Jornitz has held several advisory positions. He was the former chair of the PDA board of directors and science advisory board, and member of multiple PDA task forces. He now serves as a working member of ASTM E55, an advisory board member of the Biotechnology Industry Council, ICAV, Bondwell, DIANT Pharma, and multiple scientific journals.



GURUTZ LINAZASORO

CEO, VIVEBIOTECH

Linazasoro is a neurologist, the founder and CEO of VIVEbiotech, and the director of the Advanced Therapies Program for Parkinson's and Alzheimer's at Policlínica Gipuzkoa. He also writes for the "El Árbol de la Ciencia" section of the El Diario Vasco, a daily morning newspaper for the Basque region.

"Cooperation is the main behavioral characteristic that differentiates humans from other animals. It has been – and continues to be – the major engine for human progress. All the challenges we are facing as a species can only be overcome by means of a generalized cooperative behavior."

JAN VAN DE WINKEL

PRESIDENT AND CEO, GENMAB

Van de Winkel has over 30 years of experience in the therapeutic antibody field. Under van de Winkel's leadership, Genmab has achieved many key milestones, including the approval of five medicines for treatment of cancer and other diseases, and 20 industry partnerships.

"Throughout my 35 years in the immunology field, I have had a desire for lifelong learning that I don't think will ever go away. I'm a naturally curious person, which has led me where I am today. And there is nowhere else I'd rather be – connected to science and always working towards making a real difference to the lives of patients."



HANNS-CHRISTIAN MAHLER

CHIEF ENABLEMENT OFFICER
(CEO) AND BOARD MEMBER,
TEN23 HEALTH

Mahler is the current CEO of ten23 health, a CDMO dedicated to human-centric and sustainable pharmaceutical development. He spent much of his career leading product development services with roles at the likes of Merck, Hoffmann-LaRoche, and Lonza. But his interests are not limited to drug development... One unknown fact about him? "Surely the most little known: I have played in the same band since 1993 and we are about to complete a new album."



JOHN V OYLER

CO-FOUNDER AND
CHAIRMAN, BEIGENE

Though Oyler began his career as a management consultant at McKinsey & Company, his pharmaceutical experience is extensive. He served as the co-CEO of Genta (1997-1998), president of Telephia (1997-2002), CEO of Galenea Corp (2002 to 2004), and president and CEO of BioDuro (2005-2009).

"In the past decade, the industry has achieved tremendous breakthroughs that have had a profound impact on cancer patients. I am proud of the industry and the role we play in delivering great science. That said, I believe that the



MIKE REA

CEO AND FOUNDER, IDEA
PHARMA AND PROTODIGM

Rea wears many hats within the industry. Beyond his role at IDEA Pharma, he is also a contributor to several publications, senior fellow at the Milken Institute, an advisor to BioEthics International, and a strategic innovation advisor at Nanoform. In 2020, he wrote the book Positioning Pharmaceuticals and developed the Pharmaceutical Innovation and Invention index in 2010. When asked how pharma could improve he said, "We need better decision making in development. Instead of 'follow the science,' it should be 'follow the decision science.'"

one thing we must try to do is to make medicines more affordable and accessible to patients across the globe."



ADVANCED MEDICINE

MASSIMO DOMINICI

ONCOLOGY PROFESSOR,
UNIVERSITY HOSPITAL OF
MODENA AND REGGIO EMILIA
AND SCIENTIFIC FOUNDER,
RIGENERAND

Massimo Dominici holds an MD degree from the University of Pavia, and undertook a postgraduate internship at Vienna University, a residency in hematology at the University of Ferrara, and served as a postdoctoral associate at

St Jude Children's Hospital in Memphis. He has authored more than 150 papers. He also has a passion for orchids...

"I have a passion for orchids, they are difficult plants but become generous and beautiful once given the space, light, and nutrients they need. A bit like growing cells..."



MIGUEL FORTE

CEO, BONE THERAPEUTICS, AND
PROFESSOR, LISBON UNIVERSITY

Forte is the incoming president-elect of the International Society for Cell & Gene Therapy (from June 2022–2024). Forte holds an MD and Specialist in Infectious Diseases, a PhD in Immunology, and a certificate on Health Technologies Economics from the Stockholm School of Economics.

"The COVID-19 pandemic proved our ability to adapt and respond to a new and challenging situation. Through doing work and business remotely, we survived. It was as if the old funding roadshows became Zoomshows!"



JACQUES GALIPEAU

DON AND MARILYN
ANDERSON PROFESSOR OF
ONCOLOGY AND ASSOCIATE
DEAN FOR THERAPEUTICS
DEVELOPMENT, UNIVERSITY
OF WISCONSIN - MADISON

Galipeau is the president-elect of the International Society for Cell Therapy and the director of the University of Wisconsin Advanced Cell Therapy Program. He is an internationally recognized expert in the translational development of cellular pharmaceuticals.



"In the world of cell and gene therapies, there may be an underdeveloped niche in place-of-care, vein-to-vein manufacturing and the profitable deployment of living synthetic therapeutics.

Whoever figures this out may disrupt the onerous central manufacturing model and own the secondary markets of emerging economies..."

FABIAN GERLINGHAUS

CO-FOUNDER AND
CEO, CELLARES

Gerlinghaus is driven by a strong sense of purpose and is passionate about building the future of cell therapy manufacturing.



"The recent approval for Yescarta in second-line (2L) relapsed/refractory large B-cell lymphoma means that an order-of-magnitude more patients just became eligible for potentially curative therapies. As cell therapies move up the treatment paradigm and cell-based therapeutics are eventually approved to treat a range of cancers, the spotlight will turn (again) to manufacturing capacity."

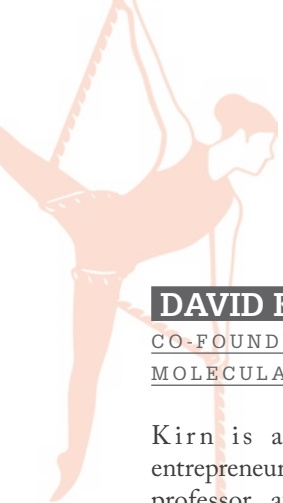
QUEENIE JANG

CEO,
INTERNATIONAL
SOCIETY FOR CELL
& GENE THERAPY



For Jang, the emergence of the advanced medicine field is akin to evolution from analogue to digital platforms in the IT sector. But she believes that cost-of-goods optimization is key to broad healthcare adoption of ATMPs.

"The story of CAR-T is remarkable. Over the past several years, multiple autologous therapies have been successfully translated from bench to bedside and received marketing authorization as potentially curative therapies for patients with recalcitrant cancer indications."



DAVID KIRN

CO-FOUNDER & CEO, 4D
MOLECULAR THERAPEUTICS

Kirn is a physician-scientist, entrepreneur, new medicines developer, professor, author, and CEO. At the University of California, Berkeley, he is Adjunct Professor of Bioengineering. He was SVP of Clinical R&D at Celgene, and VP at Onyx, where he worked on five drugs that were eventually approved.

MARIANTHI PSACHA

GLOBAL HEAD CELL &
GENE THERAPY, SANTEN
PHARMACEUTICAL

Psacha leads a global team guided by the purpose of changing the lives of patients around the world living with inherited retinal diseases, using cell and gene therapies to address significant unmet needs in ophthalmology by building capabilities and creating a sustainable, scalable platform.

“In recent years, pharma’s reputation was brought into question regarding marketing unnecessary drugs, prioritizing high margins over unmet needs, and so on. However, the pandemic pushed us to unify and to solve a life or death issue at unprecedented speed and scale. We took collective responsibility, and we should hold on to it.”



“An entire industry has been born from utilizing patients’ and donors’ stem cells and a modified version of the AIDS virus to cure leukemia. This is truly a mind-blowing advancement that combines so many complex processes and biologics and really showcases the power of creative investigators to come up with amazing new treatment solutions.”

CHRIS VAN DER WALLE

EDINBURGH CENTRE DIRECTOR,
CELL & GENE THERAPY
CATAPULT

Van der Walle obtained his PhD in peptide chemistry from King’s College London. At the beginning of 2022 he became the Edinburgh Centre Director of the Cell & Gene Therapy Catapult, where he switched his focus to scientific and industrial collaboration, technology transfer, and clinical trial acceleration.

“Pharma could be improved through in silico simulation of bioprocessing steps to explore new approaches and select those which are most promising. For example, to enable the closure of open manipulations during the manufacture of cell therapy products.”



BRUCE LEVINE

BARBARA AND EDWARD
NETTER PROFESSOR
IN CANCER GENE
THERAPY, UNIVERSITY OF
PENNSYLVANIA

Levine believes the success of COVID-19 vaccine development carries lessons for cell and gene therapy by validating the benefit of long-term investment in research. He is looking forward to improvements both in viral vector manufacturing and viral-free methods of gene delivery.

“My work is well-known, but people may not know that I can trace one branch of my family tree back 19 generations to Judah ben Eliezer ha-Levi Minz, a prominent 15th century Italian rabbi, or that I coined the name ‘Cellicon Valley’ for the Philadelphia cell and gene therapy ecosystem.”



PAUL K. WOTTON

CEO, OBSIDIAN
THERAPEUTICS

Wotton has experience spanning scientific research, product development, and corporate growth accumulated over a 30-year career. He most recently served as the founding President and CEO of Sigilon Therapeutics. In previous roles, he served as president and CEO of Antares Pharma as well as CEO of Topigen Pharmaceuticals. He is a named inventor on numerous patents and was the Ernst & Young Entrepreneur of the Year Regional (NJ) Winner Life Sciences in 2014.

“A little-known fact about me? In a past life, I was a window cleaner.”



Welcome to The Medicine Maker's inaugural Company of the Year Awards!
Here, we celebrate six victorious companies contributing to drug
development and manufacture.

How were the winners chosen? For each category, we selected 10 top contenders based on factors such as market presence and impact. But we turned to you for the most important task, by asking

you to vote for your top picks via our website. Importantly, we offered you the opportunity to submit your own nominations in all categories, in case your top company was not listed; we

appreciate the industry is highly diverse – with plenty of top performers in the shadows!

Huge congratulations to all six winners!

BEST BIG PHARMA COMPANY: PFIZER

Credit: U.S. Secretary of Defense / flidr.com

The COVID-19 pandemic has dominated conversations over the past two years, so it's no surprise that a major player in this area would take the category by storm. The Pfizer BioNTech vaccine was the first COVID-19 vaccine to be approved for emergency use and it has seen huge success.

The company was founded in 1849 in New York by Charles Pfizer and Charles Erhart. At first, the company was a manufacturer of fine chemicals but pivoted to more research-based pharmaceuticals in the 1950s. Over the years, the company has had countless success stories, including Lipitor – touted as the biggest selling drug of all time. Another famous success story for the company is Viagra; while the drug was undergoing clinical trials for

treating heart disease, scientists realized that it was not sufficiently efficacious – but also noted that it did have an unusual side effect...

As of February 2022, the company had 27 product candidates in phase I, 25 in phase II, and 27 in phase III.

RECENT NEWS:

- ➔ *Pfizer acquires ReViral and its portfolio of respiratory syncytial virus therapeutic candidates*
- ➔ *All profits from Pfizer's Russia subsidiary will be donated to causes that provide direct humanitarian support to Ukraine*
- ➔ *David M Denton named company's Chief Financial Officer*

- ➔ *Pfizer-BioNTech COVID-19 vaccine receives expanded EUA from FDA for an additional booster in people aged 50 years and older*

KEY FACTS

Global headquarters:
New York, USA

Number of
employees:



79,000

Sales Revenue
in 2021:

**US\$ 81.3
billion**

HONORABLE MENTION:
MERCK, SHARP & DOHME

BEST BIOPHARMA EQUIPMENT COMPANY: SARTORIUS STEDIM BIOTECH



Sartorius' roots go all the way back to the 1870s when Florenz Sartorius founded "Feinmechanische Werkstatt F. Sartorius" in Goettingen, Germany. Although initially starting out as a company specialized in weighing and balance equipment, Sartorius has evolved over the last 150 years to become an important partner for the biopharmaceutical and life science industries.

The company has grown its products and services through acquisitions as well as organic growth and internal innovation. The Stedim acquisition about a decade ago brought single use bags and film technology to the company's portfolio. Today, the company has a full suite of scalable products for upstream bioprocessing. Most recently, Sartorius expanded its downstream portfolio. For chromatography solutions in particular, with products acquired from Danaher, BIA Separations and most recently

Novasep, Sartorius has solutions to assist with emerging modalities, such as mRNA, pDNA and AAV, as well as mAbs and traditional vaccines.

At the company's annual general shareholders' meeting in March 2022, the company said that group sales revenue in 2021 increased by almost 50 percent compared with 2020, with growth in the lab products & services division, as well as the bioprocess solutions division. The company is currently focusing on expanding its global footprint to better serve its customers, with the goal of doubling capacity for key product groups by 2025.

RECENT NEWS:

- ➔ *Sartorius acquires majority stake in ALS Automated Lab Solutions*
- ➔ *Company completes acquisition of Novasep's chromatography division*

- ➔ *Sartorius grows operations in France and is investing 100 million euros by 2025*

KEY FACTS

Global headquarters:
Goettingen, Germany

Number of
employees:

Annual sales revenue
in fiscal 2021:

Global Footprint:



14,000
Approx.

**EUR 3.45
billion**

**60 sites in
more than 30
countries**

**HONORABLE MENTION:
DANAHER**

BEST API SUPPLIER: BASF

Credit: U.S. designandfoamart / Pixabay.com

BASF is one of the world's biggest chemical companies – and evidently a clear favorite with readers of The Medicine Maker! The company was founded in 1865 as Badische Anilin- und Sodafabrik in Mannheim, Germany.

BASF has a long history of innovation. One example is the development of PVP. The company says, “More than 80 years ago, the chemists of our Ludwigshafen plant in Germany mastered acetylene-chemistry to produce – in just five steps – a new monomer called N-vinylpyrrolidone. According to a 1939 patent by BASF chemist Walter Reppe, vinyl pyrrolidone reacted in the presence of catalysts to form the polymer we now know as poly vinylpyrrolidone – or PVP. This initial application data regarded PVP as an additive in the textile industry due to its great affinity to dyes, and as a binder and thickening agent.”

During this same time, the Second World War was ramping up and access to blood plasma in Germany was extremely difficult. By the end of 1940, BASF's

Kollidon PVP gained its first medicinal application as a synthetic blood plasma substitute. Its use was simple: Kollidon was combined with water and inorganic salts and used in intravenous infusions. The higher the PVP content, the greater its efficacy in maintaining blood volume. The application was patented in 1941 by Walter Reppe and researchers from Bayer pharmacological laboratories.

Today, the company offers APIs such as ibuprofen, L-menthol and omega-3, as well as excipients for biopharma, parenterals, orals, topicals, and solubilization applications. The company also boasts an enormous chemical raw materials portfolio including catalysts, reagents, solvents, chiral auxiliaries, building blocks, and more.

RECENT NEWS:

➔ *Jeffrey DeAlmeida appointed to role of Senior Vice President, Pharma*

Solutions and Nutrition & Health Americas

➔ *Company reaffirms ambitious climate targets, including goal of reducing greenhouse gas emissions by 25 percent (compared with 2018) by 2030*

KEY FACTS

Global headquarters:
Ludwigshafen, Germany

Number of
employees:

111,047
(as of December 2021)

Sales revenue
in 2021:

**EU€ 78.6
billion**



HONORABLE MENTION:

TEVA ACTIVE

PHARMACEUTICAL

INGREDIENTS;

PFIZER CENTREONE

BEST CDMO SERVICE PROVIDER: PFIZER CENTREONE



Pfizer CentreOne is a CDMO backed by Pfizer resources and a supplier of specialty APIs and intermediates. In essence, CentreOne is a self-contained organization – with its own dedicated teams – that sits inside Pfizer.

Pfizer has been providing contract manufacturing services for more than 45 years, but the name ‘Pfizer CentreOne’ was only introduced in 2016, following Pfizer’s acquisition of Hospira. Hospira’s One 2 One sterile injectables CMO and Pfizer’s CentreSource API business were merged to create Pfizer CentreOne. The company has expertise in small molecules, biopharmaceuticals, oral

solids, sterile injectables, and more, spanning development services, clinical and commercial manufacturing, and lifecycle management.

Andrew Moore, General Manager of Pfizer CentreOne, says: “This recognition means a great deal to our team at Pfizer CentreOne. To be acknowledged as the CDMO of the year, among our industry peers, is truly significant. Our people work every day to live up to the confidence our customers place in us and be the partner they deserve. We are building something that is altogether different in the CDMO space and a win like this is clear evidence that we’re achieving

our goals. It makes all of us proud and determined to continue to deliver for our customers and, ultimately, for patients.”

KEY FACTS

Global headquarters:
New York, USA

Revenue in 2021:



**US\$ 1.7
billion**

HONORABLE MENTION:
LONZA



BEST PROCESSING EQUIPMENT COMPANY: IMA

IMA describes itself as “the one-stop-supplier of the pharma market,” offering a huge range of equipment, including solutions for solid dose, aseptic processing, freeze drying, packaging, and more. The company’s history in the pharmaceutical market dates back to the 1970s with the launch of a blister packaging machine. Since then, the company has gone on to develop new machines and complete lines for the processing and packaging of pharmaceutical products, and acquire new companies, leading to a vast expansion of its portfolio.

More recently, the company has been embracing the digital era by incorporating Industry 4.0 technology into its systems. For example, Domina is a highly automated tablet press manufactured by IMA Active division that makes it possible to perfectly

compress any powder thanks to self-learning algorithms that allow for the identification of the right set-up and help ensure consistent tablet quality. Domina was one of the finalists in The Medicine Maker 2021 Innovation Awards.

IMA also has a Stay Connect platform that can offer customer support through connected machines.

RECENT NEWS:

- ➔ *IMA publishes article about the autoregulation function on Domina tablet press*
- ➔ *Company publishes case study on the evaluation of next-generation container closure systems for lyophilization process development*
- ➔ *Company announces new*

overwrapping machines that can be run both with opp, recyclable and compostable films as well as with paper unrolled from reels

KEY FACTS

Headquarters:
Ozzano dell’Emilia,
Bologna, Italy



Number of
employees:

>6,200

Sales Revenue
in 2021:

**EU€ 1,688.3
million**

**HONORABLE MENTION:
ROBERT BOSCH**

BEST TALKING POINT: BIONTECH

Credit: U.S. Epizentrum / commons.wikimedia.org



Another key player in the fight against COVID-19 celebrates a win. BioNTech was founded in 2008 to focus on cancer immunotherapy. Today, individualized immunotherapy remains the primary goal, despite the company rising to superstardom in the COVID-19 field with its collaboration with Pfizer on the Comirnaty vaccine. Even before the pandemic, the company was making a name for itself by working with other large pharma companies, including Eli Lilly, Sanofi, Genentech – mainly on mRNA-based research. In 2018, the company signed an agreement with Pfizer to develop mRNA-based vaccines for influenza. This early work would eventually pave the way for a COVID-19 vaccine. Pfizer and BioNTech announced a letter of intent to co-develop a COVID-19 vaccine on March 17, 2020 –

with the work building on research from the influenza partnership.

And the rest is history.

The company recently announced its Q4 and full year financial results for 2021; total revenue exceeded 18.9 billion euro and net profit was around 10.3 billion euro.

RECENT NEWS:

- ➔ *BioNTainer modular mRNA manufacturing solution launched to support scalable vaccine production in Africa*
- ➔ *Company has expanded collaboration with Regeneron to advance its FixVac candidate BNT116 in combination with Libtayo (cemiplimab) for advanced non-small cell lung cancer*



Credit: JFCfilms / Pixabay.com



- ➔ *Research collaboration with Matinas BioPharma announced to evaluate novel delivery technology for mRNA vaccines*
- ➔ *Three-year collaboration announced with Medigene to develop T-cell receptor based immunotherapies against cancer*

KEY FACTS

Global headquarters:
Mainz, Germany

Number of employees: **1300**

Sales Revenue in 2021: **EU€ 18.9 billion**



HONORABLE MENTION:
MODERNA



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^{the} **Medicine Maker** INNOVATION AWARDS

AND THE SUPREME
INNOVATOR IS...

Read on for the full results of
The Medicine Maker 2021
Innovation Awards

The votes came in, we tallied them, and now we have our winner: **Nuvolo Connected Workplace – Calibration**. It seems the software engineers have come out on top this year, so congratulations to all the coders at Nuvolo!

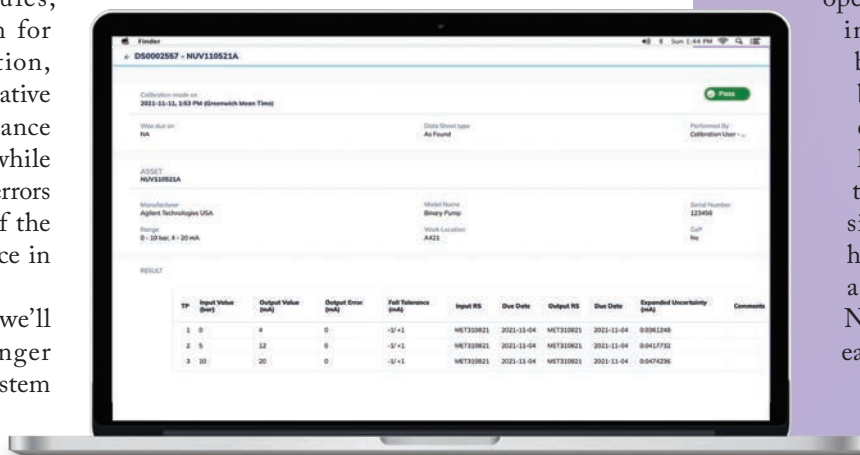
The annual Innovation Awards are a longstanding tradition here at The Medicine Maker. Each year, you nominate (and we handpick) the very best new technologies in pharmaceutical development and manufacturing, then we reveal our list of finalists and put it to a vote. It's a great way to champion the machines and modules that are pushing the industry forward. In late 2021, we published a list featuring our latest finalists, and next it was entirely up to you – the readers – to choose the winner by ballot.

GRAND WINNER:

NUVOLO CONNECTED WORKPLACE – CALIBRATION

Perhaps it's no surprise that you voted Nuvolo's tech right up to the top spot. In the wake of the COVID-19 pandemic, the importance of efficiency and resilience remains burned into the industry's collective consciousness. And in a world swinging from crisis to crisis, disparate systems and segregated spreadsheets are nobody's friend. The Connected Workplace – Calibration software offers companies the means to centralize their plans, schedules, and documentation for equipment calibration, easing the administrative burden on maintenance and quality teams, while also cutting down on errors and grievous waste of the most valuable resource in the world: time.

Watch this space; we'll be publishing a longer piece on Nuvolo's system very soon.

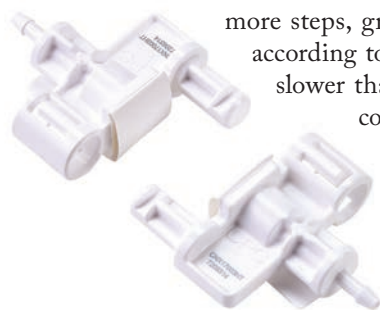


Nominations for 2022

Innovation doesn't stop here. Entries for the 2022 Innovation Awards will be open very shortly! Keep your eyes on www.themedicinemaker.com and sign up for our newsletter to be the first to find out when nominations open. To be eligible, the innovation must have been released in 2022 or be due for release by the end of the year. We are looking for technologies that could have a significant impact on how drugs are developed and manufactured. Nominations will close in early November.

RUNNER UP: CPC'S MICRO CNX SERIES CONNECTORS

These aseptic connectors connect tubing in small-format assemblies, and ask no more than a simple "pinch-click-pull" of their users: a "pinch" to remove the protective cover, a "click" to join the connector halves, and a "pull" to lift the protective membranes. This is a solid improvement from traditional tube welding, which demands



more steps, greater precision and – according to CPC – is four times slower than their tech. Aseptic connectors also take tube welders and their associated costs out of the equation, and can be incorporated into pre-made tubing assemblies.

RUNNER UP: WATERS' BIOACCORD SYSTEM WITH ACQUITY PREMIER

This system is designed to solve the prime problems of cost and complexity faced by all biopharma companies taking a crack at liquid chromatography–mass spectrometry adoption. The BioAccord System does this by eliminating analyte-to-metal surface interactions, simplifying the detection of critical quality attributes using high-quality mass spectral data, and boosting the recovery of hard-to-detect sample analytes and assay-to-assay reproducibility. The software uses machine learning to allow the system to monitor its own performance, helping to improve productivity by maximizing system uptime and minimizing reanalysis.



The Future of LNP Formulation Technology is Here

More and more researchers are exploring the exciting potential of mRNA, most often in combination with encapsulation into lipid nanoparticles. For this, they require lab-scale systems that support their R&D efforts. To address this need, KNAUER has developed the IJM NanoScaler for lab-scale lipid nanoparticle production.

By Paul Pietsch

Pre-pandemic, mRNA was already an exciting field, but the overwhelming success of the mRNA-based COVID-19 vaccines has led to even more activity. Conventional therapeutics involve the production of an API in a lab or factory,



Paul Pietsch is Head of Engineering Solutions for Knauer's LNP production equipment. This team helps customers adapt LNP systems to their needs, and offers customers support and improvements.

which is then delivered and administered to the patient. mRNA vaccines flip this notion on its head. mRNA vaccines contain the code that enables the body to produce proteins that have a therapeutic effect. Essentially, mRNA vaccines turn the body's cells into their own therapeutic producing factories. The "recipe" for the protein required is delivered by means of the mRNA's genetic code, which is then translated into a protein by the cell's ribosomes.

It's a completely new – and incredibly exciting – approach. In fact, I could even go as far as saying that it has the potential to revolutionize medicine. mRNA vaccines can be modified much faster than conventional vaccines; even now, work continues to update the current COVID-19 vaccines to confer better immunity to new coronavirus variants.

But the potential of mRNA is not just limited to this pandemic – or even to vaccines. Research is also being carried out to produce therapies for a diverse range of difficult to treat diseases, such as cancer, HIV, rabies, and malaria. mRNA could also bring us closer to the era of personalized medicine – where patients are given therapeutics that can be tailored to their own genome.

A helping hand against the pandemic
Prior to the pandemic, mRNA technology was generally limited to small-scale clinical trials. With COVID-19, however, came the need to scale up production – and fast. And that's where KNAUER came in.

KNAUER has 60 years of experience in the development and production of scientific equipment. Our main expertise has historically been in the field of liquid chromatography and accompanying equipment. Liquid chromatography takes place at high pressure and requires highly accurate pumping, dosing, and liquid handling systems to be effective.

Shortly after the outbreak of the

"With COVID-19, however, came the need to scale up production – and fast. And that's where KNAUER came in."

pandemic, we received a request from a mysterious customer who was interested in our pumping and dosing technology. We were excited to find out that the customer was a well-known pioneer in mRNA technology – and is now one of the world's foremost vaccine producers. The customer needed help in overcoming the bottleneck of liquid nanoparticle (LNP) encapsulation. We worked intensely in collaboration on this project – the end result being that our IJM (impingement jets mixing) units were used for LNP formulation for COVID-19 vaccines.

Essential encapsulation

mRNA is an extremely fragile molecule and can degrade and break down easily without protection. As its structure contains the instructions to produce the protein required for the therapeutic effect, it is very important that it stays fully intact.

Encapsulation protects the mRNA nucleic acid degradation and helps overcome physiological barriers; in an LNP, the mRNA can enter cells by means of endocytosis. Put simply, mRNA therapies would not work without LNP encapsulation. And because encapsulation is so important, the parameters used in the process must be exact to ensure high efficiency and



Our CEO, Alexandra Knauer, in front of one of our IJM NanoProducer Units – the systems that are being used to produce mRNA coronavirus vaccines

homogenous particle size distribution. In fact, the conditions required to achieve these goals depends on the specific lipid composition and the mRNA strand being used. It's also worth noting that the use of lipids, which can be modified, also shows promise for targeted therapies; for example, lipids modified to favor endocytosis with cells showing cancer markers could be used for targeted cancer therapies.

Our IJM Units use KNAUER's high-precision pumping technology to jet mix mRNA in aqueous solution with a stream of lipids at high velocity. It is inside our IJM that the magic happens – the mRNA is encapsulated in the interior core through electrostatic interactions with the lipids to form LNPs. This nanoparticle structure increases stability in physiological fluids and protects the mRNA from nuclease degradation.

Research accessibility

Our technology showed outstanding performance in the large-scale production of mRNA encapsulated in LNPs for use in COVID-19 vaccines, but what about the small scale? There has been a clear gap in the market for researchers who want to develop new mRNA therapies, so we have launched a new benchtop system for R&D purposes. The IJM NanoScaler is suitable for pre-clinical research on therapeutics

encapsulated in LNPs, including mRNA vaccines and other therapeutics. The system is robust but compact enough to sit on the bench of an R&D lab. It allows for the production of LNP-encapsulated mRNA therapeutics in volumes of several milliliters.

The Nanoscaler has five different impingement jets mixers – allowing researchers to test different process parameters and formulations to perfect their LNP encapsulation. Or customers can implement their own mixing device. Once the optimum operation parameters have been identified, the process can easily be scaled for GMP-production using one of our IJM NanoProducer units.

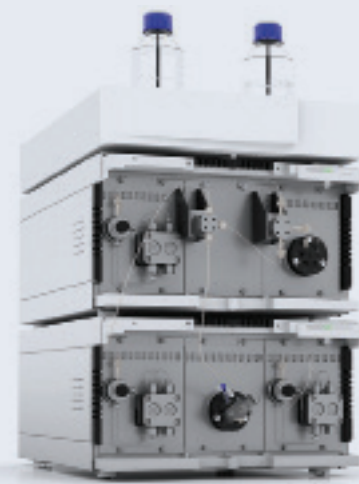
Right now, mRNA is one of the biggest trends in the industry. There is a lot of investment entering the field – and because of that, many research institutions are focusing on mRNA therapeutics. They want to use the best technology for their work, including, of course, our proven IJM technology! Therefore, we downscaled a system from our production technology to create the laboratory-scale IJM NanoScaler, which makes the R&D phase for LNP formulation more accessible to researchers.

The IJM NanoScaler is designed to make the R&D on LNP encapsulation a simpler, faster, and more cost-effective process

as this system allows the use of small mRNA volumes in μL scale. This allows both screening for the best encapsulation conditions and small scale production on the IJM NanoScaler, which can then be scaled up to the g scale using the IJM NanoProduction systems.

By testing formulations and mixing conditions on a smaller benchtop system before large-scale production, money is saved; proof-of-concept testing is able to take place before large-scale investments are made. KNAUER offers the whole range of LNP production equipment from preclinical to cleanroom compatible production scale, allowing reproducible and scalable production of lipid nanoparticle–mRNA formulations.

I said before that I expect mRNA therapeutics to revolutionize medicine – from personalized medicines to the treatment of intractable diseases, such as cancer. KNAUER is extremely excited to have played a part in this revolution so far – and equally excited to supply further forward momentum with our new lab-scale system for the production of new lipid nanoparticle formulations. The future of pharmaceuticals is here.



KNAUER IJM NanoScaler – for research and development on lipid nanoparticle formulation.



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Core Topic Cell & Gene

Of Mice and Men. Did you know CAR-T cells work better in humans than mice? In a recent interview with the Society for Immunotherapy of Cancer, Carl June discussed the long-term efficacy of early CAR T-cell therapies. Two of his first leukemia patients were cancer free a decade later – and actually still engrafted with the CAR-T cells. June and his team had used a mouse hybridoma as a binder to CD-19, and thought that eradicating the leukemia would also eradicate the CARs because they were expressing a mouse protein that they weren't tolerant to. However, this did not prove true. Instead, the team found long-term expression of the autologous T cells that express the mouse anti-CD-19.

CRISPR for your cat? Desperate for a feline friend at home but held back by an allergy? Scientists at InBio may have found your answer. They carried out a study on Fel d 1, the main culprit behind feline allergies. By studying genomes from wild cat species, the researchers found that the genes encoding the protein – whose evolutionary utility remains unknown – are not essential. The researchers also expressed confidence about the amenability of Fel d 1 to gene editing – having used CRISPR/Cas9 to knock out the gene in vitro with up to 55 percent editing efficiency – which would open up the pathway to creating “manmade” hypoallergenic pet cats. Now to discuss the ethics...

ET, Edit, and Edi. Beijing's Edigene has secured a worldwide intellectual property license to “methods and compositions” for disrupting BCL11A expression to increase fetal hemoglobin levels, which scientific evidence suggests could serve as a means to treat faulty hemoglobin production caused by genetic mutations. Edigene obtained the IP from the Boston Children's Hospital, which is located just a few miles away from the company's US office. Edigene CEO Dong Wei said that the license is key to developing ET-01, Edigene's gene therapy for transfusion-dependent β -thalassemia. Chinese regulators granted their first approvals for the therapy, dubbed ET-01, in January 2021.

The Minuscule Reset. “Every cure has a starting point,” begins the mission statement of San Diego's Salk Institute. Now, scientists at the Institute have successfully used a cell therapy in mice to mitigate the great middle-and-end problem of life: aging. The treatment used four reprogramming molecules known as Yamanaka factors to counter signs of aging, increase lifespan, and accelerate muscle regeneration. The Yamanaka factors were able to do this by resetting the mice cells' age-induced epigenetic markers to their original, pre-aging patterns. The research was conducted in collaboration with Roche's Genentech, and supported by two Spanish institutions.

IN OTHER NEWS

Sangamo doses first patient in phase I/II trial of CAR-Treg cell therapy for kidney transplants; hopes to reduce need for lifelong immunosuppressive medications

Intelligence Squared live debate on gene editing babies sees mixture of sensible and bizarre arguments produce winning share of votes for the anti-edited-baby contingent

Gel for delivering engineered herpes virus gene therapy via skin helps cure wounds of “butterfly children” with rare inherited disease epidermolysis bullosa

Scientists at Sidi Chen's Yale lab “supercharge” T cells by scanning the genome of CD8 T cells for genes with the potential to boost the cells' cancer-killing capacities

EMA grants Advanced Therapy Medicinal Product classification to CELTIC-19, Ixaka's CAR T lentiviral vector treatment for CD19 hematological malignancies

Champions of Cell and Gene Therapy

How could the spotlight on mRNA impact the cell and gene field?

In our ongoing series, we give our cell and gene therapy champions the opportunity to answer a question on a hot topic. This time, given the rocket-like rise of mRNA, we asked how the new spotlight on mRNA could impact the cell and gene field.

Tommy Duncan of Touchlight says:

As a DNA manufacturer, we support a wide variety of technologies that make use of DNA across the genetic medicine spectrum. In the last five years, we have seen the rise of viral vector-based gene and cell therapy, with demand continuing to grow dramatically. COVID-19 has also driven a spectacular rise in the use of mRNA technologies for vaccination. The commercial validation of mRNA vaccine strategies has, in turn, triggered wider changes.

We are experiencing a marked increase in the use of mRNA to deliver genome editing reagents both ex vivo (mRNAs encoding nucleases for editing primary cell cultures) and in vivo (LNP-formulated mRNA-encoded nucleases delivered intravenously). The simplicity of manufacture and delivery combined with high protein expression is clearly opening doors for the genome editing industry. Additionally, the flexibility of mRNA as a technology offers opportunities to deliver complex payloads. Versameb, for example, is deploying mRNA technology to deliver multiple therapeutic proteins encoded on a single mRNA, enabling more nuanced strategies for targeting disease.



Tommy Duncan

Anis H Khimani of PerkinElmer says:

The transient message bearer has been in the limelight over the past decade. It served as a candidate vaccine template during the COVID-19 pandemic, with two of the multiple leading vaccine manufacturers (Moderna and Pfizer-BioNTech) using RNA encoding of the SARS-CoV-2 spike protein as a powerful immunogen to elicit an immune response against the virus.

Advances in the study of mRNA structure, target activity, packaging, and delivery have opened up multiple new therapeutic approaches. The corrected and modified mRNA delivery into cells to generate normal or immunomodulatory proteins not only has the potential of being used in



Anis H Khimani

Chelsea Pratt



vaccines against infectious diseases and other chronic disorders, but also offers the option of treating disorders such as cancer via cell therapy. Furthermore, gene editing functionality can also be delivered via mRNA encoding an enzyme, Cas9, to facilitate targeted corrections at the genome level to treat inherited diseases. Conversely, abnormal mRNA can be shut down by silencing RNA designed to block the message and inhibit abnormal protein expression responsible for a disease state.

In cell and gene therapy, the advantages of mRNA far outweigh those of DNA. Transfected mRNA in a cell localizes within the cytoplasm, which enables immediate and efficient expression. In addition, mRNA-based expression for gene correction or cell modulation

is safer since it does not integrate into genomic DNA, eliminating the risk of mutagenesis. Hence, the recent evolution of nucleic acid-based modalities, such as mRNA, evaluation of their stability, and packaging that leverages various vector designs have empowered cell and gene therapy approaches and continue to advance this novel frontier of therapeutics.

Chelsea Pratt of Bio-Rad says:

The coordinated effort of governments around the world to curb the impact of the COVID-19 pandemic brought about the largest vaccination campaign in modern history, with over 11.3 billion vaccine doses already administered around the globe.

Data is what propels scientific progress. While the pandemic brought about grim and unprecedented times, one upside we've seen over the last two years has been ample data on biodistribution and persistence, which has advanced our understanding of mRNA technology. Compared with viral vector-based vaccines (Oxford-AstraZeneca and Janssen), COVID-19 mRNA vaccines (Moderna and Pfizer-BioNTech) were more cost effective, easier to manufacture, and had fewer severe systemic side effects. This triple success reignited commercial interest in the development of mRNA-mediated therapies for genetic disorders and malignancies.

The key challenge to using mRNA-mediated therapeutics extensively across the cell and gene therapy field is how to ensure these particles reach the targeted cell type while prolonging efficacy and maintaining safety. Studies using mRNA-based therapeutics to treat genetic disorders, such as cystic fibrosis, have shown great promise and have brought us significantly closer to achieving effective delivery and producing proteins for days or weeks at a time. This technology has opened the door for additional treatments beyond infectious diseases and helped increase the already-bright spotlight on the cell and gene therapy field.

Applying lessons from recent developments in mRNA will empower cell and gene researchers to progress effective and affordable treatments for a multitude of diseases.

Want to vote on the question that will be featured in our next issue? Sign up for our Cell and Gene newsletter on our website

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Core Topic Bioprocessing

Ending high insulin prices. Civica Rx says it is planning to manufacture three biosimilar insulins (glargine, lispro, and aspart) that will be sold at a recommended price of no more than \$30 per vial, and no more than \$55 for a box of five pen cartridges. It expects the first insulin dose to be available in 2024. In a statement, Martin VanTrieste, President and CEO of Civica Rx, said, “More than 8 million Americans rely on insulin to live, but many can’t afford to take the amount they need because of the historically high and prohibitive cost of insulin. We know that to really solve the insulin cost and access challenges so many Americans face, we need a process – from manufacturing to setting a transparent price – that ultimately lowers the cost of the drug for those living with diabetes.”

Plant power. Researchers from Lumen Bioscience have used genetic engineering to turn spirulina (an algae) into a biomanufacturing platform for producing biologic drugs, which can be delivered orally. The company has developed large-scale cultivation and processing methods, and says it is interested in pursuing the work for campylobacter infection, which is a major cause of infant death in developing countries. The work has been published in *Nature Biotechnology* (BW Jester et al., *Nature Biotechnology*, 2022).

Expansion bonanza. A number of companies have announced expansion plans recently. As part of a \$1.5 billion global expansion plan, Cytiva is getting a new 11,000 square meter site in Cardiff, UK, for the manufacture of single use bioprocessing technologies, including mixer bags, flow kits, and tubing assemblies. In France, Catalent has completed a \$30-million project that will transform its Limoges site into a center of excellence for biopharmaceutical development, drug product fill-finish services, and packaging. In other facility news, Amgen has broken ground on new manufacturing facility in Holly Springs, North Carolina; facility due to be operational in 2025

News at the FDA. The FDA has updated its guidance around Emergency Use Authorization for COVID-19 vaccines, including recommendations for data and information needed to support authorization. The guidance replaces previously issued guidance in May 2021 and covers areas such as Clinical Trials, Vaccines and Related Biological Products Advisory Committee meetings and how the agency authorizes vaccines. In other FDA-related news, the agency has put in its budget request for fiscal year 2023. The agency is requesting \$8.4 billion – an increase of almost 34% compared with 2022.

IN OTHER NEWS

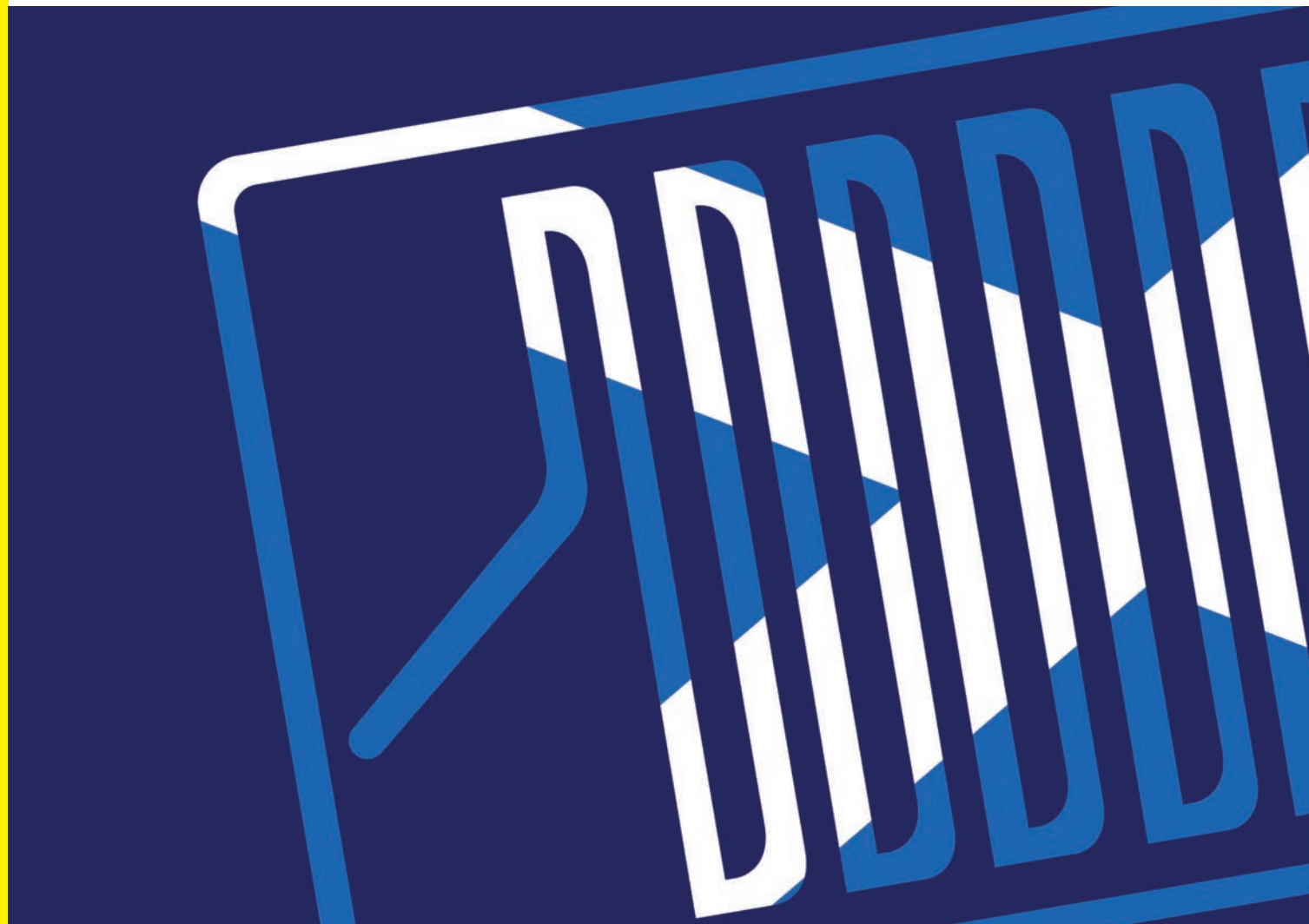
ten23 health expands sterile drug product manufacturing site and adds 1000 square meters of clean room space in Visp, Switzerland

Eli Lilly receives FDA Complete Response Letter for sintilimab recommending additional clinical study

G-CON's off-the-shelf standardPOD cleanrooms are now available in Europe for delivery in 3 months or less; range comprises six PODs and three different dimensions

Scientific Bioprocessing and BioMADE provides free bioprocessing equipment to community and technical colleges through SBBI Digitally Simplified Bioprocessing Fellowship

ILC Dover launches single use bioprocessing bags; company also planning to expand offerings of sterile liquids and pre-filled and non pre-filled powders



uBioprocess

A microfluidics-based separation technology aims to overcome common issues in biomanufacturing

By Angus Stewart

A Scotland-based company is preparing to commercialize a microfluidics-based separation technology that provides a low-shear flow regime to help preserve cell integrity. The young enterprise, uFraction8, was founded by engineering expert Brian Miller and multi-award-winning scientist Monika Tomecka.

Their aim is to target monoclonal antibody viral vector production, and potentially even cell and gene therapy processing.

According to Tomecka, the harvesting of cells from bioreactor systems is currently underserved by existing filtration, flocculation, and centrifugation technologies. She explains, “Filters clog frequently and require labor-intensive cleaning and maintenance. Flocculants are expensive, often inedible/toxic, and complicate downstream extraction processes, which limits their utility. Centrifuges are highly effective, but are incredibly energy-intensive. In addition to these direct cost

considerations, product recovery is also affected by these technologies, which can, on average, destroy 5–15 percent of the total yield.”

The uFraction8 technology has low-shear forces acting on the cells while being processed, and the company has independently validated results from the National Physical Laboratory that show no detectable changes to the viability or reproduction capabilities of CHO and HEK cells that pass through the instrument. “This should translate into a scalable stem cell separation system that won’t induce unwanted differentiation during processing,” says Tomecka.

One common challenge with

“One common challenge with microfluidics, however, is scale up.”

typically hundreds of times larger than a pore. “Early studies suggest that even over extended operation, our systems maintain 100 percent permeability to target proteins,” she says. “This could boost yields by up to 8 percent from identical titers of culture.”

The improved efficiency of the technology could also offer knock-on benefits in sustainability. In fact, Tomecka and Miller had this in mind from the start. “The reduction in energy requirements and options for sustainable land and energy use that our technology offers falls in line with several UN sustainable development goals,” says Tomecka. “But efficiency savings also cash out economically. In the past, several bio-manufacturing companies have gone bankrupt due to the problems with unfavorable techno-economics of their production. In part, this was caused by the cost of downstream processing. uFraction8’s technology will tip that balance, making bio-manufacture profitable and opening new possibilities in the space.”

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2. B Miller, “Cascading and Parallelising Curvilinear Inertial Focusing Systems for High Volume, Wide Size Distribution, Separation and Concentration of Particles”. *Sci Rep*, (2016). DOI: 10.1038/srep36386

microfluidics, however, is scale-up. By multiplexing microchannels into device arrays (1), Tomecka says that uFraction8’s scale-up should be straightforward, since the technology can distribute flow equally to ensure that each device in the array functions the same way (2). “This capability allows scientists to expand their drug development processes from the lab to full-scale production without any changes in technology, unlike most other options currently on the market,” she explains. “This could also lead to faster translation from the discovery phase to drug manufacturing.”

Tomecka adds that the technology can overcome certain problems inherent in

existing mAb and protein production, such as the gradual decline in permeability of porous-based separation systems over time, which leads to yield losses. “This problem derives primarily from the adherence of proteins to the inner surfaces of pores and gets steadily worse over the duration of operation. This is especially relevant in continuous perfusion-based production systems,” she notes.

Because the uFraction8 technology works with open microfluidics channels and hydrodynamic flow effects, protein adherence is unlikely to greatly affect the performance of their systems. According to Dr Tomecka, the smallest aperture of uFraction8’s systems is

Welcome to the Microbe Factory

How can smaller companies navigate scale up and complexity in microbial biomanufacturing?

By Axel Erler, Director of Commercial Development at Lonza

With an increased focus on smaller next-generation biologics, such as antibody mimetics, novel scaffolds, and vaccines, interest is shifting back to microbial biomanufacturing as an effective and cost-efficient platform. But the arena of microbial biomanufacturing comprises technical requirements that increase the already inherent complexity of biologic drug development. Unlike mammalian cell culture (where platform processes are routinely used), microbial manufacturing requires customized processes tailored to the characteristics of the specific molecule, leading to variations in product titer and yield.

Though microbial biomanufacturing can potentially reduce development timelines and costs, it also presents significant challenges. There is a growing number of small biotechs that choose to see their project through to market on their own to reap a larger ROI. However, with limited experience in late clinical and commercial project planning, limited understanding about the intricacies of planning (such as BLA filing), and little experience in scaling up from lab-scale process to commercialized production, these companies can run into many challenges.

It's important for a biotech to focus on early planning of process scale-up and BLA activities to maximize the chances of success. After all, in an increasingly competitive and faster-to-market landscape, it is critical to avoid delays by securing a right-first-time (RFT) approach.

Smaller biotechs sometimes think they need to finalize their chemistry, manufacturing, controls (CMC) activities and launch strategy before they engage a prospective manufacturing partner. However, a CDMO familiar with microbial-derived molecules often does not need the entirety of this information to begin planning for commercialization. A CDMO can also offer invaluable process and manufacturing insight. During scale up, issues not present at the clinical scale can emerge (steps like chromatography fractionations and protein refolding are notoriously difficult to scale). A good expert can look at a process as early as phase I and identify opportunities that may increase titer/yield, process robustness, and development speed.

It also goes without saying that quality by design (QbD) should be kept in mind.

In my view, combining manufacturing

experience with design of experiment approaches and automation facilitates the application of QbD principles. By establishing operating ranges during process characterization using design of experiments, you can increase process design space and, as a result, introduce optimization opportunities that will prevent BLA filing changes later.

Some companies develop unit operations suitable for R&D scale which may not be suited for large-scale manufacturing. Unoptimized processes with regard to raw material use (for example, expensive resins and membranes) will also add to the cost of goods. Early discussions and thought should go into the selection and combination of media/feeds and unit operations, including choices of membranes and resins. Operational limits of the anticipated large-scale manufacturing asset (for example, available column sizes, membrane holders, tank volumes, buffer prep capacities) must also be considered. Though some limitations can be solved with a capital investment, others may require partial or even sizable process adjustments to fit the anticipated manufacturing asset. And that can be particularly problematic when discovered too late and when the budget is no longer available.

Emerging and small biotechs are the engine for innovation. To help bring their innovations to market, they should consider collaborating with partners with commercial expertise who can provide insights on a scale-up and BLA strategy. Engaging a good partner, especially early in phase I, means the design of the strategy will be tailored to the specific product, process timeline, and risk tolerance without compromising RFT. And the more successful biotechs there are, the better public health becomes.





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The Pandemic Impact: Focusing on Security of Supply

Cytiva is transforming in the wake of COVID-19 – but what lessons can the wider biopharma industry take forward?

At the end of 2019, when information began to emerge about clusters of a novel coronavirus in Wuhan, China, many were complacent about the risks – and no one predicted the intense global disruption that would occur. But despite lockdowns and fragile supply chains, the biopharma industry rose admirably to the job of developing new vaccines and therapeutics. Companies have implemented new technologies, such as mRNA platform approaches, and embraced digital transformation. The manufacturing ramp up and increase in capacity has been nothing short of remarkable – especially when considering that vaccine manufacturing is complex, requiring specific know-how and equipment.

However, unplanned spikes in demand for raw materials, packaging, equipment, and consumables has resulted in supply chain disruptions to biopharmaceutical manufacturers. The need to manufacture COVID-19 vaccines and therapeutics, quickly and at-scale, has far reaching implications on wider biopharma manufacturers. And that intense pressure would have a serious impact on the production of essential medicines, if supply allocation and communication were executed poorly. In some cases, disruption continues today, with shortages in critical raw materials, such as polymers and microchip parts, affecting not just the biopharma industry but other industries as well. To ensure input supplies for current and predicted manufacturing

capacity, short-, medium- and long-term solutions are needed.

Jon Van Pelt, General Manager, BioProcess Single Use & Enterprise Solutions at Cytiva, believes that suppliers have an important role to play in addressing the challenges. Cytiva, for example, has been working on well-thoughtout supply allocation and communication principles throughout the pandemic to ensure continuous supply of raw materials and technologies to its customers – enabling them to continue to produce life-saving drugs and vaccines. We caught up with Van Pelt to find out how Cytiva is making supply chains more reliant and embracing digital transformation to benefit customers.

What is your background at Cytiva?

I've been in the biopharma industry since 2015. Originally, I was the Americas Commercial Operations Leader at Cytiva, but I then transitioned into general management of our Enterprise Solutions business in 2016. In 2019, my responsibilities expanded further to include our single use technologies portfolio.

How has the COVID-19 pandemic affected the industry? Are there any silver linings?

I think everyone reading this is familiar with the material and supply chain constraints that have affected most industries throughout the pandemic. For biopharma, this has forced the industry to rethink the definition of supply chain flexibility and resiliency – and I suppose that can be considered a silver lining. First, being flexible; the industry had to find new ways to adapt because it was tasked with supplying important vaccines and other medicines. In addition to supporting the rapid development and deployment of COVID-19 vaccines and therapeutics, the industry is moving quickly to add the necessary capacity to support long-term growth in other areas. For resiliency, decentralizing supply chains has benefited the industry and product/raw

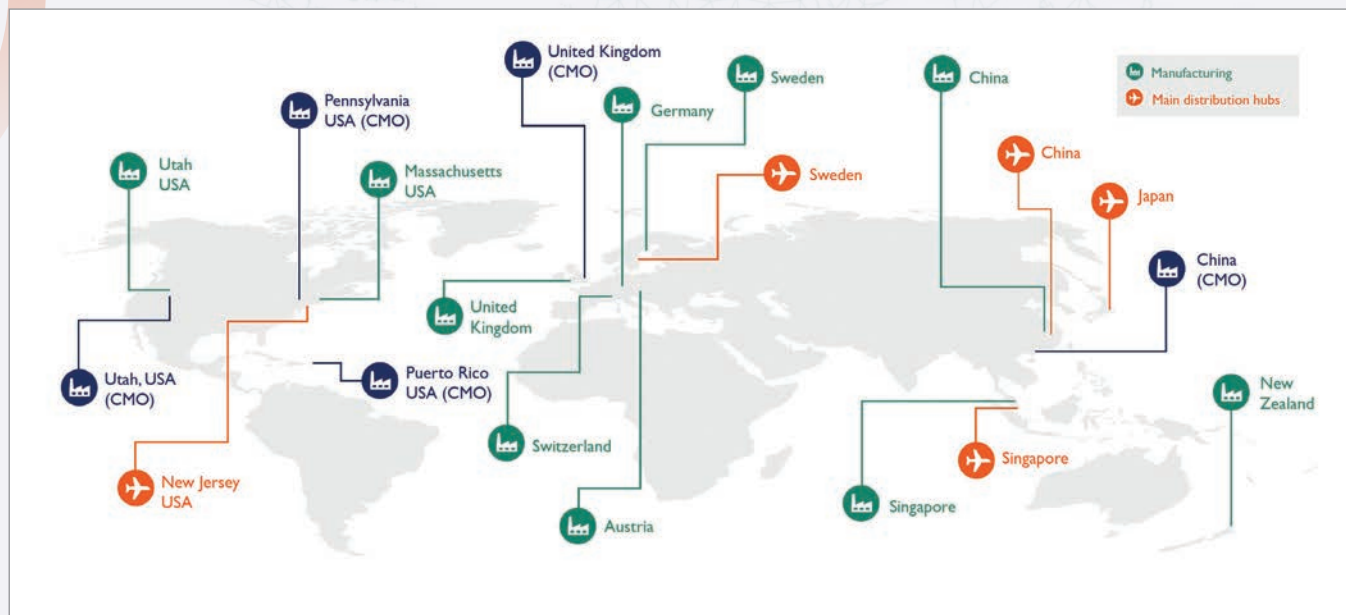
material interchangeability has started to gain attention among the industry – fitting well with the implementation of ICH Q12 by major economies.

Has the pandemic affected specific supply chains? And is disruption still being seen today?

The demand for single use hardware and consumables experienced unparalleled growth in 2020 and 2021. Manufacturing capacity, labor shortages, and material availability have all contributed to industry disruption and longer lead times. Overall, I think the industry's supply chain is becoming more resilient. For example, at Cytiva, we're working very closely with customers and suppliers to build more security of supply in our manufacturing network. In some parts of the industry, there are still disruptions due to shortages of certain materials, but I feel that Cytiva's supply chain is stronger now more than ever before because of the investments we've made globally. Cytiva was able to quickly ramp out the production capacity of single use assemblies in China to meet the demand of customers in the Asia region – with many of them manufacturing COVID-19 vaccines for COVAXX.

Have you noticed any emerging trends in collaborations or customer relationships throughout the pandemic? In our experience, customers have been very flexible and adaptive throughout the pandemic. Given the supply challenges and material constraints, they have partnered with us to provide a more granular view of their product needs. And that enhanced demand signal has allowed us to lessen the disruption in the industry.

Customers have also been very supportive in qualifying new manufacturing sites and new vendors. The security of supply is improving dramatically, and we are working very hard to partner with customers to provide high quality products from an expanded supply base.



Digital transformation has been accelerated during the pandemic because of increased demand and the need for efficiency. What action is Cytiva taking in this area?

Like so many other industries, there is much to be learned and applied by capturing and analyzing process data. With the right digital tools, we can help our customers optimize the performance of their equipment and eliminate unwanted variation between batches. Cytiva's Integrated Process Development platform, for instance, enables customers to quickly optimize and scale their operations. The pandemic has made on-site customer supports difficult. We have deployed a custom Computational Fluid Dynamics (CFD) tool, without charge, to address customers' manufacturing deviation issues and bioreactor scale up challenges. And our bioreactor scaler tool helps customers efficiently scale their processes up or down. Understanding the importance of educating our customers on our equipment design and operation principle, Cytiva moved very quickly to implement virtual Factory Acceptance Test (FAT) during the early days of the pandemic, ensuring no customer would miss out on learning

opportunities. These are just a few examples of how we're driving digital solutions within the industry.

How else is Cytiva reacting to the pandemic to better support customers? And what other trends do you foresee in the industry – such as regional organization and future capacity planning?

Cytiva's supply base has expanded rapidly to support broader "in region – for region" supply capabilities – and this has also enhanced our near- and long-term security of supply position for customers.

I'd also like to highlight the fact that Cytiva is leading several key initiatives in sustainability. Our mission of advancing and accelerating therapeutics is our "north star", but we also have a plan and strategy to deliver on our impacts for people and our planet and grow in the process, which very much aligns with the United Nations' Sustainability Development Goal. Our sustainability plan is a strategic intention focusing on designing sustainability into our policies, processes, and collaborations across the value chain with measurable targets on value creation to our customers, society, the environment and our associates.

Supply chain resilience is just one lesson that can be learned from the pandemic. What other lessons have been learned in terms of improved processes and efficiency in biomanufacturing?

The biopharma industry is notorious for requiring (or demanding) high levels of customization in hardware and consumables. However, as we partner with our customers, we're finding unique opportunities to drive more configured solutions, which will drive more scale and efficiency while reducing lead times.

Overall, I think the biopharma industry has learned many lessons from the pandemic. The industry has been becoming increasingly reliant on global supply chains over many years – driven by cost efficiencies through economies of scale. COVID-19 didn't necessarily create supply chain challenges, but rather highlighted the need to reevaluate operational strategies and more effective collaboration. For example, better supply chain design for suppliers, and increased regional production while securing stronger networks with raw material suppliers globally to enhance security of supply. The industry should collaborate on efficient supply chain information sharing while leveraging other industries' best practices, and evaluation of sustainable materials to mitigate the risk from scarcity of natural resources.



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Nitrosamine Testing Solutions

The presence of the nitrosamine, N-nitrosodimethylamine (NDMA), in certain sartan API's has resulted in several regulatory warnings and recall of contaminated products. Concerns over the presence of this class of genotoxins has now widened to include other medicines such as the well-known diabetes drug, Metformin. The US Food & Drug Administration (USFDA) and European Medicines Agency (EMA) have responded by publishing documents for the pharmaceutical industry that address requirements and limits related to nitrosamine contaminants. Pharmaceutical Manufacturers are now taking a pro active approach to risk assessment and mitigation of genotoxic contaminants within global pharmaceutical supply chains. Central to these activities is a coordinated analytical capability to identify and quantify contaminants across global geographies and regulatory zones.

Why use SGS

SGS Health Science has considerable expertise in the method development of nitrosamine determination in pharmaceutical products. SGS has established a specific method for NDMA which can be applied to various different matrices. Alternatively, a platform method, based on trace-level detection by LC-MSMS, is also available and provides rapid and simultaneous determination of up to ten different, targeted nitrosamines. Although with more limited application, the SGS network is also able to support specialist methodologies such as GC-MSMS. Our experience in optimizing extraction allows application of these methods to drug products, API's, and raw materials.

By establishing these nitrosamine methods within centers of expertise across a global laboratory network, SGS can provide an unrivalled service offering that incorporates a harmonized methodological approach together with flexible management of capacity and capability requirements. SGS offers a variety of partnership models and can collaborate in such testing programs using fee-for-service to outsourced staffing models all exploiting resources of the SGS network.

About SGS

SGS is the world's leading inspection, verification, testing and certification company. We are recognized as the global benchmark for quality and integrity. With more than 96,000 employees, we operate a network of more than 2,600 offices and laboratories around the world. Our conveniently located network of laboratories and clinical trial facilities offer an array of integrated services and expertise, providing you with the knowledge, flexibility and ability to scale.

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- Size and diverse testing capabilities matching biologics and small molecules needs
- International network across America, Europe and Asia-Pacific

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WHEN YOU NEED TO BE SURE





Core Topic Small Molecule Manufacture

Animal-free testing. EFPIA has issued a statement outlining its intention to support the reduced use of animal testing. The body has partnered with ECHA and the European Chemical Agency to collect the data held by pharmaceutical companies that will help optimize the industry's understanding of structural activity relationships. The group has invited companies to share physicochemical, toxicological, and ecotoxicological data that are no longer of economic value to them.

Digital designed drugs. AI-driven company, Iktos is collaborating with Teijin Pharma to develop new small molecule drugs using Makya, its computer aided drug design technology. The drug platform automatically designs candidates, which the company claims will bring "efficiency" to R&D processes by speeding up molecule identification while helping to ensure their safety and potency. Teijin plans to use the identification tool to address bone, joint, rehabilitation, neurology, respiratory, cardiovascular, and metabolic diseases. Iktos is also developing an additional platform, Spaya, which it intends to use for retrosynthesis to further optimize drug development.

A tactical approach. The EMA, in collaboration with the European Commission and the Heads of Medicines Agencies, has issued initial advice for sponsors on managing the impact of the war in Ukraine on clinical trials. Where possible, sponsors are advised to "use the experience gained during the COVID-19 pandemic and apply the approaches and flexibilities agreed in this context." The Clinical Trials Coordination Group is developing further recommendations for sponsors

New and improved. Almac Sciences, has announced that it has invested £500,000 to improve its analytical services. The cash will be used to acquire NMR instrumentation – a step the team believes will help them adhere to regulatory requirements. The investment will support the purchase of two pieces of equipment – a high resolution instrument to aid in the characterization of small molecules and a 500MHz NMR system to provide an additional layer of security particularly when faced with urgent analyses. In a statement, the company's Analytical Manager said, "The additional NMR technology installation in our cGMP lab allows increased security, flexibility, and capacity enabling us to provide an enhanced service to our clients."

IN OTHER NEWS

Akebia strikes off more than 40 percent of its workforce after FDA rejects its anti-anemia drug, vadadustat

AMR Action Fund announces first round of investment in companies steering antimicrobial drug development

US Pharmacopeia releases findings on API distribution and risk factors, with hopes that it will trigger policy reform

Researchers at Ecole Polytechnique Fédérale de Lausanne develop chemical library that relies on FAIR principles (findable, accessible, interoperable, and re-usable) to enable optimized experimentation and minimize trial and error in R&D

Opening the floor to questions on naloxone use, FDA discussed with pharmaceutical stakeholders how the drug could help minimize opioid-related overdoses and deaths

“We Want to Return to the Lab”

How the Russian invasion has disrupted drug discovery in Ukraine



On March 3, we spoke to Ed Griffen of UK AstraZeneca spinoff MedChemica about his company's partnership with their Kyiv-based partner Enamine. The full article is available online (<https://bit.ly/tmm-ena>). Here is a snapshot of the discussion, which also includes more recent remarks from Enamine's Principal Scientist, Oleksandr Grygorenko.

Are your colleagues at Enamine safe?

EG: Prior to the crisis we traded emails daily. Much of these communications have halted, but they have told me that they want to return to their labs ASAP. In the meantime, they want us to tell their story.



OG: Nearly all our chemists are indeed very eager to return to the labs. Some people have joined territorial defense forces, others are helping volunteers; many evacuated to a safer place in Ukraine or abroad.

What were Enamine and MedChemica collaborating on?

EG: We've worked on DNDi's COVID Moonshot for two years straight. As the invasion hit, we were due to meet one of our key milestones. Our colleagues at Enamine cannot join us to celebrate – and that feels awful.

More broadly, how does the war in Ukraine affect pharma?

EG: Put simply: a great deal of very early stage research is done in Ukraine, particularly in chemistry. This conflict won't cause delays to the shipment of medicines, but it will disrupt the supply chain of intermediates for people doing discovery work.

On one hand, that disruption will be managed. In the short term, we can cope with it. But in the longer term, it is extremely frustrating – not to mention upsetting.

Do you expect the situation to worsen?

EG: I choose to be hopeful, but regardless, I am preparing for it to get worse. We have to carry on, COVID isn't stopping just because of the heartbreaking situation in Ukraine.

OG: I do fear possible further escalation and brutality from the Russians that are being cornered – but I am sure the overall situation will soon improve.

Done Deal: Creating Anti- COVID-19 Equity

An industry agreement could help bring affordable COVID-19 treatments to low- and middle-income countries

Though COVID-19 restrictions are relaxing in many parts of the world, there are still people – particularly in developing countries – who are waiting for appropriate interventions against the disease. Helping to ensure medical equity for the 53 percent of people living in low- and middle-income countries, the Medicines Patent Pool

(MPP) has secured a sublicensing agreement with Pfizer that will help an anti-COVID-19 small molecule cocktail reach patients.

The sublicensing deal will allow 36 international generic drug developers to manufacture the raw materials necessary to develop Pfizer's protease inhibiting drug, nirmatrelvir. It will also enable them to copackage the much-needed intervention with ritonavir, which has historically been used to treat HIV but has demonstrated anti-COVID-19 activity.

"We have established a comprehensive strategy in partnership with worldwide governments, international global health leaders, and global manufacturers to help ensure access to our oral COVID-19 treatment for patients in need around the world," said Albert

Bourla, Chairman and Chief Executive Officer at Pfizer in a statement. Pfizer will not take royalties from the low-income countries participating in the scheme. Middle- and high-income countries will pay royalties of 5 and 10 percent, respectively.

Manufacturers from 13 countries will participate in the deal, with Ukrainian company, Darnista, being the latest to sign the agreement. Speaking about the new sublicense, Charles Gore, Executive Director of the MPP said, "We are delighted that Darnitsa has felt able to sign a sublicense agreement with us at such a challenging time. This is the first time we have granted a sublicense to a Ukrainian company and is part of our commitment to ensure as wide a geographically dispersed manufacturing base as possible."



Your guide today, tomorrow,
and for the future

Bridging the Gap

Quality Assured: How PCI Pharma Services helps to bring life-changing therapies to patients

By Rob Frater and Arthur Stevenson,
PCI Pharma Services (Hay-on-Wye, UK)

PCI is a CDMO with global presence. Our services include lyophilization and sterile fill-finish manufacturing; the development, clinical and commercial manufacture of high-potent and non-potent drug products, including solid oral, liquid and semi-solid medicines; clinical trial supply services including packaging, labelling, storage and distribution; and finally, complete commercial packaging solutions and launch capabilities. This fully integrated offering

positions us as a true end-to-end supply chain partner, able to work with clients to deliver their drug products to patients anywhere in the world.

CDMOs play an essential role in the pharmaceutical industry, supporting companies to deliver products to patients swiftly and efficiently. Moreover, PCI's flexibility and agility ensures we are well positioned to assist with any number of challenges that may arise. Biopharmaceutical drug development remains a key trend, demanding specific expertise and capabilities when it comes to Quality Assurance.

PCI has been focused on becoming a trusted CDMO partner by building strong working relationships with our clients, providing high quality on-time in-full (OTIF) services and the bespoke packaging solutions needed to meet

often unique requirements. At the heart of that relationship lies effective communication as well as understanding that customers need their products to be produced at the right time, and of the right quality.

As a CDMO, we must provide consistency in approach, reliability in service, flexibility in meeting the varied nature of requirements, and true expertise in the areas contracted to us. A strong focus on identifying any issues

Meet the Authors

Rob Frater: Laboratory Manager

I have worked at the Hay-on-Wye facility for nearly six years totalling 28 years' experience in the industry where I started out as an analytical chemist. Today I am responsible for the day-to-day lab operations, as well as managing the planning, execution, and delivery of specific client projects. I believe that the growth in biopharmaceuticals and large molecule R&D presents an interesting area of focus from an analytical perspective. Product testing is significantly different from traditional small molecule work, with challenges in terms of learning about new techniques (such as capillary electrophoresis), new applications of traditional techniques (such as liquid chromatography), and the

nuances of sample handling. There are also unique challenges when it comes to biosimilar products and as such, it is a very rewarding field to work in.

Another field that interests me is the use of pre-filled syringes (PFS) and auto-injector (AI) dosage formats, and the requirements to test the functionality of such devices. Tests such as break/glide force on PFS or injection time for AIs are again a departure from typical oral dose format testing.

Arthur Stevenson: QP Services Manager, Qualified Person

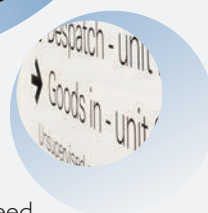
I have worked in the pharmaceutical industry for over 20 years, starting in QC laboratories and then moving into Quality Assurance, becoming a Qualified Person in 2014. I'm familiar with many areas of the industry, including traditional small molecule manufacturing, but as

my university degree had a heavy focus on biology, biopharma manufacturing interests me at a more fundamental level.

There are many areas working at PCI that excite me but specifically I get a lot of satisfaction working directly with clients and supporting them to get their products to market or clinic as efficiently as possible, or resolving their supply chain/compliance challenges.

Biotech and biological products have a huge role in meeting unmet patient needs by delivering life changing medications, and it is exciting to be part of that at PCI.

Both authors are based at PCI Hay-on-Wye, a commercial packaging Centre of Excellence specializing in cold chain, biologics and high potent packaging operations. The site also provides a number of support functions, including QP services, serialization, clinical trial support, analytical testing, and stability services.



and pursuing corrective and preventive action (CAPA) in a timely manner is also of core importance. Never should a CDMO's skill set ever be in doubt, and everything we do should be underpinned by a robust quality framework and an understanding of the challenges specific to our customers' products.

Four trends that matter in biopharmaceuticals

Right now, we are noticing four areas in biologics that appear to be major talking points for our customers, which means they're also of fundamental importance to PCI.

First, there is emphasis on the development and validation of cold chain packaging processes. As has been demonstrated with the supply of vaccines during the pandemic, it's clear that robust cold chain management is vital. During packaging, there must be appropriate processes in place for controlling time-out-of refrigeration, and effective controls for handling materials and the associated risks. Customers also need packaging

designs that maximize shelf-life and protect the product throughout the cold chain supply cycle. PCI is investing heavily in its facility in Hay-on-Wye, increasing cold-chain storage to meet the growing needs of the industry.

Second, we are seeing more interest in packaging design, with a focus on flexibility and agility, particularly for clinical trial supplies. Commercial market demands are also a major influence, and there really isn't a one-size-fits all approach. Being able to think creatively as a solutions provider is therefore critical in this area.

Third, we are seeing demand from customers for a wide range of batch sizes, from small-scale clinical batches of a few packs (typically packed by hand) up to fully-automated, large-scale commercial packing runs. Having the flexibility and capability to provide all solutions whatever the scale vastly enhances the level of bespoke service that can be offered to clients.

Fourth, there is more recognition that method transfer management is crucial when it comes to outsourcing. Again, PCI is well accustomed to method transfer – proven time and again as new clients and projects are on-boarded, and we are trusted to support their analytical needs. However, managing biopharmaceutical method transfer can create some specific challenges. The need for advanced analytical instruments and techniques means that some testing might need to be outsourced; in such cases, PCI will work to facilitate and manage transfers between a client-contracted lab on one side and a PCI-contracted lab on the other.

With any method transfer, it's important to quickly build up a solid understanding. We do this through research and by asking subject

matter experts the right questions about the principles underlying unfamiliar techniques, including a deep dive into the critical parameters and how they may be influenced. Even where testing is on more familiar ground, such as with HPLC-based techniques, the subtleties and nuances of sample handling have to be understood and considered; even using the wrong type of HPLC vial can impact the results.

An eye on the next need

PCI is constantly monitoring the landscape to ensure that we adapt and evolve to meet customer needs, whether this be through enhancing our services, increasing cold-chain storage, adding grade-D classified packaging rooms, or investing in new skills and equipment. We also keep a keen eye on new regulations and any region-specific changes that may affect the supply chain. For example, post-Brexit, trading arrangements have unsurprisingly created challenges in the industry. However, PCI's ability to leverage its global network means we have a robust solution: with a significant footprint in the EU, PCI is able to perform QP release upon import. The close working relationship between all sites in our network – particularly between the UK and EU sites – ensures that any challenges posed by Brexit are managed efficiently and effectively without impacting our customers' supply chain.

At PCI, we pride ourselves on maintaining robust and effective customer communications. After all, regular and fluid communication between a customer and their chosen CDMO is essential to ensure a smooth, productive relationship, as well as resolving any issues that arise in real time. We work hard to ensure the CDMO–customer relationship is collaborative and positive which ultimately ensures that we are able to deliver on our mission of being the bridge between life changing therapies and patients.

Top Tips for mRNA Sequencing

mRNA has become a superstar thanks to the success of mRNA-based COVID-19 vaccines, but its importance was known long before the pandemic. Bellal Moghis from the Diagnostics and Genomics Group at Agilent Technologies tells us about the potential of mRNA – and the challenges of working with and analyzing it.

What attention was on mRNA prior to COVID-19?

mRNA has been key to understanding molecular pathways that underlie disease susceptibility or drug response. For this reason, scientists have used techniques such as quantitative real time-polymerase chain reaction (qRT-PCR) to understand how genes are regulated within a molecular pathway, or microarrays to understand how multiple genes are modulated in response to cellular changes. Insights from these experiments have allowed scientists

to develop therapeutics to target faulty gene pathways that lead to disease. Now that high-resolution technologies such as next-generation sequencing are more accessible, mRNA is being considered at the individual sample level, allowing us to realize the benefits of personalized medicine. Most recently, just prior to the COVID-19 pandemic, mRNA was used to increase the clinical utility of diagnostic genetic tests (1). By conducting mRNA sequencing alongside DNA sequencing, some variants of unknown clinical significance can now be elucidated, improving diagnostic yield and aiding treatment.

What are the challenges of analyzing mRNA?

mRNA sequencing has long been a core workflow in many labs; however, it has a unique set of challenges. mRNA degrades significantly faster than DNA, so it is often frozen at -80°C for long-term storage. Before mRNA can be used in a sequencing workflow, its quality must first be assessed using reliable, automated benchtop capillary electrophoresis systems. Because genes are differentially expressed, experimental design is another important consideration to ensure that all genes of interest are detectable and quantified properly, with scientists required to choose between sequencing the global gene expression profile of a sample or enriching certain genes to study them in isolation. Once the samples have been sequenced, the scientist is then tasked with analysis, which can be cumbersome for new users. Luckily, there are several analysis software solutions on the market today that guide users and aid in interpretation.



How are technologies for mRNA sequencing advancing?

Sequencing technologies are becoming more accessible, allowing scientists to leverage large mRNA data sets to aid in clinical and diagnostic research. Though there is much more to be done in understanding how mRNA can provide clearer insights to disease, the information we currently have is already being used in labs across the world to gain more clinical utility from sequencing data. It is my belief that cancer diagnostics and treatment management has advanced significantly from these studies. Today, targeted treatments can be prescribed based on the mRNA profiles of cancer patients – namely, the presence of fusion genes that have been shown to directly cause cancer, such as BCR-ABL fusions found in some types of leukemias. As clinical research scientists continue to make advancements in understanding how mRNA can be used as an effective biomarker for cancers, pharmaceutical companies and molecular diagnostic providers can continue to develop effective diagnostic tools.

What are your top tips and best practices for sequencing mRNA? Although there are many commercially available kits to guide new users through the process of sequencing mRNA, here are a few important considerations:

- As mentioned above, RNA is less stable than DNA, so sample preparation must be handled with care. Decontaminating workspaces during RNA isolation is a critical step to avoid introducing RNase, an ubiquitous enzyme that rapidly degrades RNA, into your sample. Although storage of your RNA will require a -80°C freezer, thawed RNA in use should remain on ice throughout library preparation.

- Assessing the quality of your RNA sample is key to ensure that your time and resources are not wasted preparing a sample that is destined for failure. There are many solutions that can help you understand both the quality and the quantity of your starting material, so take advantage!
- It is important to consider different approaches (either mRNA capture or ribodepletion) based on the quality of your samples. Since mRNA capture typically requires a 3' poly-A tail, mRNAs that are fragmented and missing the 3' poly-A tail may be missed. Ribodepletion, in which the highly abundant ribosomal RNAs are removed from the sample and the remaining mRNA is sequenced, is often considered in these cases.
- Maintaining consistency between sequencing runs is critical for comparing samples run in different batches. Like qPCR experiments, the preparation, sequencing, and analysis of samples should be normalized.

How excited are you at the future potential of mRNA?

The impact of mRNA as a diagnostic tool or, in the case of vaccines, a medicine, will continue to improve outcomes in cancer, genetic disorders, and infectious disease. By quickly producing RNA vaccines in vitro to specific antigen targets, precious time and lives can be saved. The potential of RNA vaccines is immense and in its infancy, but the highly positive results from the COVID-19 vaccines have shown the world what is possible. And, in the future, even more cutting-edge solutions will be available.

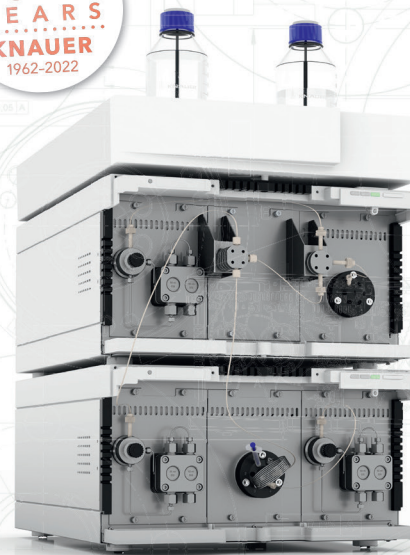
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Industry 4.0: The Invisible Hand

We all know that Industry 4.0 + Pharma = Pharma 4.0 – but are artificial minds and augmented realities changing anything tangible?

By Angus Stewart

Exactly 258 years have passed since the invention of the spinning jenny: the multi-thread device that replaced traditional sewing machines and paved the way for the first industrial revolution. Two and a half tempestuous centuries later, the fourth wave of industry is breaking upon our shores. But what can Industry 4.0's cybernetic toolbox do for pharma in the 2020s and beyond? This is one of the big questions addressed by a new report from CRB Group (1), which breaks down predictions and preoccupations regarding the birth of "Pharma 4.0" and other emerging themes across 105 data-packed pages. To dive a little deeper into the next era of industrial technology, we spoke to CRB's Senior Automation Engineer and Digitalization Lead, Yvonne Duckworth.

If there's an Industry 4.0, what were 1.0, 2.0, and 3.0?

All four stem from what we used to call the industrial revolution. The first industrial revolution saw the entry of machinery into production, and it was powered by coal, steam, and the birth of factories. The second industrial revolution was all about massively scaled-up production, powered by electricity and the assembly

line factories most famously associated with the Ford Motor Company. The third industrial revolution was triggered by the addition of computers and mechanical automation – much of the work I do day-to-day has its roots in this phase.

Today, we're living in the time of the fourth industrial revolution. This term – and the whole idea of there being four big transformative eras – began with a 2018 paper by Klaus Schwab, the founder of the World Economic Forum. His vision of Industry 4.0 is all about connectivity. It marks the arrival of networked digital technologies like smart manufacturing and cyber-physical systems.

Some of the devices driving these capabilities sit right at the cutting edge, while others came into being closer to the turn of the millenium. Under this rather wide umbrella we have robotics, AI, predictive analytics, RFID, the Internet of Things, cybersecurity, 3D printing, and pretty much anything using the cloud.

When a client tells me, "We want to incorporate Pharma 4.0 into our facility," they could be referring to two of the above categories – or all of them. Pharma 4.0, just like Industry 4.0, is rhizomatic – the vision is one of a decentralized network more

easily pinned down by an overarching theme than a neat hierarchical order.

Describe one strong example of Industry 4.0 in action...

One striking example sits just outside Greater Manchester, in the town of Macclesfield – not far down the road from The Medicine Maker's UK headquarters, funnily enough. There, AstraZeneca runs what is known as a "lights out warehouse." Put simply, that means it is fully automated to the point that people do not enter it. Everything within is dimly lit, and closely packed with very narrow aisles. This system leverages robotics to streamline handling, storing and retrieving items in the warehouse, while interconnected to their enterprise resource planning system. To reduce risks of a fire hazard, the oxygen level is set to approximately 14 percent – much too low for human workers. Anyone who does venture inside must be equipped with the appropriate personal protective equipment (PPE) for a low oxygen environment. Perhaps my description of this robotic system sounds a little eerie from our human perspective, but it's also a solid demonstration of what



could be possible industrywide and what is being incorporated where the volume justifies the investment.

Where does pharma sit with Industry 4.0 more broadly?

Uptake has been slow. This is disappointing, but from another point of view it is hardly surprising as the pharmaceutical industry faces strict regulations compared with many other industries. In addition, implementing Pharma 4.0 is not simply a case of gathering all one's desired technologies and switching them on. A more holistic approach is required – one which considers many different aspects including value, cost, and impact to workforce and culture.

First, one needs to understand each particular digital technology on a technical level. Then, one needs to understand what value each technology can offer from an ROI perspective, as well as evaluating what the associated costs are including initial investments as well as any annual recurring costs. Some technologies are more costly than others. Some technologies have varying degrees of impact to the workforce. In some cases such as automated warehouses, one can expect decreases to the workforce. Many can introduce new safety concerns. These are financial, ethical, and technical questions that no responsible company should rush past.

Data is another key piece to the puzzle. AI and integrated systems capable of communicating with each other can generate a huge volume of data. To analyze that data, it may be necessary to hire data scientists or data analysts. Recommendations from these experts may lead to a shift in the culture and structure of the company. Nothing is simple. Even the choice to go paperless has complex implications. Management has to be open to acknowledging these changes, as they must be the ones to implement them at every level – from top to bottom.

Is setup cost a serious hurdle?

As part of my job, I review the applicable technologies, evaluate which ones are best suited to recommend for CRB's clients, and then help estimate the costs. These estimates can be pretty steep, depending on the technologies involved. Larger companies may be able to absorb such costs a little more easily, but the price tags are harder for smaller companies and startups. Often, they will choose to kick the can down the road, waiting for the day when their balance sheets can take the initial hit.

To players like this, I tend to recommend a phased approach. Rather than kicking that can down the road, a company can be smart and set up some of the necessary infrastructure in advance. Then, when more funds are available,

everything is ready for the next steps in implementing Pharma 4.0.

Did the exodus into the internet during lockdown change the game? During lockdown, we all became more virtual professionals, and that did make a difference. One example from my own work springs to mind; CRB had a client with a process equipment skid that was ready for a time-critical factory acceptance test. Under the “normal” circumstances of the past, our client would travel (often fly) to the on-site location of that equipment, and test it in person.

This time, our client was in a hurry. Travel restrictions had just come into place, so the usual fly-and-test routine wasn't an option. It was at this point that they reached out to CRB for help. In response, we sent our client one of Microsoft's HoloLens headsets, and worked with them to carry out a virtual factory acceptance test. Within 90 minutes of opening the box, our client was ready to begin the test. After that, we couldn't keep up with demand! Every other client wanted to have a go at playing with the new normal.

How is the buzzword “metaverse” perceived within pharma, if at all?

The term “metaverse” isn't really commonly used within the industry yet, but the way we are able to use virtual reality and augmented reality does work along those lines. The word captures the basic concept of working collaboratively in a virtual environment. Being able to see through the eyes of a colleague using augmented reality in another part of the world can be incredibly useful – not only for factory acceptance testing, but for remote troubleshooting as well.

At CRB, we use virtual reality when we are creating a 3D model design of a new facility. After donning a headset, you can see and explore everything you've designed. You can touch every

panel, enter every room... and you need not do it alone. Clients anywhere can join you in experiencing a collaborative, walking tour of the facility, and share feedback by voice and chat. If you spot a fault while exploring your virtual model, you can draw a circle around it or add a note that everyone else will see.

How does AI sit within the Pharma 4.0 framework?

For a commonly-used, straightforward way to assess the progress of Digitalization in different companies within the industry, we can utilize a guide developed by the BioPhorum Group called the Digital Plant Maturity Model (2). This model has five levels:

Level One – The facility is based on predominantly manual processing with a low level of automation, as well as being primarily paper-based. Applications are standalone with minimal or no integration.

Level Two – The facility is based on “islands of automation” with digital silos. Some processes are manual, while some may be automated. Batch records may be semi-electronic or “paper on glass”. There is limited integration across functional silos.

Level Three – The facility is a more interconnected facility which includes vertical integration between enterprise systems such as ERP and MES along with the process control system layer. Data is collected in a site historian from process equipment as well as environmental monitoring. Electronic batch records along with review and release by exception are included. Industry standards such as ISA-88 (recipe) and ISA-95 are adopted.

Level Four – The facility is based on enterprise integration with internal integration from the plant to the value chain. Predictive facilities also include the integration of product development and manufacturing. This facility also

includes proactive, predictive analytics which leverages AI to spot patterns and tendencies, model where they are likely to lead, and very often flag a warning if the predicted result could be dangerous or result in production downtime.

A Level Five facility is adaptive. This means it includes full end-to-end value chain integration from the suppliers to the patient. This is done in a modular, mobile and collaborative manufacturing environment. Level Five also includes a plug and play environment, zero downtime, and self-aware, continuously adaptive autonomous manufacturing. “Adaptive” also indicates the presence of AI software that is able to carry out analyses and then use them to adjust and self-regulate, further minimizing the need for human intervention.

Right now, there are no true fully adaptive and autonomous Level Five companies in existence. You do, however, see Level Five elements scattered here and there, which would lead me to believe that the rest won’t remain on the horizon forever.

Turning to another buzzword: blockchain. What can it do for pharma?

From my point of view and judging by the insights published in CRB’s report, data security could be crucial in the years and decades ahead because one of the great predicaments posed by Industry 4.0 is the proliferation of data. Running dozens of parallel devices and systems all in communication with each other, all producing highly accessible data, inevitably calls for a rebalancing via much more rigorous cybersecurity.

After all, there are horror stories. We have heard about pharmaceutical companies getting hacked and left with no option but to pay a hefty ransom to regain access to absolutely crucial data. Nobody wants to find themselves forced into that position.

At present, we aren’t seeing pharma make much use of blockchain, but I do think some of the larger companies are willing to pursue a certain level of implementation. For smaller companies, it’s not a popular option at this time. There are four main barriers stopping them: new security risks, implementation costs, computational costs, and validation.

Are there any other less headline-grabbing aspects of Industry 4.0 that also deserve a mention?

I think biometrics deserve more attention – and it comes with a much lower price tag, making it a great entry point for less titanic or wealthy organizations. A biometric device could be as small and simple as a smart watch, or even a bracelet. Such a device can grant the wearer the capability of logging into ten, twenty, or thirty different systems with a tap of the wrist. Coupled with this, that same wearable could also provide electronic signatures for process operations, as well as card access throughout a physical facility. That is just one very quick reason why I feel biometrics could do with a little more hype.

Web cameras need more love, too. Their veteran status in the toolkit can mean we easily take for granted the sheer range of applications these devices can have. While speaking to vendors, I have heard about some incredible ways they have been put to use. In the case of processing tanks, for example, setting up a networked camera inside the tank replaces the traditional task of lifting up the lid to check for foam buildup or CIP verification with remote monitoring. Cameras are also a great means for collecting data, as all the video streaming through the system can be archived and passed on to the company’s data historian.

I should also mention the use of 360° cameras as well as drones on construction sites. At CRB, we utilize 360° cameras to capture existing and

current site conditions, as well as provide progress tracking. The 360° photos can be utilized for integration to the 3D design model using BIM 360. In addition, we have licensed drone pilots who are able to remotely monitor and scan construction sites with weekly flyovers for progress tracking of construction sites. Scans from these drones can then be translated over to the VR space, and fully integrated to the 3D design model.

Do you see any other major obstacles standing in the way of Pharma 4.0? As you will see in our Horizons report, cost is obstacle number one. Risk management is another major concern. For example, issues to consider

include risks to manufacturing operations, unscheduled downtime, safety, and security concerns to protect data and intellectual property. Trust in automated processes plays a significant role. For the implementation of Pharma 4.0 to move ahead, we will need to see trust in the safety and added value of the relevant hardware and software associated with digital technologies. Skillsets are another very valid concern. Operating new devices, managing new data, and carrying out validation on new systems could necessitate additional hiring and training.

As companies begin their journey to digitalization, there can be many barriers to entry. There is something of a scarcity of fully-tested technology

available. Many companies are piloting new machines and systems, but the doors of the Industry 4.0 superstore remain partially closed – for the time being. That said, innovative technologies are continuing to rapidly advance the pharmaceutical manufacturing industry, breaking down many of these barriers. By following our roadmap and implementing a strategy for Pharma 4.0 adoption, companies can easily integrate digital technologies into the design of their facility.

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The Coperion K-Tron pharma feeders are ideal for both batch and continuous applications. The overall concept is specifically designed for quick cleaning and disassembly, requiring only a matter of seconds to disconnect the feeder bowl, agitator, feed screws and hopper assembly from the gearbox. www.coperion.com/pharma-feeders

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Drug Containment Considerations for Bringing mRNA Drugs Successfully to the Market

In the last two years, mRNA technology has come to the attention of the world as a result of the COVID-19 pandemic. Although researchers have been investigating this technology for the last couple of decades, until now its application in commercial drugs has been limited. The COVID-19 pandemic accelerated the adoption of mRNA technology and opened the door to a broad field of drug therapies, and it is probable that more mRNA drugs will be commercialized and make a positive impact on our overall health care system.

Leading mRNA pharma companies have started working on expanding their mRNA-based drug pipeline with other prophylactic vaccines against infectious diseases, including shingles and flu. Other therapeutic classes, such as rare diseases and oncology, could also benefit from this breakthrough technology. These drugs will need a primary packaging container for storage, transport and injection. A number of considerations will influence the selection of the drug containment solution to ensure that the primary container contributes to the success of the drug launch.

In pandemic situations, supplying the drug to the market for mass vaccination is going to be the top priority. But in non-pandemic situations too, the drug launch strategy might be based on being the first on the market. In these cases, a vial offers great benefits in meeting the goals of drug availability and a rapid

time-to-market. The borosilicate glass vial is a well-known product with existing fill and finishing equipment, low risk for drug incompatibility, multiple sourcing possibilities, and a low-risk regulatory pathway. It offers a broad range of options in terms of coating types for leachable-sensitive drugs, as well as reduced adsorption and optimized vial strength. But as the life cycle management of a drug progresses, a more convenient primary packaging product might be considered. A prefilled syringe (PFS) eliminates most of the drug preparation steps; this not only saves time but also reduces the risk of medical errors. The manual preparation steps required to transfer the drug from a vial into a disposable syringe are a potential source of contamination and particles, as well as dosing errors, and even possible infections. The single-dose prefilled syringe makes it easier and faster for health care workers and safer for patients.

Moving from a vial to a prefillable syringe is not an easy task and raises many technical questions, particularly

for mRNA-based drugs. These drugs are highly sensitive and require low-temperature storage conditions, which make it even more demanding to offer them in a prefilled syringe. There are a number of considerations that could influence the choice of syringe type and material. First, drug stability plays a huge role, with lipid nanoparticles that could have sensitivities towards silicone oil or or tendency towards adsorption. Second, the extremely low storage temperatures reduce plunger sealing because of the difference in shrinkage rates between the rubber components and the syringe barrel combined with the loss of the viscoelastic properties of the plunger at these extremely low temperatures. This could ultimately lead to the failure of container closure integrity.

The next topic of concern is plunger movement. Too much plunger movement can create a breach in the sterility barrier because the plunger moves into the unsterile area of the syringe. Choosing the right syringe, plunger, and fill-and-finish parameters can control this



“SCHOTT offers a wide range of glass vials, glass- and COC prefillable syringes which have been tested and proven for mRNA applications”

phenomenon. Finally, normal syringe functionality needs to be guaranteed even after low-temperature storage. Injection forces, the mechanical stability of the syringe and its components, and optical properties could all be affected after freezing.

Different syringe materials and technologies offer different advantages. Borosilicate type I glass is the gold standard in vaccine delivery and has been in use for decades. It supports a well-known regulatory pathway and allows for a multi-sourcing approach, while the established processing network endorses hassle-free drug filling. SCHOTT's syriQ® glass PFS has been rigorously tested in conditions that simulate mRNA vaccine storage down to -50°C.

Another potential syringe material is Cyclic Olefin Copolymer (COC). This high-quality polymer is inert, has no ion or heavy metal leaching, offers great mechanical resistance, and displays superior transparency and optical properties. In addition, containing the entire production process in one cleanroom guarantees an extremely low

sub-visible particle burden. SCHOTT TOPPAC® polymer PFS are ideally suited for applications down to -80°C. The proprietary siliconization process, which uses an immobilized cross-linked silicone, provides lower extractable silicone quantities and fewer particles than other siliconization technologies. Furthermore, the similar shrinkage rates of the COC material and the plunger material ensure container closure integrity at low storage temperatures.

Irrespective of which primary packaging product or material is chosen, drug stability is key. This is however a complicated matter, and no one-size-fits-all solution can be presented. The storage conditions, drug concentrations, buffer solution, and even the mRNA carrier technology all have a significant influence

on the drug stability in the primary packaging. SCHOTT Pharma Services have more than 40 years of experience in offering support and guidance with chemical analytics to characterize drug-container interactions during the primary packaging selection process.

SCHOTT overall offers a wide selection of vials, glass- and COC prefillable syringes which have been tried and tested for mRNA applications. The company is investing 1 billion euro in ensuring a robust supply chain by expanding capacity in multiple production sites and across all product groups to support the growing demand. Data packages on container functionality and drug-container interactions are available to help decide which primary packaging is best for any given application.





Speaking the Language of Pharmaceutical Success

Sitting Down With... Ludovic Helfgott,
Executive Vice President, Head of Rare
Disease at Novo Nordisk

What sparked your interest in pharma? I come from a long and well-established line of doctors, pharmacists, and veterinarians. Simply put, healthcare has always been a part of my world. But I chose a slightly different path. Rather than pursue a patient-facing career, I chose to commit myself to a degree in health economics. I was intrigued by public health and how it could change societies and even history on a fundamental level.

Although I trained to be an economist, I strongly believed that my professional life would be within the pharmaceutical fold. In my view, pharma was the sector where important decisions were made. But my entry into the industry wasn't linear. I worked as a civil servant for several years – helping to optimize the cost of medicines for payers before joining a pharmaceutical company in 2005. Though my career path wasn't straightforward, I ultimately found my way into the industry I had set my mind on.

How did your background in economics help?

It helped me put myself in other people's shoes. When you understand that everyone affected by a particular decision-making process needs a seat at the table, you have a better grasp of their mindset and you can begin to create more pertinent public health strategies. I had the ability to speak the same "language" as the stakeholders I interacted with. There were no ambiguities between us, so when it came time for us to make important decisions, we were able to do so quickly.

I also believe that my past experiences helped me understand that the patient ultimately wants a holistic solution. Although the drug itself is essential to treatment, so too are the devices, diagnostics, digital applications, and real-world data that support their use. Health economics allows those who engage with it to recognize the importance of these solutions and their ability to enhance or

worsen the patient experience.

With the lessons I have learned, I hope that I can work to create solutions and interventions most relevant to patients – particularly those living with rare diseases.

How did you first get involved with the rare disease space?

In 2017, Lars Fruergaard Jørgensen, CEO at Novo Nordisk, asked me to join the company – taking their rare disease portfolio and transforming it into a long-term sustainable business unit. It may come as a surprise to some that the company has over 40 years of experience in this space; after all, the company is renowned for its diabetes arm and rightly so! It has helped change the lives of people living with diabetes through its product offering and its ability to push treatment boundaries through the exploration of new therapeutic interventions.

But with such a long and rich history in improving health outcomes for people living with rare diseases, it was time for the business segment to find the recognition it deserved. When I finally joined the company in 2019, I made it my mission to achieve this.

How did you tackle such a big mission?

The high-level response: I'm responsible for the rare disease business unit – integrating R&D, commercial and lifecycle management, and product supply. By bringing these elements of the company together, we can enhance the value chain and continue to help patients receive the benefits of our medicines and therapeutics.

In more detail, I developed a three-phase plan. The first phase has already been completed. This three-year strategy saw my team and I work on tactics for the relaunch of our R&D efforts, the acceleration of timelines, and the creation of sales and commercialization programs. We're now entering the second phase of the journey, where our products are finally being launched.

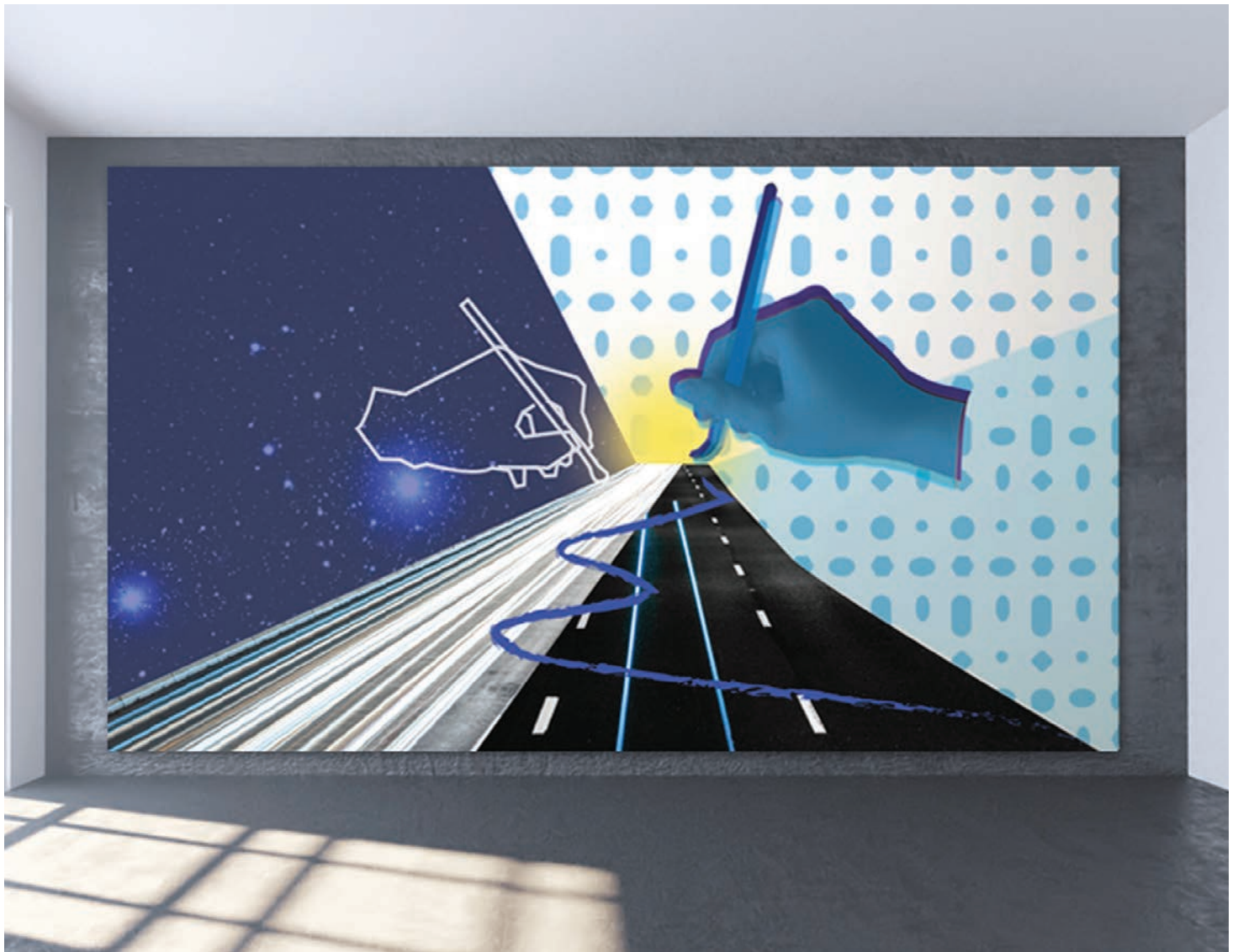
It's exciting to see how rapidly we have found ourselves in this position. But the final part of the plan may arguably be the most exciting. We have traditionally developed solutions for haemophilia and endocrine disorders, but we expanded our research and offerings to cover more rare and ultra rare diseases. I am thrilled by the possibility of reaching more of the patients who have been left behind when it comes to pharmaceutical innovation.

What do you keep in the forefront of your mind as you lead this venture?

I've been fortunate enough to hold a variety of positions in my career. I've worked at an operational level, consulted businesses, and held C-level positions. These opportunities have allowed me to engage with people from varied backgrounds and with unique perspectives – from the strategic all the way through to the scientific.

As we work to raise the profile of the diverse and urgent unmet medical needs of those living with a rare disease, I believe that it's essential to create space for all to share their points of view. In doing so, we can identify the best approaches that will help us achieve our shared goals of better treatments, and for more patients.

Equally important is the chance to share my knowledge with others and support their professional development. I was lucky enough to find excellent mentors at every stage of my career. Every meeting I had with them left me feeling enriched. They were able to impart their knowledge and share their experiences in a way that added value to my career. As my team and I continue to implement our plan, I can only hope that I am able to encourage and support those working in the rare disease sector in the same way my mentors did for me. Their successes will ultimately help impact the lives of people with rare and ultra rare diseases.



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