

the Medicine Maker[®]

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Remembering Henrietta

*By decentralizing clinical trials, pharma can fix a broken system
– but patient consent must never be overlooked*

Editorial



Henrietta Lacks, a mother of five from Maryland, did not live a long life. Diagnosed with cervical cancer in January 1951, she passed away nine months later – on October 4 – at the age of 31. Henrietta would never know the impact she would go on to have on medical research. From the creation of the first polio vaccine to driving modern cancer research, her influence has been huge... albeit non-consensual. During her treatment at Johns Hopkins hospital, tissue samples were taken from her cervix and used to develop the immortal human cell line known as HeLa. Though admittedly not unusual in the 1950s, Henrietta was not informed nor was she given the opportunity to consent – and zero profit from the distribution of the cell line over the last seven decades has found its way to her family. On the 70th anniversary of her death, in a bid to partially rectify this latter wrong, the Lacks estate filed a lawsuit against Thermo Fisher Scientific – one of several companies who commercialized the HeLa cell line (1).

This recent legal case is a stark reminder of the importance of informed consent as the pharma industry continues to innovate. Companies are rapidly beginning to adopt digital technologies – helping fuel the decentralized trial landscape and enabling companies to connect with and recruit a broader spectrum of participants. But with this improved access comes the responsibility to ensure that all trial recruits understand their roles and rights. Trial sponsors must provide clear and thorough information to ensure that any breakthroughs don't come at the patient's expense.

But is this easier said than done? Gaurav Dave, a member of Medable's Patient Advocacy Group, commented in our June issue that "patients are often lost in the ever-growing maze" of clinical trials (2); "not knowing what questions to ask, not understanding the medical or research jargon, not having the resources, and not participating in joint decision-making perpetuate this problem," he explained.

The industry certainly has a tough juggling act on its hands, but, as Dave says, "It is incumbent on pharmaceutical companies to be intentional and invest in building and sustaining a relationship with the public [while being] transparent and accountable."

On page 28, we take a hard look at the clinical trial arena and ask what companies can do to ensure the best experience for patients, while improving recruitment and retention rates. What's evident is that patients must be at the heart of all decisions made.

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Maryam Mahdi
Deputy Editor



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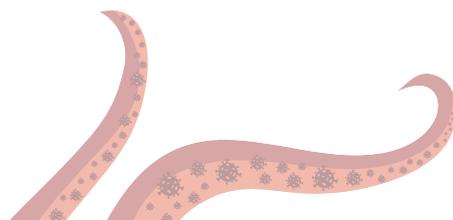
How CMOs survived and navigated the pandemic

Upfront

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X2: Researchers United

BioMed X launches new projects in immune homeostasis and oral delivery of macromolecules

At the campus of the University of Heidelberg, Christian Tidona's BioMed X is storming ahead with two new projects backed by J&J's Janssen Research & Development (1).

One team will be led by Mojca Frank Bertonecelj, arriving at the institute from University Hospital Zurich. Her group will seek to understand the molecular mechanisms that promote pro-resolution responses in immune and stromal cells to restore homeostasis. The goal is to enable high-throughput testing and bring about the discovery of novel joint-protective therapeutics.

Captaining the other project is the University of Kentucky's Kyungbo Kim. To him, the mission is clear: "Characterize the human intestinal epithelial barrier and thereby gain insights into how macromolecular therapeutics may be orally delivered." The endgame, CEO Tidona speculates, could be a juggernaut. "Just imagine the benefit for patients if macromolecular

drugs, such as monoclonal antibodies, could be administered via a pill instead of an injection," he says.

BioMed X is something of a chimeric organization – neither industrial nor academic and, in Tidona's own words, a place to nurture "the world's brightest early-career research talents."

The team-up with J&J is no rogue incident – BioMed X is a magnet for partnerships with major pharma companies such as Merck, Boehringer Ingelheim, Roche, and AbbVie. Each new alliance targets a major research challenge, then spends up to five years mentoring a first-class team of new recruits as they set about their task. Seven of eight completed BioMed X projects have continued evolving in the

labs of their respective industry partners.

The two J&J projects have been assigned a timescale of four years. In that window, BioMed X also plans to expand further. Toward the end of 2021, the institute will open its first subsidiary (beyond Heidelberg) in Israel with the support of the Israeli government and six major players in pharma, tech, and venture capital.

"During the next five years, we will jointly use our innovation model to generate 20 startups in the field of artificial intelligence for drug discovery and development," says Tidona.

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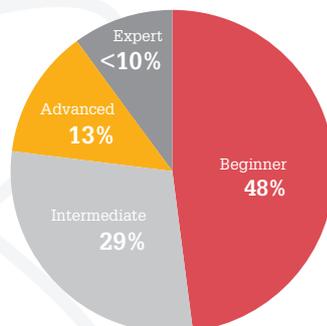
INFOGRAPHIC

Who's Ready for First Contact with Quantum Computing?

A survey sheds light on life science professionals' readiness for quantum computing applications

Source: Pistoia Alliance (2012). Available at: <https://bit.ly/2XLxFVW>.

How would you define your understanding of quantum computing (QC)?



What is the greatest barrier to launching QC projects?

Lack of understanding of QC and the inability to articulate valuable uses: 35%
Lack of skills: 29%
Lack of access to QC infrastructure: 15%
Cost: 11%
Other: 10%



BUSINESS IN BRIEF

Bills, Brits, and buildings... What's new in pharma this month?

- Three members of the US Democratic Party expressed their intention to oppose a policy that would allow Medicare to negotiate and lower the price of many prescription drugs. The dissenting lawmakers, who represent California, New York, and Oregon, believe that the policy would grant the federal government unnecessary powers when interacting with drug companies. To pass the legislation, the Democrats need zero defections in the Senate and no more than three in the House. The Republican party uniformly opposes the proposed bill.
- In a bid to manage outbreaks and prevent hospitalizations, England's National Health Service is preparing to deploy antiviral tablets to treat COVID-19. NHS England is working with the UK government's Antivirals Taskforce on the project, which is headed by Chief Pharmaceutical Officer Keith Ridge. The deployment will make use of findings from



California representative, Scott Peters

Credit: <https://nara.getarchive.net/>

- domestic and overseas antiviral treatment trials.
- In a US\$14 million expansion to its operations in Singapore, Takeda has built a "zero energy" building near an existing manufacturing plant. The development is the first of its kind within the Singaporean biotech industry. The company claims to have achieved carbon neutrality across its operations last year and believes the new building will help in its goal of becoming net-zero by 2040.
- The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and South Africa's H3D-Foundation have announced a three-year partnership to strengthen health innovation in Africa. The collaborators will seek to scale up existing initiatives and boost the careers of young scientists on the continent. IFPMA will provide short- and mid-term support to the foundation using various networking tools.



The Innovation Awards Are Back!

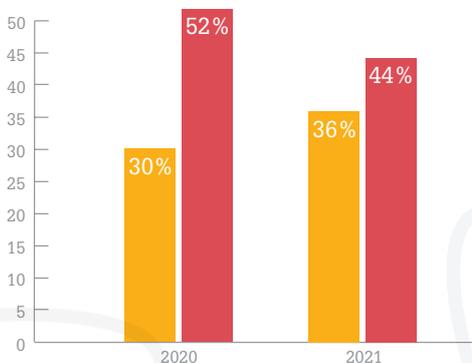
Tell us which technologies rocked your world in 2021

You did it. You made it. Despite all the odds, you and the industry survived 2020. You'll remember that relief was short-lived; before you knew it, 2021 was beating you over the head. We all knew something had to give – the signs were hardly subtle – and now the times, they are a-changin'. Perhaps there has never been a better year for The Medicine Maker Innovation Awards.

We want you to nominate the tech you think is making the change that matters most. The Awards – to be published in our December issue – will celebrate the highest-impact pharmaceutical development and manufacturing technologies released in 2021. What's eligible? Equipment, software, formulation technology, drug delivery methods – in fact, any reasonable advance you can point to.

We only have one rule: the innovation must have been released (or planned for release) in 2021.

Nominations close on Thursday, 28 October. Visit tmm.txp.to/innovation2021



How soon will OC impact the biopharma industry?

2020 versus 2021



Swing in expectations from 2020 to 2021

How soon will OC impact the biopharma industry?

Within the next five years:

+6%

Within the next ten years:

-12%

Flipping the Tortoise

Could a pill developed at MIT replace injections for monoclonal antibodies?

A pill-shaped device that can deliver monoclonal antibodies orally has been developed. Designed by collaborators at the Massachusetts Institute of Technology (MIT), Brigham and Women's Hospital, and Novo Nordisk, the blueberry-sized device can administer doses of up to 4 mg upon delivery to the stomach (1).

Giovanni Traverso, an assistant professor at MIT, explained the unconventional inspiration that drove the project. "Our drug delivery system built on previous work that explored how the geometric self-righting capabilities of both leopard tortoises and weeble-wobbles – an unflippable egg-shaped toy dating back to the 1970s – could be applied to create new options for patients," he says.

When swallowed, the device uses its unique shape and weight distribution to orient its injector towards the stomach tissue. Traverso says, "The device uses its weighted bottom and pointed top to

autonomously rotate back to its preferred configuration, where its injection mechanism is flush against the tissue wall. This ensures that the drug enters into the tissue and isn't degraded by enzymes present in the stomach."

Relying on a humidity-sensing compressed spring, the device can inject a hollow needle into a thin layer of the stomach wall lining, through which a liquid drug can be administered. After administration, the capsule retracts the needle back into its shell for safe passage through the gastrointestinal tract.

The use of liquid formulations, Traverso explains, was a key component to the

device's patient-centric design. "The delivery of a liquid formulation enables drug uptake and effects within five minutes following capsule ingestion," he says.

The work follows six years of collaboration between MIT and Novo Nordisk. Through the partnership, Traverso's team has developed a suite of devices now able to support the delivery of biologics from the oral cavity to the stomach and intestine.

Reference

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A Moonshot for COVID-19

Meet the international coalition working to tackle COVID-19 in low- and middle-income countries

An open-science consortium fighting for accessible COVID-19 treatments has received £8 million from the Wellcome

Trust, a London-based charitable foundation focused on health research. The group, COVID Moonshot, was born in the early days of global lockdown. At that time, an international cross-section of scientists, academics, pharmaceutical research teams, and students began a collaborative race to identify new molecules that could block SARS-CoV-2 infection and to develop pills ready to roll out to those most in need of affordable medicine.

Alpha Lee, of the University of Cambridge, noted that Moonshot's early

efforts – focused on repurposing existing small molecule drugs and rapidly developing monoclonal antibodies – have now shifted to developing new antiviral therapeutics in light of the likely persistence of COVID-19 as a global threat.

The Wellcome Trust funding comes just as the project approaches its next phase: tweaking, optimizing, and testing identified molecules to develop safe treatments – expensive work that the £8 million will help to cover.





IMAGE OF THE MONTH

Toes Less Tiny

A systematic review led by the Murdoch Children's Research Institute (MCRI) found that in countries where malaria is endemic, the common antibiotic azithromycin reduced low birth weight and premature births if taken during pregnancy.

Credit: Atharva Whaval

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QUOTE of the month

"Covishield ... is a licensed product of a UK company, manufactured in India, of which we have supplied 5 million doses ... at the request of the [British] Government. Therefore, non-recognition of Covishield is a discriminatory policy, and does impact on our citizens travelling to the UK."

Words spoken by Indian Foreign Secretary Harsh Vardhan Shringla in the first official response from the Indian government to British travel rules.

<https://bit.ly/in-uk-covi>

Closer to the Boundary

New research brings medicine one step closer to effective membrane-permeable drugs

Of all drugs capable of crossing the cell membranes, most are too small to affect intracellular protein–protein interactions (PPIs) – but new research published in the *Journal of Medicinal Chemistry* could help change this (1). Led by Jiwon Seo, an associate professor at Gwangju Institute of Science and Technology, Republic of Korea, a team of scientists have found that a peptide, cyclosporin O (CsO), could help produce medicines capable of crossing cell membranes and interfering with PPIs.

Seo's team investigated various properties of CsO and its derivatives and compared them with cyclosporin A (CsA), a similarly promising, but flawed, candidate for membrane-crossing, PPI-disrupting medicine. They found that CsO did not cross membranes as effectively as CsA, but outperformed CsA in terms of pharmacokinetic profile and plasma concentration.

Although further study will be necessary, Seo remains optimistic that his team's work could open up new avenues for tackling undruggable targets including cancer, neurodegenerative disorders, and metabolic diseases.

Reference

1. D Lee et al., *J Med Chem*, 64, 8272 (2021). DOI: 10.1021/acs.jmedchem.1c00211.



What a Difference a Year Makes

AstraZeneca's George Kirk offers an update on Koselugo – a medicine developed to treat a rare and burdensome condition – one year post approval

Last August, we had the opportunity to speak with George Kirk, Global Product Leader at AstraZeneca, who discussed the harrowing experiences that patients – particularly young children – living with neurofibromatosis type-1 (NF1) with plexiform neurofibromas (PNs) may face. From severe pain to disfigurement, the wide-ranging challenges caused a significant burden for patients and families living with the condition.

AstraZeneca's Koselugo, he explained, was expected to make a huge difference in their lives. The drug did, however, face some setbacks in its early days. Despite the initial challenges, Koselugo was finally approved for use by the US FDA in 2020 and has now been approved in other markets. But what impact has it had on the NF1 community? We ask Kirk, who led the development, to give us his view.

Since our conversation, what progress has been made with Koselugo?

It has been just over a year since our first approval of Koselugo in the US for the treatment of children with NF1 and symptomatic, inoperable PN. We have made significant progress in ensuring patients have access to the drug. Despite the challenge of launching Koselugo during a global pandemic, we have reached over 1000 patients in the US with this new treatment, which gives them hope for reducing the size of inoperable tumors, reducing pain, and



improving quality of life.

In addition, since the start of 2021, we have received approvals in six markets around the world: the EU (including EEA), United Arab Emirates, Brazil, South Korea, Israel, and Singapore.

Do you have plans to expand access further?

Yes! We have further submissions planned, particularly in Japan and China. We have ongoing clinical trials in the Japanese and Chinese NF1-PN patient populations to support these regulatory submissions.

What's next for Koselugo?

Throughout this time, we have continued our development in NF1-PN and are working closely with our colleagues at the National Cancer Institute to monitor patients who are still receiving Koselugo in the SPRINT pivotal trial. In addition, we are starting two new clinical trials – one in adult patients who have NF1-PN and another using a new, alternative formulation appropriate for pediatric patients.

Our vision for the future is to be able to detect PN growth early and prevent these tumors from reaching a size where

they become debilitating and cause significant morbidities.

What have the advances made so far meant for patients?

Until now, the only options available were medication to control secondary conditions and, where safe and feasible, to have tumors surgically removed. It is exciting to have Koselugo available for so many patients and to see the difference it can make to their lives and the lives of their families. I have been fortunate enough to meet some of the amazing children who suffer from this disease and they have been an inspiration to me and the Koselugo team at AstraZeneca!

I am proud to have been part of the team that worked collaboratively with our colleagues at the Cancer Therapy Evaluation Program and the National Institute of Health to deliver the regulatory approvals we have received thus far in this pediatric patient population. The NF1 community is strong and I am privileged to work with them. I hope we can continue to develop further treatments. The Koselugo approval is only the start of the future treatments for patients who suffer from NF1...

Top: Arman Shahriar
Bottom: William Stauffer

The Price Ain't Right

Two studies scrutinize extreme drug pricing, sounding alarms for industry and policymakers

It's no secret that in pharma, drug prices can be a sensitive issue for patients and companies alike. This is certainly true in the US, where the uninsured and underinsured are disproportionately affected by rising costs. Exploring the ramifications of this challenge, researchers from the University of Minnesota Medical School have outlined how factors including state legislation and pricing shifts have influenced drug access across the country (1,2).

Arman Shahriar, a medical student at the university, who is investigating the impact of legislation on the situation, explained that the profits made by pharma often dwarf those of other Fortune 500 companies. The industry's financial growth, coupled with its consistent price hikes, have spelled trouble for the nation's most vulnerable. "Manufacturer price increases disproportionately affect uninsured and underinsured patients, many of whom are immigrants and socioeconomically vulnerable," he says. "The goal of our work is to help state lawmakers design as effective a policy as possible to prevent unnecessary price increases that can cause problems for these patients."

Along with his colleagues, Shahriar grouped all 15 relevant state laws and 94 percent of relevant bills proposed into three areas of concern: transparency, affordability review, and anti-price gouging. The researchers noted that most of these laws were enacted in the last two years – and most were guilty of failing to cover the bases necessary to adequately protect patients from

extortionate price increases.

"Though states alone will likely not be able to solve the problem of high drug prices, we hope this research will help reduce unnecessary price increases and trigger their reduction in states that decide to pass new legislation," he says.

Although Shahriar's findings could potentially help initiate change at the state level – ultimately helping vulnerable patients – William Stauffer, professor of medicine at the medical school, noted that even "those with good insurance" are affected by drug pricing issues today. His research group studied how price jumps between 2010 and 2019 had affected access to antiparasitic drugs albendazole and mebendazole. They found a strong correlation between extreme increases in price and a significant decrease in quality of care. For example, the price of the anti-pinworm medication albendazole increased from \$14.81 to \$130, preceding a drop from 81 to 28 percent of patients receiving appropriate treatment. The reason such a broad spectrum of patients (including the insured) could be affected, he explained, was insurance company practices. "In clinical practice," he says, "we sometimes find insurance companies increasing co-pays, putting up very difficult pre-approval processes, or simply refusing to pay the exorbitant charges, which deter treatment altogether, or encourage a shift to an inferior drug. You might think you get more for your money when you pay more, but what we found is that as the



price goes up, fewer people receive appropriate, or any, treatment."

Stauffer noted that, despite the complex nature of drug pricing, specific problems can be identified and concrete steps taken. He named opacity and anticompetitive practices as causes of extreme price rises. As antidotes, he recommended legislation for pricing transparency, enforcement of existing regulations, FDA reform to include consideration of drug accessibility in the approval process, and importation of therapeutic equivalent drugs – echoing Shahriar's sentiments.

In the near future, Stauffer and his colleagues will examine further categories of drugs within Marketscan, a large insurance database previously designed by the team, and investigate other barriers to accessing essential medicine for neglected conditions in the US. But Shahriar and his team have a different focus. He says, "We hope to distribute our results to state lawmakers involved in prescription drug price legislation across the country."

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The Smart Choice

Using the right chromatography resin can make all the difference for companies who need to drive productivity and efficiency gains in antibody fragment manufacture

By Jonas Wege, Application Specialist

Monoclonal antibodies are a well-established target molecule in the biopharmaceutical industry landscape and can treat an extensive range of conditions. Today, their production is well understood and generally easy to scale. However, the biopharma innovators aren't resting on their laurels when advancing the science behind these therapies. Antibody fragments are among the most promising formats, improving delivery to target sites and increasing binding affinity. Moreover, progress in engineering allows the recombinant production of antibody fragments at economically viable titers.

As antibody fragments are relatively new technologies, proper analysis and purification make all the difference in providing safe and efficient therapies to the patients. Our biopharma partners do not only rely on Tosoh Bioscience's high-quality chromatography solutions; they also trust our experts to enable them to develop the most cost-effective processes.

Easing the burden

Biopharma manufacturers constantly aim to produce a high concentration product at the antibody capture step so that all subsequent operations, including the polishing step, are as cost-effective and time-efficient as possible. This was

historically a challenge for fragments, as they cannot bind to traditional resins like Protein A (which relies on Fc binding). Protein L is now the first port of call for such purification challenges.

The proteins on the surface of the Protein L resin matrix bind to antibodies via their kappa light chains (present in many antibody fragments) to remove impurities. Though well suited for the task, Protein L is a much younger medium when compared with its counterparts – and developers report that traditional resins often exhibit a lower dynamic binding affinity. Simply put, only low quantities of the target molecule can be loaded onto a column, thus limiting its performance, resulting in a more costly and time-consuming antibody capture step.

Another potential hurdle for manufacturers is the low chemical stability of the resin over the repeated cleaning cycles. After a column has run, it is usually cleaned with an alkaline solution. However, the poor chemical stability of traditional Protein L resin often resulted in a partial loss of performance. To overcome this issue, the resin needs to be exchanged after a low number of cycles – leading to increased costs and workload!

To address those challenges, Tosoh has developed a leading-class alkali-stable Protein L called Toyopearl AF-rProtein L-650F. First and foremost, it has been designed with high dynamic binding in mind, which means that more protein can be loaded

onto the column and that fewer runs are needed to purify the same amount of target molecule. In fact, our Protein L affinity resin's dynamic binding capacity is at least two times larger than other commercial products for Fabs at any residence time, which clearly helps optimize manufacturing efficiency and productivity. We have investigated not only the performance of the antibody fragment capture step but also the reusability of the resin during a whole purification campaign. Thanks to its improved alkaline stability, more purification cycles can be run on the same column. Lastly, our extensive experimentation with different washing solutions and our expertise in packing helps improve product purity and resin lifetime. Down the line, our biopharma partners need less resin, which allows them to develop the most effective processes, and they rely on our expertise to help them develop their processes as fast as possible.

The science behind the success

Though our Protein L is helping to revolutionize the capture of antibody fragments, we recognize that sustained improvement is mandatory – and, for us at Tosoh, that means a continued focus on high-quality research and development. Indeed, we are committed to several extensive research programs – both internally and with our partners – that aim to optimize overall manufacturing productivity. For example, we are currently evaluating how a Protein L mediated capturing step can be transferred onto a continuous system. We expect that this productive, efficient option will expand possibilities for our customers.

Ultimately, Tosoh is dedicated to developing increasingly efficient solutions for the purification of antibody fragments.

With an established history and wealth of technical expertise, I believe we are the best partner for drug developers looking for cost savings and increased productivity.



Resolving Problems

Wacker Biotech bundles WACKER Group's biopharmaceutical activities. The company has years of experience under its belt when it comes to the production of antibody fragments, using *E.coli* as an expression system. But the process is not without its challenges. Here, Ilona Koebsch, Business Development Manager, and Thomas Walther, Expert Downstream Processing at Wacker Biotech outline some of the manufacturing challenges the company has faced – and how Tosoh's support fed into the solutions.



What are the most interesting antibody fragment subclasses?

Koebsch: Antibody fragments differ in terms of size, structure, and function. But Fabs – and all variants containing antigen-binding sites – represent the most interesting antibody fragment technologies from a therapeutic point of view. Notably, the smaller size of the fragments permits penetration into tissues inaccessible to full-size mAbs – and that's essential in many therapeutic and immunohistochemical aspects. In addition, these fragments can be more easily and cheaply manufactured using prokaryotic expression systems, such as *E.coli*, because of their relatively small size.

What are the main challenges in the production of Fabs?

Walther: Depending on the structure, Fabs can be soluble or can assemble into

inclusion bodies (aggregated recombinant proteins). Manufacturers must also maintain their folding and structure during fermentation and downstream processes to ensure the Fab is biologically active.

For upstream processing, the main task is always to find the best combination of the expression system (host and plasmid) and cultivation parameters to achieve an efficient but robust manufacturing process. But, in my view, the most critical challenge is finding appropriate models to simulate certain outcomes or to mimic large-scale processes on a laboratory scale.

In downstream processing systems, the main challenges relate to the complexity of the sample matrix, development times, and the low tolerance of affinity resin against many common cleaning solutions.

What is WACKER's approach to tackling the challenges?

Koebsch: WACKER has developed two unique *E. coli* based expression systems enabling highly efficient production of different antibody fragments. ESETEC® is a unique expression system that allows for the controlled secretion of correctly folded recombinant protein products in a fermentation broth. In short, it helps simplify primary recovery and purification processes which brings down cost-of-goods.

For hydrophobic antibody fragments, we offer FOLDTEC® technology, which consists of highly efficient *E. coli* producer strains, an antibiotic- and phage-free plasmid maintenance

system, and comprehensive refolding know-how.

We do not have a proprietary technique to overcome issues in downstream processing. Chromatography resins with high capacities, good resolutions, low back pressure, easy handling (in terms of column packing), short delivery times in combination with a long shelf life, and low nonspecific binding behavior are all needed!

How did Tosoh support WACKER tackle those challenges?

Walther: On the recommendation of a colleague at another WACKER site, we used the Tosoh AF-rProtein L-650F resin in a project where our preferred resin failed due to a very low binding capacity.

We compared Tosoh's resin against three others that claimed to support Kappa light chain affinity binding. The AF-rProtein L-650F resin showed a significantly higher binding capacity (around three times higher) than the competitors, as well as good recovery of the target protein. The number of proteinogenic impurities was also the lowest of the tested resins.

Finally, AF-rProtein L-650F exhibited better flow rates than the other tested resins, which allowed us to use smaller column volumes to house the resin – with real cost advantages for our customers. We also had great support from Tosoh's packing and technical sales specialists, who made recommendations for the best types of columns to use with their product.

It was apparent to us that Tosoh's Protein L resin is a strong competitor – and it should make other suppliers rethink their current product lineups.

Autoinjectors: Through Thick and Thin

Once we overcome the complex challenges presented by self-administered parenterals, we create a win-win-win situation: happier patients, better healthcare, and lighter workloads for doctors

By Hans Jensen, Global Business Development Director, Bepak by Recipharm, UK

The pharmaceutical market is seeing a rise in new medications that require parenteral delivery to patients – whether through intravenous, intramuscular, or subcutaneous injection. Forecasts indicate that the injectable drug delivery market will grow at a compound annual rate of 12.9 percent to reach US\$1250 billion by the end of 2027 (1). However, rather than administration in hospitals and clinics, there are clear advantages to enabling patients to self-administer injections.

Clearly, parenteral products for self-administration face one challenge in particular: the need for patient-friendly delivery. Auto-injectors have become the go-to delivery device, but many injectable drug products in development have higher viscosities, which often leads to issues when used in conjunction with existing auto-injectors.

Let's consider the drivers of high viscosity formulations.

First, biologics contain large, long-chain molecules often at high doses – especially in the case of mAbs, which typically range from >80 mg all the way up to 1000mg (2). Viscosity increases

exponentially with protein concentration – but a high concentration is needed to keep the injected volume below ~2 ml (commonly recognized as the maximum volume to be delivered in a single SC dose).

Second, therapeutics designed for sustained or controlled release in the body following administration often contain polymers with high molecular weights, which makes the resulting formulations highly viscous – sometimes more than 1000cP.

Third, in some formulations the solvent itself is highly viscous; for example, oil-based formulations (used to alter release rates or for poorly water-soluble drugs) often have high viscosity.

Existing technologies can reduce viscosity levels in some cases; however, not all formulations can be reduced to a viscosity that allows delivery with conventional spring-based auto-injectors. The natural alternative to altering the formulation is to move away from standard auto-injectors towards

devices tailored for administration of viscous formulations. In fact, I'd argue that by improving delivery devices we not only overcome the challenges of viscosity, but also optimize the self-administration experience for patients. For example, devices with compact energy sources based on liquefied gas

“Clearly, parenteral products for self-administration face one challenge in particular: the need for patient-friendly delivery.”

In My View

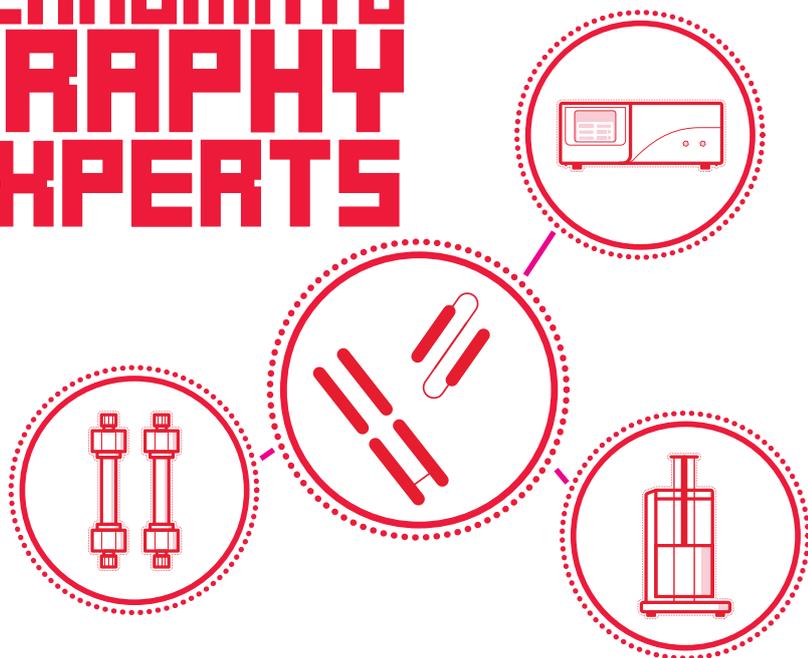
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rather than spring power can enable delivery of highly viscous liquids through a fine needle.

Alternate energy sources actually allow for greater flexibility in device design compared with conventional spring-based auto-injectors. By tailoring gas composition, developers can achieve desired performance characteristics, such as delivery time with a particular combination of fill volume and needle gauge, for any given formulation. Additionally, liquefied gas provides a constant pressure profile, lower peak forces, and reduced risks of damaging the primary container through high impact forces.

That said, the risk of damage to the syringe when dealing with the higher forces needed to deliver viscous formulations using an auto-injector should be a key consideration during design. Most autoinjectors on the market use glass syringes, which can break under high pressure. Recent improvements to the design of containers and other materials have significantly reduced the likelihood of such breakages, but the risk persists. One solution is to use polymeric primary containers, such as those based on cyclic olefin copolymer (COC/COP). Such syringes offer a number of advantages over glass syringes, including improved strength, lower frequency of breakages, and tighter tolerance – all of which help to overcome the challenges presented by high-viscosity delivery devices.

Special, thicker-walled versions capable of withstanding forces well above 300N are also being developed by COC/COP syringe manufacturers. However, despite the longstanding availability and numerous advantages of COC/COP syringes, they cannot serve as a straightforward replacement; they still require early consideration in drug development programs in which a high viscosity auto-injector is an option on the table.

In my view, the key to successful development and commercialization of parenteral products is to consider the device requirements right from the start of the project. Merely considering the device in the late stages can lead to complications not only in terms of ensuring the device is fit for purpose, but also in potential interactions between the formulation and the device. It is imperative that the device and formulation teams work closely from the outset to ensure the best outcomes. Their mission must be to not only streamline a product's journey to market, but also ensure the final product is suitable for the end users.

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Unspent Media

Biopharmaceutical development needs more speed, and greater efficiency – and multi-omics could well be the answer

By Paul Gulde, Manager of R&D Multi-Omics at Thermo Fisher Scientific, New York



Current biopharmaceutical process development requires the use of living cell lines with highly specific nutritional and environmental needs, which poses a number of complex challenges – least of all finding the optimal cell culture media formulation. But getting the media formulation right is crucial; the nutritional composition has a direct effect on cell growth – as well as the yield and quality of the biotherapeutic molecules they produce. By fully optimizing media, biopharmaceutical developers can dramatically improve productivity and cost-efficiency.

As with all scientific processes, the key to successful optimization is understanding data – in this case, it's about understanding how each medium component influences the

cells. Traditionally, these data have been collected using a technique known as “spent media analysis.” This iterative, empirical approach compares levels of different components in media samples before, during, and after cell growth to provide insight into component utilization over time, which feeds into optimization of media.

However, despite its longstanding use, the level of detail that can be obtained using spent media analysis is fundamentally restricted. And that's true for both understanding the components themselves – as the technique only permits analysis of major metabolites such as vitamins and amino acids – and how they are being used. The latter issue arises because spent media analysis can identify only a limited number of molecules that are taken up or secreted by the cells, rather than identifying global molecular changes, such as signaling, and which metabolic pathways the components are involved in.

The solution? Multi-omics analysis. Specifically, in the case of media optimization, the application of proteomics and metabolomics, which refers to the molecular characterization of proteins and metabolites, respectively. Much like spent media analysis, these techniques rely on an iterative approach to identify how media components are being used by cells, and then use this insight to optimize the media. Unlike spent media analysis, the level of detail that these two techniques can obtain is unparalleled.

By enabling precise identification and quantification of the proteins expressed by the cells, proteomics enables identification of the intracellular pathways that are being activated or inactivated. This information can then be layered upon metabolomics data to establish how individual metabolites are flowing through these pathways. As a result, potential pathway bottlenecks, which could be impacting cell growth

“In my view, the only way to accelerate the development of next-generation biopharmaceuticals is to leverage next-generation analytical solutions.”

or product quality and yield, can be discovered. The combined knowledge can then inform the design of additional experiments to further optimize the media formulation.

For example, consider a process where the amino acid serine is rapidly depleted despite relatively low consumption by the synthesized therapeutic protein. In this scenario, a hypothesis for where the serine is used could be developed and tested using spent media analysis, but this would be a time-consuming process. By using proteomics and metabolomics instead, the actual intracellular pathways can be followed and the specific component that the cells are synthesizing using serine can be identified. Knowing this, the developer can then undertake further investigations to determine whether to add the missing component to their media, rather than more (potentially unnecessary) serine.

This example illustrates the considerable impact of using multi-omics rather than spent media analysis in the design of experiments undertaken during media optimization. In particular, it highlights how the extra level of granular intracellular



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“To make full use of advanced process development analytics, there is an onus upon the entire industry to think big in terms of potential applications.”

detail that multi-omics provides can enable developers to either gain actionable results through less experimental iterations or – with an equal or higher number of iterations – gain increasingly more information.

Notably, I’d be the first to agree that spent media analysis has been an invaluable tool over the years, playing a pivotal role in the development of numerous life-saving biotherapeutics.

However, as interest in biologics continues to grow, it is clear that we need to render their development and manufacture even more efficient and cost-effective. In my view, the only way to accelerate the development of next-generation biopharmaceuticals is to leverage next-generation analytical solutions.

To make full use of advanced process development analytics, there is an onus upon the entire industry to think big in terms of potential applications. For example, the combined use of proteomics and metabolomics is not restricted to new media optimization projects; it could also be applied to existing processes to enable efficient and reliable media troubleshooting in the event of unexplained product and process variations.

Beyond media optimization, the use of further omics analyses – such as genomics and transcriptomics during cell line development – holds even more promise. By applying these techniques collaboratively at different workflow stages, biopharmaceutical developers could not only benefit from a significantly improved process, but also from an expedited development timeline and, in turn, an accelerated speed to market.

Another area where collaboration

(albeit between more diverse scientific disciplines) has the power to further advance process development is the management and use of the data collected during these analyses. By working with computer scientists to implement AI processes using machine learning, we can create models based on data collected from thousands of experiments. And as more and more data are collected, these metabolic pathway models will become a vital part of the multi-omics toolbox by allowing process developers to escape the traditional limitations of so-called local “tribal” knowledge. Instead, they will have direct access to detailed company-wide – or even industry-wide – global knowledge, which can be used to support new optimization processes.

I’ll admit I have good reason to be biased – but I truly believe multi-omics analysis should be considered an essential part of a modern cell culture media optimization process. And if we spread our wings further to consider the full spectrum of its applications across the entire development process – not to mention how it could be enhanced by cutting-edge data science – the introduction of multi-omics analysis could even contribute to a tipping point in overall biopharmaceutical development.

A Reawakening of Small Molecule Drug Development

New technologies are driving a small molecule renaissance

*By Marcelo Bigal, CEO,
Ventus Therapeutics*



Small molecule drugs are the mainstay of medicine, representing around 90 percent of all approved medicines and 75 percent of all new medicines approved in the US in 2020 (1). They also still make up the lion’s share of prescriptions, and are useful in non-genetic, prevalent, and multifactorial diseases, which affect a broad spectrum of patients. With predictable properties, small molecule drugs can be manufactured cost-effectively with less complexity than biologics.

However, small molecules feel like

yesterday's news to some industry players: lacking in glamor, excitement, and venture funding. One key reason small molecules have been forsaken is the perception that they have run their course. The yet-to-be drugged therapeutic targets are thought to be out of reach for small molecules because of the scarcity of identifiable druggable binding pockets. Consequently, drug developers pursue these targets with newer drug modalities, forcing an unattractive tradeoff – shifting to riskier, more complex, and more expensive drug modalities for biologically validated targets.

Nevertheless, many protein targets are, in fact, druggable with small molecules. New technologies that combine advanced protein dynamics and computational chemistry analyses are driving massive data iterations that identify binding pockets by shining a light on areas of the protein that were previously beyond the sight of conventional tools. What are some of these technologies and strategies allowing us to see proteins in a new light?

- Exploring all possible protein conformations. Although increased computational power allows broad sampling of protein conformations, traditional approaches to process these data required significant user bias. Use of a completely unsupervised proprietary processing approach eliminates this bias. In this way, one can distinguish pockets that exist in some but not all conformations and are often not present in the most frequent conformations.
- Determining dynamic hydration protein structures. New technologies can be used to determine each conformation's

“Our job as small molecule drug developers is to create new medicines for prevalent diseases, and build a compelling case to investors by identifying patients with a higher chance of responding to therapies.”

accurate dynamic solvation structure, since pocket desolvation is the principal driving force of small molecule binding.

- Correlating structure and function. Dynamic attributes – protein dynamics, conformations, and water molecular dynamics – can then be correlated to protein function. In this manner, validated targets can be pursued with the predictability of small molecules.

Once new binding pockets are identified using these approaches, current technologies can conduct virtual binding screens in over 3 billion virtual compound libraries.

In my view, companies pursuing these approaches need to reach across the aisle – to not only conduct the computational modelling and virtual screens, but

also to test and develop the molecules suggested by these screens in traditional wet labs to learn more about them. This information can then help inform all other phases of drug discovery – from binding site identification and lead identification to lead optimization in end-to-end, interactive, continuously improving processes that will progress until functional drug candidates are selected.

Why is this relevant? Well, a foremost advantage of small molecules is their suitability for polymorphic, prevalent diseases; their development must embody the same innovation and boldness as their discovery. Most newer drug modalities, including gene therapy, RNAi, and CRISPR, are tested in rare monogenic diseases or genetically defined disease subsets, leaving prevalent diseases out of their scope. Our job as small molecule drug developers is to create new medicines for prevalent diseases, build a compelling case to investors by identifying patients with a higher chance of responding to therapies, and then implement rigorous decision points before advancing the most promising drug programs. As with new medicines of all types, success is also defined by embracing patient-centricity. And that means including virtual clinical trials, adopting patient-relevant endpoints, selecting pragmatic designs, and incorporating real-world evidence.

I believe that the importance of small molecule drugs in the armamentarium of innovative medicines will remain on the increase. But we need to capitalize on today's opportunities and so bring new technologies to the field of medicinal chemistry, driving the renaissance of small molecule medicines.

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FMS Outsourcing

WEATHERING *the* STORM – TOGETHER

By Stephanie Sutton

*M*uch praise has been lavished on pharma companies for quickly developing effective COVID-19 vaccines, but big pharma rarely works alone. CDMOs tend to fly under the radar of the general public, but their efforts have been absolutely crucial in our collective pandemic response. Here, we ask five CDMO gurus how they reacted to COVID-19 – and how the pandemic will shape the future of outsourcing and collaboration.

Back at the very start of the pandemic, what concerns were you hearing from customers? Were companies complacent about the future?

Cannon: There were concerns at the time about travel and supply chain disruptions, as well as more general worries that the pandemic would present significant challenges for the industry in terms of timelines for preclinical work, IND filings, clinical trials, LA filings, product launches, and commercial supply.

Customers were not complacent; they were keen to know specifically what measures their CDMO partners were taking to secure supply chains and ensure delivery from manufacturing sites. We provided many assurances to customers and had to take new measures to further secure supply long term.

Butler: Looking back at the outset of the pandemic from today's viewpoint, I don't think many customers or suppliers were contemplating the extent and duration of the impact we have experienced. At the time, concerns being expressed were primarily on supply chain security and the robustness of business continuity plans (BCPs), which CDMOs were expected to have in place. I suspect if we had tested these plans against the scenarios of infection rates, extensive lockdowns, travel and transport restrictions, workplace furlough, and the rapid move to homeworking, most would have fallen a little short of readiness! I don't think this was a demonstration of complacency; perhaps more an unrealistic expectation on what BCPs can have in terms of full response plans already laid out. The CDMOs that have had most success throughout the pandemic are those that have proven their ability to respond at speed to clients' changing needs as the situation developed. It has been crucial for CDMOs' customer-facing teams to maintain frequent contact with clients – and continuity plans proved to be reliant on agile response teams.

Conway: Supply was the major concern. With China's lockdown occurring early in the pandemic, many pharmaceutical companies were very concerned about their supply chains and whether they could source from China. Those CDMOs with robust supply chain management were able to survive the disruption. We relied on resources at our 23 sites across three continents, as well as the global supply chain supporting these locations. Existing efforts to dual-source from different geographies and establish suitable stockpiles also helped – and, in my view, the pandemic has accelerated discussions around reshoring and rebalancing supply chains.

Speed was another concern that quickly became apparent. Whether it was vaccine research and development, COVID-19 treatments, or drugs in the pipeline, CDMOs were under pressure to work very fast. And we no longer had the luxury of months-long contractual obligation discussions!

Berger: We also received early concerns about China. Because the virus was initially perceived as a regional issue in China, customers

“I do not think the global response to COVID-19 would have been anywhere near as effective without the CDMO industry being as flexible and collaborative as it has been.”

had questions about supply chains and how reliant they were upon materials from China and other countries that were affected early.

We quickly mobilized working groups to look deep into our supply chains and identify potential areas of risk. And that meant going beyond the top-tier bills-of-material and our immediate supplier network to understand what – or who – they were reliant on, to consider any and all risks throughout the chain. Even a shortage of minor parts or a key consumable had the potential to affect production of important medicines, so together with procurement specialists working at a cross-company level, we set up local “war rooms” to analyze and mitigate against any foreseeable shortage of materials, including consumables and additional PPE.

As the virus spread, concerns about materials having to cross borders and local travel restrictions grew. And when the world began to realize the enormity of the pandemic, thoughts turned to longer term supply and the continuity of operations. CDMOs are an integral component in customers' supply chains – and so had to make decisions that balanced employee safety with the need to act as a trusted and reliable business partner.

Isele: Communication was important from the very start – even before we realized the extent of the disruption. We communicated with all of our customers from the outset about the state of our supply chain and our stock of raw materials. And we continued to communicate with our customers globally on a monthly basis as the pandemic went on, updating them on supply forecasts, while ensuring that we alerted them to any issue in materials or consumables supply

that could impact on manufacturing. High transparency was crucial in providing customers with confidence in a CDMO's ability to continue to support them.

When did the reality of the pandemic start to hit? And how did this affect CDMO workloads?

Cannon: The reality hit us all almost immediately. We had to rapidly build and expand manufacturing capabilities and supply chains to support our customers. We worked to deliver on the increased demand across all our business areas, from small molecules to biologics and cell and gene technologies, to increase our development service capacity and activities to enable the development and manufacturing of new COVID-19 treatments and vaccines.

Berger: Our clinical supplies business is often a bellwether for change, and was the first part of the company that had to creatively address multiple logistical challenges to make sure that investigational medicinal products continued to reach clinics, and that trials were not affected.

Elsewhere in our network, the company was positioned well, from both capability and capacity standpoints, to become a "go-to" partner for COVID-19 programs and vaccines. We had already initiated an expansion at our Bloomington, Indiana, facility to increase fill/finish capacity, and had recently acquired an experienced large-scale launch facility in Anagni, Italy; it would later become a European center of excellence for vaccine fill/finish.

But operations could not continue without a highly skilled workforce. In addition to protecting their safety at work, we had to take additional steps to provide alternatives to public transport for commuting, and helped when employees faced issues providing care for family members.

I do not think the global response to COVID-19 would have been anywhere near as effective without the CDMO industry being as flexible and collaborative as it has been.

Isele: I think that, for many CDMOs, the first issues to arise were delays in the arrival of PPE, including cleanroom clothing, mouth and face coverings, disinfectants, gloves, and other items all critical to maintain an aseptic environment within cleanroom areas.

The next challenge was a shortage of primary packaging material to meet additional pharmaceutical demand. Both shortages were exacerbated by delays in exporting and importing caused by COVID-19 restrictions at international borders.

The Gurus



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A third issue that many CDMOs had to contend with was the implementation of shift work groups to create “social bubbles.” These were crucial to avoid unnecessary employee contact to limit the spread of COVID-19 and to minimize the number of people having to self-isolate in the event of a positive COVID-19 case.

All of this did affect productivity. But we mitigated the disruption as quickly as possible by diversifying our supply chains for PPE and packaging to identify more reliable, robust, and local sources. We also invested in production lines to minimize the impact of reduced employee numbers on site.

Butler: I would point to the onset of lockdowns; that’s when the traditional ways of working had to change quickly. We had to rapidly establish global priorities of ensuring staff safety, whilst also ensuring continuity of supply to patients. Ensuring the safety of our workplaces increased workload due to the need to ensure COVID-19 secure controls were properly designed, risk assessed, implemented, and monitored. It was a huge effort, but it was essential to allow the business to continue operating as normal as possible to meet the needs of customers.

Conway: For us, the effect was fairly immediate. As lockdowns occurred across the globe, CDMOs – like virtually every other industry – needed to make adjustments and find new ways of working to meet obligations and join the effort to find solutions to COVID-19. At the outset, we established a cross-functional task force that met daily to evaluate the current situation, provide guidelines, establish policies, and communicate updates regularly to the global organization, while interfacing weekly with our executive leadership team. Our communications reinforced our commitment to put employee health and safety first.

As for our facilities, we took a very conservative, data-driven approach to staffing essential laboratories and facilities; people worked from home, where possible. Because we were able to socially distance, move to dual shifts at most sites, and provide the proper protective equipment and sanitization measures, we were able to maintain our workloads and meet customer needs. We continue to stay the course and, because of that, our absenteeism due to COVID-19 has been minimal throughout the pandemic. The ancillary benefit is that all of our sites have stayed open and productive.

Has there been enough CDMO capacity to cope with the surge in demand?

Isele: I would say yes. Demand surged for products to support COVID-19 therapy, but at the same time demand for products

to treat other conditions decreased because healthcare providers (HCPs) across the globe were prioritizing treatment of COVID-19 patients. In simple terms, the shift enabled many CDMOs to switch production on many of their lines to the processing of COVID-19 treatments without impacting on their ability to meet demand.

In addition, many CDMOs continued to invest in their capacity throughout the pandemic, enhancing the efficiency of existing lines, and introducing new ones. These efforts were essential in providing the capability to ramp up production – of both COVID-19 treatments and therapies for other conditions – further if needed.

Berger: In an ideal world, the industry would have had the people, supplies, and facilities with spare capacity, ready and waiting to take on the challenges of the pandemic. However, the reality is that this would have been expensive and inefficient, so Catalent – and the CDMO industry in general – has had to work in parallel to maintain constant supplies of existing medicines, while rapidly introducing new capabilities and capacity to meet the need for new treatments and vaccines against COVID-19.

Financial strength has proven important, as has a willingness to invest “at risk” to upgrade facilities and install equipment without firm orders or any guarantee that programs would receive regulatory approvals. Our actions have included initiating around-the-clock shift patterns alongside accelerating investments in strategic capacity, including the procurement, installation, and commissioning of new fill/finish and packaging lines. Together with our partners, we’ve taken steps that the company would probably not have considered during “normal” times, including the hire and training of thousands of additional people, and airlifting entire lines across to reduce transportation delays.

Even before COVID-19, the growth of biopharmaceuticals, together with other new modalities undergoing research and development, necessitated an increase in capacity – not just in manufacturing but also in allied infrastructure (for example, cold chain handling and storage and distribution to support clinical trials). Many CDMOs were investing in capacity before the pandemic.

Butler: The entire life sciences ecosystem responded remarkably to the pandemic – mainly thanks to the capabilities developed over many years in an increasingly complex environment made up of both large and small pharma companies, CDMOs, service providers, equipment manufacturers, consultants, and regulators. Clearly, redundant capacity was not simply waiting to meet the demands of a pandemic! But whether there has been demand for the supply



“Whether there has been demand for the supply of existing medicines as therapies or for new vaccines, the capacity has been created and deployed.”

of existing medicines as therapies or for new vaccines, the capacity has been created and deployed.

What other issues have CDMOs faced during the pandemic?

Cannon: The entire industry experienced an increased demand for single-use equipment for biologics manufacturing. And that led to longer lead times for many critical single-use materials – and the need for mitigation plans to ensure manufacturing timelines are not impacted. Other issues include pressure on pricing caused by a robust increase in funding within the biopharmaceuticals market, coupled with demand for access and affordability.

Isele: Another challenge was managing personnel remotely. As with other sectors, CDMOs have limited the number of onsite staff to essential personnel only, with many office-based team members working from home. The sector has had to adapt ways of working to accommodate this hybrid model, ensuring employees continue to have the support they need to work effectively, even when some are working remotely.

The implementation of hygiene rules above and beyond stringent cleanroom requirements on factory floors has also been crucial. Supporting employees to maintain high hygiene standards as they move around and away from production lines has been an important part of limiting the spread of COVID-19 within production facilities.

Another challenge has been maintaining the same high level of communication with both customers and suppliers, all while working remotely. Many companies have needed to take steps to establish effective virtual communications channels.

Aside from the pandemic, what other trends are shaping the outsourcing landscape?

Cannon: Generally speaking, the trend of building in-house manufacturing capacity is changing, and we see more drug developers focusing on the drug pipeline instead. The customer base for CDMOs has experienced a shift away from traditional “big pharma” companies to more emerging and small biotechs, whose products now comprise nearly 80 percent of the total

development pipeline.

With an increased therapy success and maturation of technologies, there is a significant growth in the field of mammalian biologics. Apart from that, an increased focus on improving efficiencies, titers, and time to delivery means that companies are implementing innovative technologies and bringing process intensification and continuous manufacturing into their practices.

Conway: I expect that we’ll continue to see industry consolidation amongst CDMOs. It could be similar to what we’ve seen with CROs, where niche players are acquired to expand capabilities and deliver scale.

Butler: The increased need for speed has become clear. The ability to achieve speed in the outcomes of clinical trials or the outcomes of establishing new product supply is an increasing expectation that customers have of their CDMO partners. Having standardized ways of working across the CDMO business with multiple sites and client interfaces is fundamental to ensuring speed can be achieved reliably and in compliance.

Another trend that has been evident for some time is the increasing expectation for outsourcing service providers to extend their service offerings; for example, integration up and downstream of the core capabilities offered to reduce the interfaces for the client – and increase the ability to form long term strategic partnerships. By doing so, CDMOs increasingly act as the bridge between customers’ medicines and patients.

Berger: The industry has seen a surge in emerging pharmaceutical companies, not only in early development but all the way through the cycle, including commercial launch. This boom was fueled by increased access to funding from public markets, private equity, and venture capital backed firms. These companies outsource more, as they are unlikely to have manufacturing capabilities in-house or the depth of knowledge needed in other key areas, such as regulatory compliance or analytical testing. Larger customers have also focused more on new modalities, and required more help from partners than they would have for more established manufacturing platforms, where they reduced investment. As a result, the overall outsourcing rate has steadily increased over the last few years.

Drug discovery and R&D has yielded a wide range of promising new drugs, but challenges exist in commercializing candidates into commercially-viable products. With the emergence of so many new modalities – from mRNA technologies to allogeneic and autologous cell

therapies to gene therapies to CRISPR to microbiome enhancing treatments – the industry will be hard-pressed to integrate development and commercial manufacturing scale capabilities. The challenge, which we have witnessed and overcome for the introduction of other new therapies, will be in transforming concepts into real medicines that can be produced at an appropriate scale and cost.

What types of services/projects do companies generally prefer to outsource?

Conway: It can be anything across the board. Right now, there is a lot of focus in biopharma companies on the “next generation” of biopharmaceuticals – whether it’s mRNA and lipids, drugs for rare and orphan indications, cell and gene therapies, or highly potent products. Often, expertise for these emerging fields cannot be found entirely within pharmaceutical companies. Additional capabilities, capacity, and know-how can, however, be found in CDMOs.

Butler: The outsourcing services market is extremely diversified, with a wide range of services available. Whether a customer chooses to outsource or not will generally depend on their size, business model, and the stage of the medicines lifecycle they are engaged in. Outsourcing initially began with customers wanting to focus on their core business and looking for CDMOs that complement internal capacity or capability. Today, clients are increasingly looking to work with partners who bring technical expertise with capabilities that are not duplicated in house

Cannon: Some companies may choose to outsource development or manufacturing that require very specific know-how or technology, such as bioconjugation/ADCs, live biotherapeutic products, or services targeting their specific drug product needs.

Has the pandemic increased demand for CDMOs who can work with mRNA?

Conway: One major positive effect of the pandemic is the successful development and utilization of mRNA vaccines. These vaccines have proven to be safe and effective, with substantial advantages in development time and production scale. This opens the door for more mRNA products. We have seen a significant number of new therapeutic programs that are based on mRNA and lipids, which is encouraging CDMOs to invest in new expertise to deliver end-to-end solutions for mRNA developers.

Cannon: The pandemic definitely sped up the development and testing of mRNA-based vaccines. With proven efficacy of mRNA vaccines against COVID-19, the potential of this new modality has been fully unlocked

“Right now, there is a lot of focus in biopharma companies on the ‘next generation’ of biopharmaceuticals – whether it’s mRNA and lipids, drugs for rare and orphan indications, cell and gene therapies, or highly potent products.”

and we should now expect new programs that target other infectious diseases arising soon; for instance, influenza, Zika, rabies, or even more complex targets, such as malaria and HIV. These developments will certainly create more demand for CDMO services.

Isele: I agree. Demand for mRNA-specialist CDMOs has increased considerably as a result of the pandemic. Nevertheless, there are few CDMOs with this capability, and this lack of supply is causing a bottleneck for development projects. In addition, a lack of specialist equipment and consumables is further restricting capacity.

Many CDMOs with mRNA expertise are currently investing in their production to meet increasing demand. They are also working with suppliers to improve security and reliability of specialist consumables and other materials to meet customers’ future mRNA development needs.

Berger: Before the pandemic, there were some CDMOs that had experience at certain stages, such as plasmid DNA or fill/finish, but few had the knowledge or the capacity to perform most of the steps in the manufacturing process. For example, mRNA requires highly specialized assays and analytical testing to properly characterize the molecule. However, interest in the field was growing and – thanks to the success of the mRNA-based COVID-19 vaccines – there are now considerable safety and efficacy data available. The numbers of mRNA programs undergoing preclinical studies and entering the clinic are increasing significantly – for infectious diseases, such as COVID-19 or influenza, and also for other indications, such as oncology and pulmonary or cardiology diseases. CDMOs with flexible capacity and the expertise to handle mRNA programs were very successful in helping COVID-19 vaccine developers to quickly scale production, and are now the best-positioned partners to support demand in this rapidly growing and evolving pipeline.

Collaboration has been crucial during the industry's pandemic response; do you think the pandemic will influence more pharma companies to see their CMOs and CDMOs as true partners rather than just service providers?

Cannon: Absolutely. And we also need to consider that the rate at which drugs are being launched by companies that have never had a commercially approved product on the market has tripled in the last decade – and these companies need good partners to help them! The investment risks associated with the development and licensure of these products, together with tight manufacturing timelines, are best managed by parties working collaboratively, rather than by any individual company.

Butler: There has been significant development of the customer/CDMO relationship over many years. A partnership team rather than more traditional buyer/supplier working relationships is typically providing more value to customers and their CDMO partners. The pandemic response has demonstrated that those CDMOs with the ability to solve problems, innovate and show speed of response are true extensions of the customer team.

Isele: The race to develop and roll out effective COVID-19 vaccines worldwide has demonstrated the benefits of collaborating with expert development and manufacturing partners. Vaccines were developed, trialled, and commercialized in record time!

I think (and hope!) we will see pharma companies working more closely with CDMOs on development projects in the future, and that CDMOs will be brought on board earlier so that they can offer their insight into key project challenges. In addition, I expect to see pharma companies in the future seeking out CDMO partners who can support them throughout the development and commercialization process, as a way of streamlining and integrating the supply chain – minimizing cost and complexity.

Berger: To expedite development and supply, innovators and their partners had to take certain commercial risks as they scaled up COVID-19 therapy and vaccine programs. There are considerable disincentives for taking such risks, but hindsight shows that if we are to reduce the timelines associated with pharma and biopharma programs without compromising quality and regulatory pathways, measured risk does have a place. This may stretch from commencing work before contracts are signed, through to procuring resource, talent, or capital equipment without the security that a development and manufacturing partner will immediately see a return on that spend. Our industry cannot take chances that could jeopardize patient safety, but with experience – and by working closely with partners – CDMOs have shown that they can respond quickly and safely to global challenges. I am hopeful that this experience and the partnerships that have been forged throughout these most challenging of times will see the evolution of longer-term collaborative working practices.

Conway: Partnering with a CDMO that can support manufacturing scale up at a commercial level has become more important as companies grow their pipelines. Increasingly, I think pharma companies are also waking up to the fact that contract partners can be very knowledgeable about new technologies and new ways of making use of data. Ultimately, partnering with a good CDMO enables agility, speed, efficiency, and quality.

What trends do you expect to shape outsourcing in 2022?

Cannon: I see significant trends to increase manufacturing speed. In addition, customers are increasingly looking for long-term capacity security ahead of launching new products – and this goal is impacting the way we are structuring deals with our customers.

There are also other trends affecting the biopharma industry as a whole, such as the rise of new and more complex modalities being developed (and outsourced). There is also a move to greater automation and new technologies, such as AI and machine learning – which are even being used to develop new therapeutic platforms. Given the rate of new technology emerging, I think we can also expect to see faster technology maturation and adaptation.

Isele: As the pandemic begins to wind down, I think we will see the production of COVID-19 vaccines transform into a seasonal manufacturing campaign. It is unlikely that we will see COVID-19 vanish as an infection. To meet the demand for boosters, CDMOs will have to maintain some capacity dedicated to vaccine production.

Berger: We foresee outsourcing rates continuing to rise because of the growing pipeline in advanced modalities in cell and gene therapy, as well as other biotherapeutics, the growth of emerging biotech companies, and niche small molecule technologies. However, COVID-19 will continue to play a critical role in the global surge and rapid utilization of biologic drug substance and drug product capacities. Right now, much of the world remains unvaccinated and the risk of variants remains, so it remains likely that there will be ongoing demand for drug substance and fill/finish capacity for COVID-19 vaccines and therapies.

Cell and gene capacity will also remain in demand, and expertise in this area will continue to be important, as the technology looks to be improved in terms of manufacturing yields and integrated upstream and downstream processing, including in the supply of critical materials, such as plasmid DNA.

Butler: It is likely that the demands of the pandemic, with priority given for capacity to the need to respond to COVID-19, has resulted in build up demand in non-COVID-19 supply chains. But we are also expecting COVID-19 booster programs, so needs will have to be balanced.

Growth in biologics and increased complexity in medicine delivery devices with patient adherence technology will also present demands on outsourcing. CDMO capabilities, technical knowledge, and competence will need to increase to accommodate these demands.

TAKING THE TRIAL TO THE PATIENT

“Thank you for signing up for this clinical trial. We expect you to visit the trial site twice a month and fill in this daily diary... Wait, why are you all dropping out?” It’s high time pharma made improvements to the clinical trial process.

Based on an interview with Rob Bohacs, Founder and Chief Solutions Officer, ClinOne



Clinical trial patients are incredibly special. They embark on a journey to help discover and provide clinical data for drugs that could help not only themselves but also patients all over the world. However, the way the pharma industry has traditionally handled clinical trials does not make participation easy. In fact, it can be quite an unpleasant experience.

First of all, it can be difficult for patients to find clinical trials in the first place, let alone be accepted for a trial, for a variety of different reasons, including often stringent inclusion/exclusion criteria. When patients do finally secure a place on a trial, a great deal is asked of them. Many patients are asked to attend a trial center once or twice a month – and I’ve even seen trials that require patients to visit once a week. Patients may also have to take part in additional imaging or biopsy procedures. Then, when they are at home, patients have to fill in diaries or electronic questionnaires on quality of life, using antiquated devices. It’s a difficult experience. In addition, although some clinical trial coordinators do an amazing job, others can be quite poor, and there can be disruption and confusion for patients if coordinators change. At times, I’m amazed that some trials even get off the ground in the first place!

I can provide an example from personal experience. A member of my family was diagnosed with stage three breast cancer. She had to call up institutions one at a time to see what trials she might qualify for. You may be surprised to learn that large academic institutions typically do not communicate or collaborate to spread information about what trials exist even with other providers on their own campus – never mind what patients they have that may qualify for trials outside of their own four walls. I’m involved in the pharma industry and even I was having a hard time figuring out how to help my family. I can only imagine how someone feels when they are trying to understand the process without the support of someone who knows the industry.

We have to change this. Patients need an easy way to access information about which clinical trials they can qualify for, and there is a huge opportunity in the industry to consolidate information and improve the clinical trials process. Given that patients can be asked to commit to a trial (and all of the above challenges) for years, it’s no wonder that clinical trials tend to suffer from low patient enrolment and high dropout rates. This will not change until pharma addresses three important pillars: the perception of clinical trials, the availability of clinical trials, and how patients are managed on trial.

Another challenge is that clinical trials are dynamic (particularly oncology trials); screening criteria change and protocols may change. At the same time, a cancer patient’s disease can change and progress, and this may affect whether a patient still qualifies for (or must be disqualified from) a trial.

MODERNIZING TRIALS WITH TECHNOLOGY

My background lies in pharmaceutical contract research management and it was clear early on that there was much room for improvement, particularly when it came to remote patient management and implementing technology. I felt there was a real need to support patients better. Patients who participate in clinical trials should be given the best experience possible.

As an obvious starting point, it would be much easier for patients if they could contribute more from the comfort of their own homes – with fewer visits to trial sites. If we want patients participating in a trial for five years, we shouldn't ask them to visit a research site every two weeks. It's a major disruption; not all patients have transport or can afford that constant time off work. What if we developed software that would allow patients to be a part of trials globally – software that could tell participants what to do every day so that they wouldn't feel lost?

I broke away from my role at a contract research organization and founded ClinOne – a company that offers a platform to connect, inform, and empower patients to help them take control of their clinical trial experience.

COVID-19 led a number of clinical trials to be placed on enrolment hold for a long time because many patients wanted to stay safe at home and manage their indication as best they could. But in some cases, patients with serious illnesses didn't have a choice and trials had to continue. Cancer patients, for example, must have treatment or take part in a clinical trial, but venturing out to a clinical trial site could expose patients to risk of catching COVID-19.

Not all companies were in a position to simply halt their trials; companies rely on clinical programs to meet funding milestones. The challenges led more companies to think outside of the box – and we saw more companies coming to us to ask about solutions. And there definitely are solutions! Prior to the pandemic, pharma companies were already exploring telemedicine to reduce some site visits, but many were having a hard time moving away from the old way of doing clinical trials because it's what they have always done. There are technologies that can touch both the research side and the patient, but for me it is the technology for patients that is really exciting. Why? Because it allows us to recruit and manage patients remotely.

It would be amazing if a clinical trial investigator had time to call Jane (the patient) every single day to ask if she had taken her medication, how she's feeling, help her arrange



Rob Bohacs, Founder and Chief Solutions Officer, ClinOne

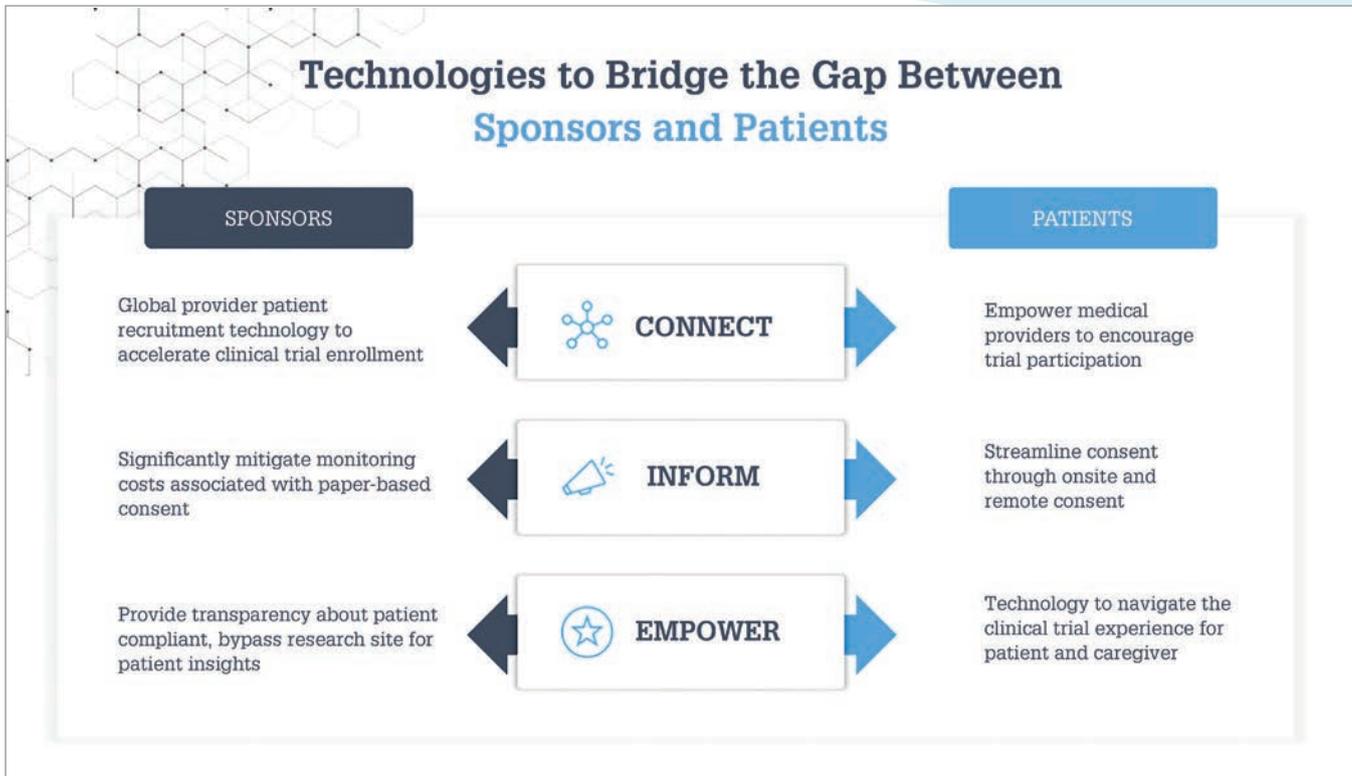
transportation when needed, and discuss her activity level. But this is impossible; investigators simply don't have the bandwidth or the time, but software does. Software can “talk” to the patient through interactive text messages or other mobile technologies. We can also equip patients with – frankly amazing – wearables that track heart rate, temperature, activity levels, and much more. If something doesn't seem right – for example, if patient doesn't get out of bed for two days – the device can alert the site. In some cases, patients may barely need to visit the trial site at all because the information can be gathered by wearables and telemedicine calls. The information can also be captured in real time – something that the FDA and the EMA continue to push forward.

There is also a lot of investment entering the remote clinical trials space. If you haven't already started, you should explore the technology landscape, consider how your clinical trials are run – and then ask yourself: “Can we do better?”

Raising Awareness

We live in a fast-paced world. We are used to convenience; packages and groceries can be ordered with same-day delivery. We cannot blame patients for not wanting to take part in archaic clinical trials or for dropping out when we constantly ask them to come to us. In this day and age, we need to take the trial to the patient.

So, how could – or will (let's be optimistic!) – clinical trials work in the future? I want patients to be able to log in from home, have the opportunity to add in their electronic



healthcare record data, and have the opportunity to see relevant trials. Imagine if all clinical trial datasets from major institutions could be pulled together so that patients could see what was available... From there, a patient could choose to participate from home, wearables could be delivered to their door, which would help keep them safe and us apprised of what is happening. And we can make it even easier. When it's time for a blood draw, the patient doesn't have to go to the clinic; again, they receive a package that allows them to do it themselves – and us to receive the data (or sample) we need. I want all of the information to be collected and integrated – and that's something we're constantly focusing on at ClinOne. My goal is for a seamless patient experience.

And with increasing innovation and convenience, I hope more patients (and their families and friends) will become more knowledgeable and more interested – even excited – about clinical trials. From the sponsor to the technology companies to the researchers... so much investment goes into the clinical trials process – but I don't think there are enough organizations

fighting to raise awareness with patients about how clinical trials are evolving.

Besides ourselves, there are many people trying to improve the clinical trials process and it's important that patients learn about the progress – it could change their lives.

On a side note, it has been incredible to see how many members of the public were willing to take part in clinical trials for COVID-19 vaccines. In less than a year, there were over 40,000 individuals participating – and many of these people had never taken part in a trial before.

We were involved in managing some COVID-19 trials and it's been very exciting. There is now a much greater awareness amongst the public about COVID-19 trials – and trials in general. I hope the experience was eye-opening – in a good way! I hope people realized that being a participant in a trial wasn't scary and that the end result was amazing.

As an industry, we should take this momentum and generate even more publicity around the fact that clinical trials move medicines forward for everyone in the world.



UPDATES READY: REBOOT NECESSARY

Clinical trials are now more complex than ever, and technology has not kept pace. Though a shift to digital decentralization has begun, all too often the solutions are just stitched onto already underperforming legacy systems.

By Temitope Keyes, Executive Director, Business Development, Cmed Technology, Horsham, UK

It is news to no-one in the industry that we have a history of bolting together disparate systems to eke out new functionality and meet emerging trial needs. The resulting patchwork of systems has evolved and expanded over time, but was never designed as a functional and cohesive whole. As such, trial data and information are, unsurprisingly, not always properly integrated. Add to the picture cascading data from high data-load sources, such as wearables, biomarker labs, and electronic patient reported outcomes, and it falls to clinical operations and data management staff to connect the dots of this vast, unwieldy matrix.

Unsurprisingly, clinical teams compensate by creating workarounds. The most common of these entails pulling extracts into Excel. In an era of inflating data volume and complexity, such practices hinder the availability of data and delay critical trial decisions. Sponsor teams are denied the benefit of a “single source of truth,” which limits patient centricity and erodes investments in upstream analysis tools by reducing the speed of reporting and visualization. We need to accept that many of the individual systems are aging and no longer fit for purpose.

The use of eSource (direct data capture), adaptive trials, and new risk-based approaches and their supporting technologies is commonly supported by regulators, but some areas of the industry seem slow to embrace them. Analytics is rarely supported or considered, which limits programming options and passively preserves a cumbersome, suboptimal process. New systems must provide effective, user-friendly visualization of trends across patients, sites, and trials. They must support multi-modal data monitoring of trial conduct and provide performance metrics against key indicators – even for the most complex trials. Ultimately, the objective is to increase data quality, improve patient safety, and facilitate rapid data aggregation and decision-making.

In my view, it's important for sites to have the opportunity and the flexibility to update their procedures and use new technology options, such as trial virtualization and central data monitoring. For example, instant data visualizations available 24/7 would increase clinical awareness and improve patient safety and oversight. DCTs require a single-technology platform that allows for improvement of efficiency through practices, such as data standardization, and training in data transformation processes. It's best to look for a clinical



trial platform that offers multi-modal and centralized data collection to help standardize quality across sites, and enable full traceability of that data for auditing purposes. No matter which system you choose, it's important to ensure that disparate data can be easily integrated and immediately available for review and decision making, as sponsors will be able to act more quickly and make optimal decisions for the clinical program, compliance, and safety of patients. With the right technology in place, sponsors can realize their goals of running flexible, dynamic DCTs. And it includes the power of big data, artificial intelligence, machine learning, and natural language processing. A radical digital transformation has long been a vision for clinical trial leaders.

Moving clinical trials forward in our new digital reality is not about loosely linked point solutions or so-called unified solutions. It is now vital to have a data strategy built around technology platforms that can truly support the current and future health innovation of sponsors – no matter where the sites or the patients might be.

THE GLOBAL STAGE

How do we overcome the challenges of taking clinical trials into emerging geographies?

By Claudia Berrón, Senior VP, Clinical Services, Avantor

From increased demand for biologic treatments to the urgent need for COVID-19 vaccines, the clinical trials industry has been challenged to develop trials more quickly than ever. To meet these demands, sponsors and CROs have been expanding capacity by conducting clinical trials in emerging geographies.

In the clinical trials market, “emerging geographies” typically refers to the BRICS block (Brazil, Russia, India, China and South Africa). Recently, the Middle East has also been an expanding geography for clinical trials. There are three primary reasons to consider conducting clinical trials in these areas: i) large patient populations that allows faster recruitment and offers broader diversity, ii) increasing prevalence of chronic diseases, such as diabetes and cardiovascular disease (helpful for trials for drugs targeting these areas), and iii) more cost-efficient trials than those in Western countries – especially when it comes to trials for comparator drugs, which are less expensive to source in emerging regions.

To benefit from conducting clinical trials in these regions, there are four key challenges that need to be considered.

I) Regulation. Over the last five years, regulations in BRICS nations have advanced to provide sponsors and CROs with greater transparency; however, the regulatory process can be lengthy and entail extensive bureaucracy that varies between countries. It’s essential for sponsors and CROs to understand regulations within all relevant jurisdictions to avoid inadvertent violations, which could add cost and time, and potentially impact local community trust. Partnering with in-country investigators, particularly during protocol development and the submission process, can help avoid these challenges. Whether working with a local CRO or an international CRO with wide expertise in conducting trials in a specific region, specialized expertise can help trials run smoothly and stay on track.

II) Culture. Many emerging regions have a legacy of traditional medicine, making it difficult to recruit community members to participate in studies for drug development. In addition, some communities have had prior experiences with clinical trials that led to lingering mistrust, which can make it difficult to recruit patients for new studies. It is important to engage with communities in these regions to build trust. Establishing or partnering with community engagement boards (CEBs) – comprised of multiple levels of local leadership, such as health care officials or rural leaders, sponsors, and CROs – can facilitate recruitment and bridge potential trust gaps.

III) Staffing. Sponsors and CROs often rely on local people to conduct trials, but ensuring that staff are properly trained in good

clinical and laboratory practices may not be straightforward. A second critical factor is that staff turnover in emerging regions tends to be higher than in Western countries. These challenges are common, so sponsors and CROs should have staffing and training plans in place before the clinical trial begins. In addition to comprehensive training programs, it is essential to ensure staff continuity with initiatives like “train the trainer” programs that can enhance a staff’s knowledge. Well-documented standard operating procedures are also an important tool for ensuring clinical trial continuity in emerging regions.

IV) Infrastructure, especially logistics. Infrastructure creates unique challenges from country to country. For example, a specific region within a country might be prone to frequent power outages, which can impact refrigerated drugs. It’s important to properly prepare a clinical trial for situations that might not typically impact a study conducted in a Western country. Sponsors and CROs can mitigate risk and create confidence in their infrastructure by leveraging external quality assurance and international audits. External audits help ensure that the work aligns with quality standards, such as Good Clinical Laboratory Practice (GCLP), common in Western regions. Though the pandemic’s impact made it difficult to establish international audits, emerging geographies were well prepared to ensure trial integrity, and it will likely become easier to conduct those audits in the near future to continue elevating clinical trial standards globally. Logistics is a key infrastructure consideration. Clinical trials require not just equipment but a continual stream of ancillaries moving across multiple jurisdictions. Sponsors and CROs should consider experienced freight management partners to transport, protect, and track valuable assets and ensure supply chain integrity. Digitalization tools can also play an important role in overcoming logistics challenges. For example, a kit with a scannable label can be tracked across the entire supply chain – from the kit assembly line to the clinical trial site to the laboratory and, eventually, to the biorepository.

As the demand for clinical trials grows, emerging regions are increasingly valued partners. But only by understanding – and addressing – the challenges, can sponsors and CROs fully benefit from potential advantages that allow researchers to get life-saving treatments to market faster.



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Staying on the Track to Eradication

If the World Health Organization aims to meet its goal of eradicating malaria by 2050, pharmaceutical companies will have to play a key role in the fight. In particular, changes will have to be made to diversify the offering of drugs available.

By Rosanne Rotondo, Business Head of Flagship Programs at Novartis Corporate Affairs & Global Health

Despite remarkable progress, the global gains in combating malaria have leveled off in recent years. In 2019, we were all reminded of how far we still need to go. The disease claimed some 409,000 lives compared to 411,000 in 2018 and is still killing more people than COVID-19 in Africa, which bears 90 percent of the world's malaria caseload (1). Every two minutes, a child dies from this preventable and curable disease with two-thirds of these children aged under five (2). This is more than just a statistic – it represents a lost generation of scientists, engineers, teachers who could have contributed to a more prosperous future.

If the pharmaceutical industry is to play its part in bringing solutions to the problem, we must consider the current treatment landscape and ask ourselves what is needed to change the situation.

Beating the resistance

In May 2021, Novartis reached a milestone delivering one billion courses of antimalarial treatment since its launch in 1999. More than 90 percent of this ACT

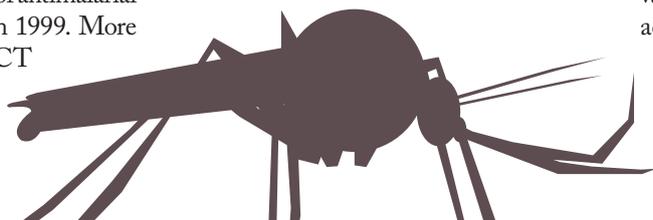
was supplied without profit to malaria-endemic countries around the globe.

Novartis and Medicines for Malaria Venture (MMV) developed the first dispersible ACT formulation for infants and young children with malaria, which was launched in 2009 and gained WHO pre-qualification as a medical breakthrough. Since launch, more than 430 million dispersible treatments for children have been distributed in malaria-endemic countries and are contributing to a significant reduction in malaria deaths.

ACTs are highly effective and well-tolerated short-course treatments for malaria – clearing the parasite in 95 percent of patients (3). However, there is still a need for better treatment options in specific,

highly vulnerable groups, such as infants under 5 kilograms. Current treatments also require a number of doses to be delivered over a minimum three-day period, which can lead to compliance and adherence challenges in under-resourced settings.

There is also still a risk that resistance to treatment will develop. In South East Asia, cases of ACT resistance have already been seen and there are early signs in Africa too. These resistant strains can be treated with extended courses of ACTs, but the emergence of more widespread resistance is almost inevitable. As with previous treatments, we foresee a future where current treatments will fail to work. In response to this threat, the world needs a diversified pipeline of antimalarials with new mechanisms of action and with activity against resistant parasites.



Improving the arsenal

At Novartis, we are contributing to the fight with three new molecules in development, including two in phase II clinical trials. Our antimalarial drug candidates KAF156, KAE609 and INE963 were selected for their ability to treat malaria in different ways from current therapies. KAF156 (ganaplacide), for example, belongs to a novel class of antimalarials (imidazolopiperazines) that demonstrated activity against malarial parasites including *Plasmodium falciparum* and *P. falciparum*, and is effective against artemisinin-resistant parasites. It acts against both the blood and liver stages of the parasite's life cycle. We are developing KAF156 as a combination with another antimalarial compound called lumefantrine. We're working in collaboration with MMV, with support from the European and Developing Countries Clinical Trials Partnership (EDCTP) to push this through clinical development, and we hope to be able to enter late-stage clinical trials with this new combination within the next two years.

Another novel agent, KAE609 (cipargamin) has the potential to be used in severe malaria, as well as in acute episodes. A phase II study in severe malaria is starting this year. Our newest compound, INE963, also has an entirely new mechanism of action and is expected to be both fast and long lasting. Preclinical data indicate that this compound may have a high barrier to resistance. INE963 can also potentially be given as a simplified regimen compared to current treatments. INE963 started a phase I clinical study in May 2021. This compound, which was discovered through phenotypic screening received MMV's Project of the Year award in 2019.

We are hopeful that we will have a portfolio of novel antimalarial combinations ready to fight any ACT-resistant malaria strain that emerges in the next decade or two. However, we will not know, of course, until the phase III trials are completed, and the products are approved.

Access for all

Whether in Africa or Asia, malaria mostly affects people who live in remote or rural areas, where access to healthcare is often a challenge. In these regions, access to treatment is only one part of a holistic approach, which must include provision of the right infrastructure and a robust supply chain, as well as access to prevention tools, diagnostics and antimalarials. We've committed to the implementation of an equitable pricing strategy to further help expand access to pediatric antimalarials and implement healthcare system strengthening programs in four sub-Saharan countries, beginning in Nigeria and Kenya, which bear a high prevalence of malaria.

We have also supplied ACTs at no profit through an agreement with the WHO from 2001-2011 and have voluntarily continued with this pricing policy after the agreement lapsed. Organizations like the Global Fund to Fight AIDS, Tuberculosis & Malaria and the US President's Malaria Initiative have provided hundreds of millions of dollars to support access to ACTs to patients who may not be able to afford it. But the issue of patient access to care remains a roadblock, particularly in Africa. One recent study found that in nine African countries, only one third of children under five diagnosed with malaria are getting the right treatment and care, though this figure is starting to trend upwards (4). For this reason, we are working with partners in Nigeria to strengthen access to diagnosis and treatment at patent and proprietary medicine vendor shops for children under the age of five; these are shops that sell medicines without a qualified pharmacist – and are often the first choice for the majority of Nigerians seeking care for a child under the age of five suffering from fever (5).

In Kenya, partnering with Save the Children, Novartis is working to provide affordable and effective healthcare to the most deprived children. This project aims to tackle the problem of under-five child

“Malaria can be eliminated as a public health problem in less than 30 years.”

mortality through treatment of malaria, pneumonia, diarrhea, and malnutrition.

In India, we are also running a malaria screening campaign in six districts in Odisha, a highly endemic state bearing almost a quarter of the country's malaria burden. When diagnosed with the disease, patients received a prescription and were advised to visit the nearest government health clinic for treatment and follow-up.

The WHO believes that with the right investment and development of new tools – including better antimalarials – malaria can be eliminated as a public health problem in less than 30 years. This would cost a fraction of the global COVID-19 response and would have immense benefits for patients. We want to be part of this elimination story by maintaining our commitment to defeating malaria.

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One Stop Shop

In a market filled with complexity, working with a single supplier simplifies the supply chain and focuses effort towards a single target

*By Adam Stops - Drug Delivery Systems
Product Manager at Stevanato Group*

The pharmaceutical industry is evolving, with a trend towards high-value products like complex therapies and combination products. The demand for these complex therapies is inspiring drug developers to think more about the right containment and delivery systems; developers are looking for system solutions that offer superior levels of quality, patient comfort and stringent regulatory requirements.

But the need for state-of-the-art packaging and delivery solutions is not just restricted to newer products. Across the whole pharmaceutical industry, drug developers are looking for improved supply chain efficiency and cost-effective go-to-market solutions. Additionally, the COVID-19 pandemic has changed the

way companies view supply chains and operations; many now recognize the challenges of working with multiple suppliers across different geographies. Simply put, pharmaceutical companies are increasingly keen to explore how a single provider can support all of their combination product needs – from sourcing the right, high-quality containment system to ensuring the appropriate manufacture of the delivery device.



With world-class manufacturing capabilities and over 70 years of industry experience, Stevanato Group excels at creating customized drug delivery and containment solutions for pharmaceutical companies.

Our ethos has always been to listen to customers and remain flexible to the needs of the customer. Moreover, our large global footprint allows us to connect with customers the world over. By working closely with a supplier who can provide a cohesive and efficient service – providing optimized glass containment and device services, as well as the appropriate equipment and analytics – pharmaceutical companies can simplify their commercial journeys. In fact, we can support pharmaceutical customers at every stage of the process – from the choice of

container to the manufacture of the delivery device for the combination product.

Delivering real quality

Stevanato Group offers a broad range of products and services to ensure that our customer's drug products are matched with the best possible containment and delivery systems. Customers can either choose all of these services for holistic support – or they can mix and match. For example, our customers can work with us to learn more about the different types of containers available for their particular needs, including support for extractable and leachable. Here, our analytical services can extract deep insight into the compatibility of a customer's final drug product with the chosen container – from extensive feasibility and development testing all the way to design verification testing that can be used as part of their combination product and regulatory submission.

Some companies are also keen to use drug delivery devices, like pen injectors (see sidebar, Alina in Focus); we can offer support here too. Stevanato Group has invested in platform technologies, like Alina, to enable more pharmaceutical companies to provide healthcare to patients. By providing platform, off-the-shelf technologies, pharmaceutical companies benefit by being able to



Alina in Focus

Stevanato Group offers a wide range of drug delivery systems to service the ever-increasing need toward self-administration. Adam Stops tells us more about Stevanato Group's Alina platform pen injector, which provides a cost-effective alternative to customers wishing to enter into Combination Products.

What is SG Alina?

SG Alina is a manually operated, variable and multi-dose pen injector. Alina was designed to be a truly patient-centric device wherein dose dialing, injection forces and dosing have

been optimized for patient comfort. The injector features visual, audible, and tactile feedback for dose setting, and a clear pre-injection dose indication to avoid underdosing; we also incorporate dose correction to avoid injection errors.

SG Alina, manufactured in our site in Germany, is suitable for all standard 3 mL glass cartridges and has also been optimized for our SG Nexa® 3 mL solutions to enhance speed-to-market.

How does Alina meet Pharma customers' needs?

As an off-the-shelf product with customizable features, SG Alina allows pharmaceutical companies to benefit from

low upfront investment costs by accessing the installed production capacity at our manufacturing site. It also enables choices on styling, color and dosing regimes from the in-built customizable options that allow the pen injector to be optimized toward specific patient groups and therapies. Another key advantage of the SG Alina platform is that it has been developed as an integral part of a full solution: we recognize the delivery device is just one important part of the combination product and so from our deep understanding of how pharmaceutical products, containers, closures, and drug delivery devices interact with each other, we have designed SG Alina to ensure an optimal system solution.



access drug delivery device technologies with a low upfront cost and a fast time-to-market. Along with the benefit of leveraging the extensive experience of our plastics and device experience at our world-class manufacturing facility in Germany, Stevanato Group can support customers in selecting the optimal devices for their unique requirements, we can even provide testing and design support in case customized solutions are required. As market trends continue to evolve, the focus on specific drug delivery systems will continue to grow.

Flexible and scalable assembly equipment is also a crucial element of

Stevanato Group's offering, with proven technologies used to develop customized solutions. Small-scale, benchtop units are available for device and process development purposes, often useful for clinical or stability batches for submission, along with rotary platforms for scale-up toward higher volume commercial production. Fully automated, linear platforms are also available for high-volume production with complex assembly tasks, in-line automated inspection and process checks, as part of high-speed, large-scale commercial production. Support is provided throughout the process – from clinical trials to fully automatic high-volume

production. Our aim is to ensure customers choose the best equipment solutions based on their production volumes and the characteristics of their devices.

At Stevanato Group, we pride ourselves on providing customers with best-in-class devices and technologies catering to different needs.

It all adds up to a streamlined end-to-end solution for pharmaceutical companies around the globe – enabling them to focus on delivering world-class treatments to patients.

Adam Stops is Drug Delivery Systems Product Manager at Stevanato Group

Giving It All We've Got: Lessons Learned from Operation Warp Speed

Best Practice

*Technology
Quality
Compliance*

A planned facility suddenly had to be up and running much faster than expected as it became part of Operation Warp Speed. Here's how it was done.

By Jarrod Wrampe, PE, Design Project Manager and Charles Heffernan, Director of Process Engineering at CRB

In March 2020, our team set about designing and building what our client wanted to be “the largest scale-out cell culture manufacturing facility in the US.” Two months later, the US government announced Operation Warp Speed (OWS) – a partnership amongst various components of the Department of Health and Human Services with the goal of delivering 300 million COVID-19 vaccine doses by January 2021. In July 2020, our half-finished project became part of the endeavor.

Building a facility in time to manufacture COVID-19 vaccine candidates was a massively ambitious project. It was also a sobering responsibility that came with the most aggressive timelines we'd ever encountered in our careers. By the time the facility started GMP manufacturing in the fall of 2020, the Army Corp of Engineers indicated the project achieved

the highest labour density possible with 100,000 labor hours in 4 months all injury-free.

Starting with a warm shell, grey space was converted into GMP clean room space in just four months. Eight bioreactor trains and associated purification equipment were installed. One hundred new pieces of equipment were purchased and qualified. To make all of this happen at warp speed, we used an integrated project delivery approach. Nevertheless, warp speed stretched us to our limits as we navigated uncharted territory. Here's what we learned along the way – and how we'll be taking those lessons into our next projects.

Locking down decisions

At the beginning of any project, it's essential to define the ultimate goal. Then comes the real work – not getting distracted from it! For our team to have a solid foundation for design decision

making, we held multiple workshops to nail down user requirements prior to starting the design process. By the end of the kickoff discussions, it was clear the client needed a single-use, multimodal, multi-product facility to support viral vector, viral vaccine, and therapeutic protein process types using suspension culture. They required high segregation, high containment, and unidirectional flow to support their projected high throughput. In short, this client wanted ultimate flexibility.

With those details set in stone, attention turned to conducting contamination prevention and process closure risk assessments. We needed to ensure all risks of crossover, carryover, and adventitious agent contamination were mitigated and that the process was completely closed. This crucial step allowed us to get things right the first time, which would prove crucial to meeting ultra tight timelines.



But knowing what the client needed and how much risk it could involve was not enough to make good decisions; projects under tight timelines also require a meeting of minds. We connected our subject matter experts with the design manager and project director for collaboration with the client that enabled informed decision making. We also brought trade partners into the process much earlier than usual so that we could use their knowledge to further expedite the decision-making process. Together, these individuals could see the big picture and identify how a small decision or adjustment might throw off the budget or timeline. By having decision-makers tightly integrated across the project, it was much easier to address potential disruptions immediately.

Needs versus wants

Once we had made the big decisions, the next struggle was keeping them

locked. Warp speed or not, most projects are susceptible to “scope creep” as new ideas are introduced once the project is underway. A piping change here; an additional valve there... It can all add up to increasing timeline, budgets, and complications.

An essential aspect of delivering a facility on-time is focusing on non-negotiable constraints: building code, safety, and regulatory compliance. When changes were requested in this OWS project, we asked: “Does it affect safety, code, or regulatory?” If the answer was yes, the team leapt into action. If not, we ended the discussion and moved on to the next issue.

There should never be shortcuts in the areas of safety, code, and regulatory issues. In fact, the speed of the project merited increased scrutiny in these aspects. With pandemic fervor all around and incredible pressure to keep the project moving forward, managers

needed to check and recheck that they weren’t rushing past any red flags. Even a small issue in one of these categories could become a critical factor in later stages, so close attention was required throughout the whole project.

As legitimate needs came along, it was important to avoid making assumptions about how best to meet them. For example, the need for speed in meeting clean room regulatory requirements seemed to make a modularized system an obvious choice. But, in fact, modular construction was a non-starter for two reasons: the required height of the bioreactors and the slower delivery time. Instead, we opted for a panelized construction method, allowing for clean construction and fast build times. The lesson? Identify a facility’s unique needs – and don’t be afraid to try unconventional solutions. No two projects are the same so there are no one-size-fits-all solutions as you sift through the needs and wants.

Engaging Warp Speed

In May 2020, the Trump administration announced Operation Warp Speed (OWS) to help accelerate and coordinate the development of COVID-19 vaccines. OWS was a partnership between the Departments of Health and Human Services (including the Centers for Disease Control and Prevention, the FDA, the National Institutes of Health, and the Biomedical Advanced Research and Development Authority) and the Department of Defense. Other federal agencies were also involved.

A number of companies working on COVID-19 vaccines benefited from OWS funding, including Moderna, J&J, Novavax, Pfizer/BioNTech, AstraZeneca, Merck, Sanofi, and

GlaxoSmithKline. Contracts were also awarded for ancillary COVID-19 vaccine supplies. For example, Corning Pharmaceutical Technologies received around \$204 million in funding for the expansion of manufacturing capacity to produce millions of additional glass vials per year, if needed.

However, the initiative was considered more controversial when it came to vaccine rollout, with states only being told how many doses they would receive on a week by week basis, making it difficult to plan vaccination programs. The quantities available every week also varied.

In February 2021, responsibilities for Operation Warp Speed were transferred to the White House COVID-19 team.

Whose line is it anyway?

We've all heard the story of everybody, somebody, anybody, and nobody. The cautionary tale concludes: "It ended up that Everybody blamed Somebody when Nobody did what Anybody could have." This story has the potential to play out on any project, but when there's a pandemic in the mix there is simply no time for indecision or passing the buck. Decisions need to be made right away, but by whom? Defining responsibility early was key to getting this vaccine line up and running.

To enable rapid decisions, it helps to include the facility owner in the team from the first day. The results can be likened to the "IKEA effect" – we tend to value something more when we've invested our own effort into its creation. Bringing the facility owner in from the beginning to take part in the decision-making process made it much easier to talk through requested changes later on in the project – and quickly settle on a path forward.

At the same time, we also think it's beneficial to encourage facility owners to

identify one or two people in each area of expertise with decision-making authority to keep the project moving forward. Rehashing decisions or making decisions-by-committee just doesn't cut it when you have such tight timelines. You need informed decisiveness to keep a facility moving forward, regardless of obstacles. Therefore, final decisions – as well as the rationale behind them – should be shared with the entire group of stakeholders.

This OWS project emphasized that decisions tend to have a domino effect. For example, an unforeseen budgetary issue can threaten any project if left unchecked. Therefore, key decision owners are needed with an overall view of a project to understand the consequences of even the smallest decision. When a roadblock springs up, someone needs to either approve a solution and remove any roadblocks or ask for a better one – all within a single day!

Teamwork makes the dream work
Forget weekly management calls – this project required at least one management

call per day. During OWS, every team member needed to be in lockstep as changes were implemented. Whether it was a financial concern or a regulatory red flag, no moss could be allowed to grow on any aspect of the project. But how could we do that when travel restrictions shut down out-of-state travel and our team was spread across multiple states and time zones?

Communication has always been a key element of any project's success, but it definitely reached new levels during this particular project. To keep things moving, we talked multiple times per day with both our colleagues and our client. We had already set the tone by bringing our client in as a full team member, so when the project accelerated to warp speed, we already had the lines of communication open.

One way we kept up the grueling pace was by optimizing our use of available communication technology. Prior to the pandemic, our team sometimes used Teams, Zoom, or other video conferencing software. But once social distancing came into play, we replaced many face-to-face interactions with video calls via smartphone or tablet. The team also used Bluebeam for project documents, so everyone could comment or write on the drawings and sets simultaneously – and we made in-progress drawings available for early review. At the same time, the design, engineering and architecture teams leveraged various building design and building information modeling programs to coordinate closely with trade partners and installation crews. And that allowed construction to begin much sooner than by using traditional delivery methods.

The pandemic eliminated the luxury of time. It was no longer logical to wait for every conceivable piece of information to be in our hands before taking a single step forward. All of the various project components, from design, engineering, construction, and vendor coordination, as well as all of the owner's concerns, had to move forward in a concert. By staying in daily contact



Cerbo Classic Bio

and fully leveraging online tools, we were able to coordinate and manage activities as they happened and prevent pileups. The main takeaway? The speed at which a facility can be built depends on how fast everyone can make decisions (and stick to them!)

Anything is possible

All project managers know the saying, “You can have it fast, you can have it good, you can have it cheap: pick two.” Warp speed demanded good and fast, so it didn’t come cheap.

Significantly shortening the duration of this project meant adding personnel and paying a premium to run construction around the clock, adding significantly to the labor bill. Working faster – while maintaining quality – will always cost more. In these cases, you need to be especially strict about distinguishing needs versus wants.

When addressing each budgetary concern, we asked: “Is this absolutely essential to code, safety, or regulatory issues? Is it so important that it must be addressed – even if it costs a lot more?” In the case of infection control measures – for example, PPE and hand-washing stations – it was a no-brainer to open the purse strings and spend whatever was needed. At the same time, we also needed to spend big bucks in response to significant supply chain disruptions and a dearth of building material.

You also need to bear in mind that getting things done faster is not simply a matter of doing the same thing as always, just faster. A sped-up version of the status quo will simply hike up costs and burn out a team. This is where an integrated approach is essential – and actually can bring a project much closer to the ultimate dream of good, fast, and cheap.

By integrating our design and construction team and creating constant engagement between them, we avoided costly errors. Other essentials in tackling concerns ahead of time – before they become budgetary nightmares – included lean construction documents, integrated document management, pull planned design milestones, and integrated scheduling.

The COVID-19 pandemic put all of us in a unique situation, and also poured accelerant on projects via public awareness and government funding. It would be nearly impossible to replicate the exact circumstances in another project, but there are many other urgencies in the industry. For example, many of our ATMP manufacturing clients use slogans on their construction sites, such as: “Save a day, save a life,” to underscore the urgency of getting the project across the finish line. They may not have the same funding as COVID-19 projects, but the pandemic has shown us that we can move fast. In terms of getting facilities up and running, in our view, the pandemic has highlighted the absolute importance of thorough scope definition, decisiveness, laser focus, team work, and excellent communication. Applied correctly, the lessons we learned could help the industry deliver quality products to patients faster, while optimizing cost.

Nolato Cerbo has launched Cerbo Classic Bio, a full range of bottles and caps, produced from biomaterials made with 90% bio-based content. Cerbo Classic Bio made from renewable resources make a significant contribution to reducing the level of greenhouse gas emissions and can be recycled in the same chains already developed for conventional plastic.

We are proud to announce that we are ready to deliver a full range today and the packaging is already in the market!

Nolato Cerbo has extensive experience in the development and manufacture of user-friendly polymer packaging for pharmaceuticals and nutraceuticals, for more information don't hesitate to contact us:

Customerservice.nolatocerbo@nolato.com
<https://www.nolato.com/pharma-packaging>

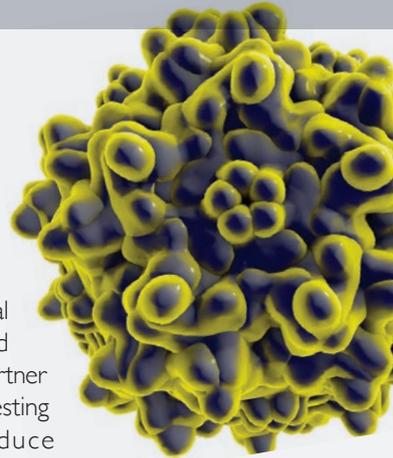
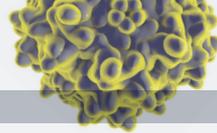


**Nolato will exhibit in CPHI exhibition
 9-11 of November in Milano, stand 06D21
 You are welcome to visit us**



Nolato receives Gold Rating in
 Ecovadis Sustainability Audit





Outsourcing Strategies to Expedite Viral-Vector Vaccine Development

How partnering with organizations that provide specialist technical and regulatory knowledge can help reduce your development timelines, risks, and costs

By Lorraine Borland, Product Manager, Viral Vaccines and Gene Therapy, at Sartorius

With the threat of COVID-19, vaccine developers needed to enter clinical development and scale-up at unprecedented speed – crucially, while maintaining process robustness and quality. Many developers turned to viral-vector candidates, which had proven regulatory records and established manufacturing platforms – and could be easily modified to target SARS-CoV-2. Based on the recent successes with viral-vector vaccines, more companies are entering the space. However, creating a new viral-vector vaccine is complex and challenging. Drug and process developers must consider vector design, the manufacturing process, and regulatory submission requirements – all of which demand a specialist skill set. Small biotech and start-up companies often focus on vector design but may lack knowledge on the regulatory pathway from drug discovery to clinical batch manufacture. With limited funding and intense time pressure to generate efficacy data, it can be challenging to assess how to simplify and accelerate this process. At this stage, it is important to correctly identify



where internal investment is needed and which areas are suitable for outsourcing.

The analytical burden

For small biotechs involved in viral-vector vaccine development, analytical requirements can be a considerable challenge. A small developer's budget may not allow for investment in expensive analytical equipment; thus, a simpler, less sensitive methodology must be used. However, high-quality viral analytics are key to good data-driven decision-making. Characterization of a viral-vector product requires multiple analytical approaches, which should address product identity, product and process impurities, product strength (quantity/potency), general product quality, and viral safety. Master and working cell banks, as well as master and working viral seed stocks must also be tested for safety and fully characterized before the first cGMP batch. In addition, the clinical batch manufacture must be sampled and tested at three points: unprocessed bulk harvest, at the end of the purification stage as a drug substance, and in the final drug form as a drug product.

Developing a quality control plan quickly becomes an overwhelming challenge when these needs are coupled together with complex guidelines from multiple regulatory authorities. And, of course, that's why many companies turn to external partners for help.

It makes sense to retain in-house activities that are heavily dependent on internal viral-vector expertise while outsourcing other aspects that require specialist facilities and regulatory knowledge. Take, for example, establishing a master cell bank (MCB), which must be cGMP manufactured, tested according to regulatory standards, and released before Phase I batch manufacture. In an integrated approach, the MCB would

be established using the optimal cell line and media for viral production and outsourced to a partner with regulatory testing services to reduce timelines and risk. Making these GMP manufacturing outsourcing decisions is usually straightforward, but what about viral-vector analytics development? Here, we need to think about the time, money, and expertise required to firstly establish the assays and then make them GMP compliant for releasing a phase I clinical batch. Companies may have the skill set in-house to develop some of the analytics – especially those needed for in-process controls; however, do they have the budget and the time to purchase expensive equipment and establish higher quality analytical techniques? Instead, drug manufacturers can work with an outsource partner to take their current methods and establish generically validated custom-designed techniques. Yes – this may involve some initial outlay of budget and investment, but it serves to provide a higher level of insight into how a process is generating and purifying the viral-vector vaccine. And that can help ensure the first batch manufacture meets the right set of critical quality attributes.

Our research shows that over 75 percent of viral-vector developers outsource. Outsourcing is attractive as it allows a drug developer to progress their programs without the time, cost, and effort needed to establish all aspects of manufacturing, analytics, and cGMP product characterization in-house. These benefits are even more pronounced for viral-vectors, which require Biosafety Level 2 laboratories and clean rooms, as well as a significant level of skilled viral-vector scientific resources that can be difficult for smaller developers to establish.

Working in partnership

When it comes to outsourcing, we are aware of several misconceptions. Commonly, companies are concerned about the loss of control of the project – an issue that manifests itself in several worrying questions. “What happens if results don’t come out as we expect?” “Will we be able to contribute?” “We are only a virtual company; how are we going to project manage all this?” “How will we pull everything together to tech transfer; and what if the timelines at the CRO and CDMO don’t match or there are delays?” “If I outsource everything to one partner, will I be locked in?”

Your best starting point to answer all of these questions is by selecting an outsourcing provider who will truly work in partnership with you. Our experience at Sartorius shows that project management is key. For example, consider a project that involves developing custom assays for viral-vector vaccines; this is complex work, requiring multiple subject matter experts and coordination with manufacturing sites. Experienced project management ensures that the customer’s voice is never lost, providing a 360-degree view of the project, and guarantees critical discussions and decision-making takes place between the appropriate stakeholders.

Some companies are also concerned about the level of resources needed to manage multiple vendors and thus choose to outsource everything to one CDMO. Here, you do effectively become locked in with the CDMO’s manufacturing platform and existing vendor relationships. In this time of high demand for viral-vector manufacturing and testing, waiting times

for capacity can often be long and misaligned between CRO and CDMO. And that’s really where Sartorius stands apart from the crowd.

We thought: what if you could start with the end in mind by choosing an integrated solution and reducing the number of vendors to work with without dealing with delays and capacity crunch? Ready-to-use products and services, such as those offered by Sartorius, can be adopted flexibly right from early process development stage and transferred easily to a wider number of CDMO partners.

Using such a model ensures agility in any project by optimizing available choices. In this way, the timeline is accelerated as the company prepares for manufacturing, ready to take advantage of production capacity to meet project deadlines. Building on our extensive experience establishing biomanufacturing processes for clients, we focus on viral expression platforms that combine cell line, media, and testing solutions. Now, a developer can work with Sartorius to establish their MCB, develop their viral-vector analytics, and perform their regulatory release testing while selecting

media that will take them from development to commercial manufacturing. Factor in ready-to-use buffers, bioprocessing tools such as the Ambr® platform, MODDE®, single-use manufacturing platforms such as Biostat® – and what the customer has is a partnership that can be leveraged to fit their unique viral vector development needs. We think the power of partner selection becomes clear.

Losing IP or technical knowledge is another common concern when outsourcing. At Sartorius, we provide ready-to-use platform assays that can be customized to your product requirements. In this way, a specific client assay is created and used for the customer’s unique requirements. Technical knowledge and IP transferred from the developer to Sartorius remains the property of the customer. By choosing to perform custom assays with Sartorius, the customer has dedicated technical expertise, essentially extending their team without the need to add expensive fixed costs like equipment, facilities, and manpower. Governing all aspects are overarching legal terms and conditions ensuring IP protection for the customer and outsourcing partner. In the end, our customers have the assurance that anything developed on behalf of the customer is effectively owned by the customer.

There has never been a more exciting time to be involved in the development of viral-vector vaccines. The science in this space continues to progress, and it’s now possible to use “backbone” vectors and platform manufacturing processes to design and produce new vaccines rapidly. For small biotechs, however, there can still be many challenges. We are here to lend a very experienced helping hand.



Cast Out the Oracles

Business

*Economic drivers
Emerging trends
Business strategies*

Some people do business by using the past to predict the future, but is this the best launch strategy for a new product?

By Angus Stewart and Stephanie Sutton

Winning regulatory approval for your hot new therapeutic product does not guarantee success. Plenty of good drugs have gone on to flop in the marketplace. There can be a number of reasons for a failed launch – from the formulation to the price – but the positioning of the drug product plays a crucial role. You can have the best formulation in the world and still have it fall apart with the wrong positioning. According to Mike Rea, CEO at IDEA Pharma, too many pharma companies adopt the same launch strategy for every single product – and also think too much about the past. In this interview, he explains why he aims to obliterate this outmoded way of thinking.

Over your career, what have been the most eye-opening moments in the industry?

Eye-openers often come out of fortune; they happen when you've been around a brand team that has done something different. I was lucky enough to be involved in the launches of Avastin and Opdivo, which were both hugely successful.

An interesting question is whether great brand teams succeed because of or despite the organization surrounding them. The launch of Lipitor is a perfect example. It was the world's most successful drug and, although there were

some good choices and strategy, there was also a huge amount of luck involved. This was a drug that was forecast to do around US\$1 billion a year six months before launch, but ended up doing \$14–15 billion a year.

Speaking to people at Pfizer at the time, however, I was shocked to learn that few saw the point of examining their success. No one seems to mind if you get the forecast wrong that way! Some of the actions the team took were because they thought it was going to be a small launch. They changed the regulatory endpoints, and the positioning. It's intriguing as a case study and some of the best positioning for a drug that I have ever seen.

In over 30 years of consultancy with pharma, my biggest frustration is still the fact that people work, but they don't think! There are so many lessons sitting around in pharma waiting to be learned. Instead, people look so hard to find one way to do everything. All drugs are treated the same. The reality is that treating drugs as individuals – almost like children – is the best way to move forward.

I spend a lot of my time listening to and loving music. I've even got a record label I run as a hobby. Musicians are loved because they know all the ways of playing an instrument. When they play

something, it's intentional. I think the same should be true of pharmaceutical strategies. Of all the different ways that you can do something, you must choose purposefully. To be like Picasso, you can't simply be talented. Like Picasso, you must focus on being something specific. I think that route is available to most drugs, if only pharma were to embrace it.

What inspired you to set up IDEA? About 20 years ago, I was working in a medical communications company that was growing fast. Then, we were acquired by a larger company who wanted to "modernize" us. I didn't agree with their plans, so I resigned, which in

"In over 30 years of consultancy with pharma, my biggest frustration is still the fact that people work, but they don't think!"



turn triggered massive changes in my life. I was put on gardening leave for six months; in that time, I went from being on transatlantic flights every Monday to watching my children grow. I decided that I would consult from now on to preserve that better balance of work and life.

IDEA Pharma was set up to help companies with lifecycle strategies. Early on, we were a band of pirates! But, in time, we took on a deliberate growth strategy and disruption approach to help elevate the brands we worked on.

Across launches and throughout companies, what are the mistakes that

you see over and over again?

I'd point to the pervasive, decades-old belief in standardization, which you see today in "marketing excellence"-type approaches. According to this way of doing things, people think you need an ad agency to do X, a market research agency to do Y, and so on. The reality is that most people only have a glimpse of the jigsaw. They bring their jigsaw pieces to the table, and that's the only way to do it.

I think we should put people over market research. I like to use a metaphor to describe where the conventional approach goes wrong: these people often look for insight under one lamppost on

a dark street – and it's the only place they look. If you are doing all your research, testing, and everything else under that one light, you never look beyond it to see what else is possible. These types of people look at the way the market has been instead of looking at the way it could be. I think this is the biggest mistake companies make when launching a new product.

I also see a lot of mistakes at the very start in basic market research. First of all, there is always sampling bias; you can only ask the people who are prepared to be asked. Their answers might not be representative of the group and companies often don't look for great

numbers anyway because of budget.

Market research also often relies on doctors, who answer like doctors and don't necessarily tell you what they truly feel. In many cases, I encourage my clients to go against what people think they think and, instead, look into the psychology driving the way they make decisions. You can't always rely on data; you need to factor in emotions, too.

Lipitor didn't have any reason to succeed. It was a fifth to market drug, but I think it succeeded because it didn't follow where others had led.

Working with our clients, I have a toolkit of basic, well-loved cheats to get them to think. For example, when somebody says to me, "This is going to be an efficacy play-out," I ask, "What do you mean by efficacy?"

In the case of a rheumatoid arthritis drug, for instance, "efficacy" could mean a reduction in pain, damage, progression, or inflammation. I believe "efficacy" is simply jargon that people throw out, assuming there is one agreed definition. Of course there isn't.

Are pharma companies aware of how their practices might be holding them back?

It's much easier for them to operate the way they always have. If the 30 people working on drugs in your pipeline all bring you the same slide deck, it's much easier for you to do a compare-and-contrast on what they're showing you – but it's also a big risk.

To have the agility to behave differently, you must trust your teams and give them room to do something meaningful. Either you decide that the people at the top are the oracles – where everyone brings them offerings and they will tell you whether you have it right or not – or you believe that the teams should be trusted to do this themselves.

In companies where progression is slow and steady, once you become senior,

you will be reviewing a brand plan every six months. What are you going to add if you're only looking at it every six months? Your underlings may need to teach you something about the therapeutic area before you can determine whether it's good or not.

In companies that have done well – like Gilead in antivirals – the leadership already understood antivirals, so it was easy for them to say yes or no to the brand plan. It depends on the organization and on how comfortable the leadership are with being challenged and with being brought into a conversation, rather than simply being presented at.

"Suppose you gave the same drug to two different companies in phase I. Would they be equally successful? Everyone knows that the answer is 'no,' but no one knows why."

Some CEOs want to look at every slide deck, every detail, and have input into everything, which is fine (if they know what they're doing). But that only works if the company is launching something meaningful...

Our Pharmaceutical Innovation Index

looks at this sort of thing. We ask, do people make a difference to drugs? Or do drugs make all the difference in their own right?

What inspired IDEA Pharma's Innovation Index?

It was born from a happy accident. One day in the office, 11 years ago, we were shooting the breeze and I happened to ask, "Suppose you gave the same drug to two different companies in phase I. Would they be equally successful?"

Everyone knows that the answer is "no," but no one knows why. You have to take into account the reasons companies tend to be more or less successful when they launch medicines. Even if a company is confident that they are good at what they do, what if there is still a better way?

Consider the English Premier League. The top 10 teams are identical in neither play nor management, so mirroring Man City is not necessarily going to guarantee Sheffield Wednesday a spot at the top of next year's Premier League. In this sense, pharma and football are the same.

We took the top 30 companies by market cap. All the data are public and we see how good they are at not losing drugs in phase III, getting market access, selling in their first or second year, and so on. Then, we were able to compare and contrast them with others who were doing the same things at the same times. The company that came out top for innovation in year one of the index was J&J. Shortly after, I received a letter (it was still letters rather than email back then!) from Paul Stoffels at J&J. He thanked me and asked, "How do we improve?" I found this intriguing. His company came out on top, but he still wanted to improve... that is something to be admired.

Today, the Index is called the Pharmaceutical Innovation and Invention Index. It's an annual publication (check

out the 2021 Index at <https://www.ideapharma.com/pii>) that shows which companies are actually delivering innovation and invention, rather than just talking about it. The top five companies for innovation in the latest Index are Eli Lilly, Roche, Regeneron, Seagen, and Incyte.

We were very specific when we added the term “invention” to the index. Innovation is about creating value from your pipeline (although many people still think innovation is about good ideas). Invention is the creation of novel ideas. So, two years ago, we added an Invention Index to reflect those people with great pipelines full of breakthroughs. They could be full of intriguing designations by regulatory groups or first-in-class molecules.

This creates quite an interesting axis. There are people who are great at pipelining and people who are great at launching. But it all comes back to this: if someone’s doing it better, you need to know about it.

Do you see commonalities between high-ranking regulars on the index?

We do see trends because of the five-year rolling view we constantly maintain. Some companies have come and gone; some operate on a “Hollywood” model – if you launch enough drugs, some will be successful. They may be the ones you’d expect to be successful, or they may not. For this reason, bigger companies tend to do better than smaller ones, simply because they’ve got more in their pipelines.

That said, the most important trend is obvious – companies that understand their therapy area extremely well do better than those that don’t. For example, Gilead in antivirals: huge. Gilead in oncology: horrible. There is, however, one caveat – you can’t stand still. Many oncology companies that were excellent 20 years ago, for example, missed the immuno-oncology wave and are now swimming like mad, trying to catch up.

Another key difference is leaders’

decision-making competency. In a recent conversation I had with Dan Skovronsky, head of R&D at Lilly, he talked about the way their company has essentially built a cluster of biotechs. He said, “If you buy Loxo Oncology because they’re a great oncology company, why would you then make them ask you whether or not something is a good idea?” I thought that was a wonderfully humble approach. Our industry is full of uncertainty and there are only two possible responses to that: you can either pretend it doesn’t exist and try to predict your way out of it (which is what most people do), or you can lean into the uncertainty. Sometimes decisions need to be faster and should be made closer to the coalface. Companies that do that tend to be better in our index.

Also, I think that associating innovation only with scientists and molecules is a failed policy. Innovation means that your regulatory people, clinical people, medical affairs people, marketeers, and more all have an impact. It is organizations, rather than molecules, that really make the difference.

Last year you wrote a book titled *Pharmaceutical Positioning...*

I never set out to write a guide to pharmaceutical positioning. Instead, it was intended to distill the lessons I’ve learned from doing this for 30 years. My company has worked on eight of the 15 biggest launches of the last five years. We positioned data that, in the case of those 15, vastly exceeded our scale as an organization. I wanted to reclaim positioning from the ad agencies and market research agencies that do it badly and, instead, emphasize the fact that positioning is a strategic activity. Positioning should be thought about at phase I, II, and III. But the positioning at each stage isn’t the same; in phase I, you’re making choices about where to launch the drug, for what indication, and in what patient segment. At phase

III, you’re essentially telling the story. Beyond that, comes repositioning.

(The book is mostly a series of small lessons instead of a big textbook, because the process, the methodology itself, is long-winded and boring!)

The “model of excellence” folks think there should be one approach to positioning. Well, you can’t have a single approach to positioning, to being first-in-class, best-in-class, and so on. It doesn’t work like that.

What are the essential rules for pharmaceutical positioning?

Rule one is that your product is not the same as the molecule. Instead, the product is a result of a thousand choices made on the way to market. One can’t know what “efficacy” looks like for one’s drug unless it is clear for whom the drug will be valuable. If one decides in advance that the drug should be an X, and then said drug fails all the studies on the way to becoming an X, it’s game over. But if one decides the drug could serve as X, Y, or Z, then avenues remain; the loss of one potential product needn’t kill off the molecule.

Rule two is that nobody’s right. Anyone should be able to be challenged on any opinion they have. Clinicians aren’t masters of market opportunity; it’s impossible for a regulator to be right about a clinical trial size; and so on. That’s why you need a team.

Rule three is ambition. I never want to work with a client without ambition. We turn down work from those who would have us help them follow convention. We’ll stay up late on a Friday night working on strategy if the client is as excited about the task at hand as we are. One of my biggest wishes for our industry is that we do more than just jump the lowest hurdle possible, which is typically Approval. Regulatory approval is relatively easy, but it is not necessarily the most useful thing you can do for your molecule.

Keeping Products Closer to Patients: In-Country Logistics

How can logistics companies meet the evolving needs of global clients while maintaining resilience in the long-term? One answer may be to adopt risk-reduced supply solutions by using local seamlessly-linked storage and delivery services.

The direct-to-site logistics model has worked well for many years, particularly for countries close to pharmaceutical manufacturing centers. But the market is evolving, and as medicines become more sophisticated and fragile, it makes increasing sense to maintain depots that support pharmaceutical storage and distribution within the end-user country. Furthermore, the pandemic has taught us the need for supply-side resilience, and this is likely to require a mix of supplier models, including in-country logistics. The key to success in this changing environment, however, will be to develop a detailed understanding of market dynamics and client needs – and to maintain a long-term focus on both. Paula Pulsoni (Senior Director, Clinical Supply Solutions, World Courier) wades in on logistics trends.



What is your background?

I started out as a pharmacist in Argentina about 15 years ago. During my training, I managed clinical trials in a hospital environment, but upon graduating, I joined World Courier, a global specialty logistics provider and a part of AmerisourceBergen. After a management position at our Argentina depot, I moved up through regional and then global roles in locations including Spain and the UK. Now I'm responsible for global operations and strategy in the World Courier depot network. We operate GMP-compliant depots for one-stop global clinical supply support and commercial drug storage and

distribution in 22 markets worldwide, spanning Latin America, Europe, Asia-Pacific and the Middle East and Africa.

You helped set up a depot in Turkey – why? We were influenced by two key factors: customer demand and market growth. With regard to the former, we found that our clients were increasingly requesting support with logistical pain-points in Turkey. As to the latter, Turkey's market growth projections – in both commercial and clinical trials sectors – were exceptionally strong. Forecasts included a healthcare sector compound annual growth rate (CAGR) of 17 percent, which was among the

fastest in the world, and an 8 percent CAGR (2019-2023) for the clinical trials sector. These growth rates were assisted by Turkey's ambitious 15-year package of investment in infrastructure – for example, a new airport in Istanbul – and healthcare systems. Together, these features made the market very attractive and boosted industry interest. Furthermore, our expansion into Turkey aligned with World Courier's mission to improve global access to pharmaceutical products. Nevertheless, we didn't make this move lightly; when I first traveled to Istanbul, back in 2012, it was to explore the possibility of local partnerships rather than to plan deployment of a local depot!

What other factors affect investment decisions?

Various needs can be uncovered through discussions with manufacturers and other participants in the supply chain. And these conversations are important because it is critical for us to understand the whole supply chain ecosystem and its ongoing evolution. Overall, a broad and deep understanding of supply chain design is essential if suppliers are to align their initiatives with manufacturers' objectives. In particular, suppliers must identify the key challenges in a supply chain and determine how they may change over time. It's too simplistic to decide on depot location purely on the basis of market size.

What challenges did you face when dealing with healthcare systems in Turkey?

We are accustomed to working with a variety of regulators, so Turkey's regulatory system wasn't a challenge – but we were surprised by the pockets of innovation that we uncovered. People are broadly aware of the push for product serialization in the pharmaceutical industry, such that each product is given a unique number, but few realize that Turkey is one of the pioneers in this field. They have one of the most advanced serialization systems. Of course, as is typical in any new market, when we work with the regulators, we share our experience of how the rest of the world works as we learn on the local particularities. I strongly believe we both benefit from this kind of cross-pollination. The pharmaceutical industry is rigid, however, and change takes time! Nevertheless, it was interesting to see Turkey adopting more flexible, direct-to-patient operations in response to the pandemic. We will see if that regulatory evolution persists.

Why have linked storage and distribution services not been offered in Turkey before now?

Historically, the direct-to-site logistics model has been popular for clinical trial supply chains to Turkey – partly because proximity to manufacturing sites in Europe made

traditional logistics easier than development of in-country systems. But as trials become more complex and medicines become more delicate, the disadvantages of the direct-to-site model are becoming clear. It's true that it is more efficient in that manufacturers don't need another partner or product-storage facility, but the efficiency gain comes at the expense of increased risk. Remember, product importation into Turkey involves customs, brokerage, local distribution to the trial site, authorization to receive the medicine, and so on. Coordination of all this bureaucracy can be complex and cause significant delays. In fact, our data shows it takes, on average, 93 hours – nearly four days – to clear an international clinical trial shipment through customs in Turkey. During the pandemic, this almost tripled for some locations! By contrast, building an in-country depot allows product to be imported in bulk and stored until needed, thereby eliminating the need for separate storage vendors or transport vendors. Much of the risk is eliminated by adopting a solution that incorporates international shipment and in-country storage and distribution to the final site. The pandemic demonstrated that supply chains must be resilient; this requires suppliers to offer diverse logistical solutions including both in-country and direct-to-site logistics. A safer option is the in-country model, which keeps products close to patients and helps ensure the products entering the country are delivered on-time and in the right condition.

Will the in-country model persist?

COVID-19 has emphasized the importance of having a plan B – and a plan C! I think that in-country storage will become an increasingly common feature of logistics. Of course, in markets such as Latin America, in-country logistics have been a feature for many years; it is a way of accommodating complex customs processes and avoiding long import delays. But in Turkey, where direct-to-site logistics were so prevalent, switching to in-country

models will take a little time. Nevertheless, it is coming. Manufacturers understand that, when there is uncertainty regarding future routes to market, bringing products closer to patients provides excellent risk mitigation. The benefits of in-country logistics in this context are very clear.

Is the Turkey depot now operational?

Yes! Right now, half of our 4000 square meter warehouse is in use, and we will expand into the other half as the market grows. In this way, the depot will meet all current and projected future needs. Our depot can accommodate storage and transport of both clinical trial drugs and commercial products – including serialized products, which is an essential feature in Turkey.

One thing we have noticed during this process is that prospective clients sometimes have difficulty in auditing the depot in a timely manner. We fixed this issue by creating a virtual audit platform which includes a real-time video tour, effectively bringing the audit to the client's desk. Our virtual audit system facilitates documentation and reduces the burden of the qualification process; in consequence, we have received client approvals faster than we would have with standard audit procedures.

The virtual audit is also a great opportunity for the manufacturer to run more frequent audits than their budget previously allowed. And, from the supplier perspective, it helps to get more personnel involved in the audit process, which builds a stronger relationship with the manufacturer. This, in turn, supports resilience; after all, a vital part of resilience is to understand your environment. Supplier–manufacturer conversations enable both parties to learn from each other, and the more people that are involved in the audit the more rich those conversations will be. The virtual audit is here to stay, but, of course, there will always be companies who prefer to travel and to be there in person – and that's fine too.

A close-up portrait of Evelina Vågesjö, a woman with light brown hair pulled back, wearing a dark blue blazer over a white collared shirt. She is looking directly at the camera with a slight smile. The background is a blurred outdoor setting with blue and white tones.

Stay True to Yourself!

Sitting Down With...
Evelina Vågesjö,
Chief Executive Officer
at Ilya Pharma,
Uppsala, Sweden

If you hadn't pursued a career in pharma, what would you be doing today?

Though I've always had an interest in science, I would have pursued a career in finance. I have two degrees in the subject, after all! However, the pharmaceutical industry appeals to me because it combines many of my interests. There are so many avenues to be explored. Take small molecules and biologics for example; they've been around for a long time, but still play crucial roles in the treatment landscape. Advanced therapies are also emerging as solutions to the residual unmet needs that haven't yet been addressed by traditional established therapeutic approaches. In my view, being a part of the growing and highly diverse industry of cell and gene therapies is extremely rewarding.

What's more, I get to explore my passion for strategy and finance by working closely with stakeholders and investors, and finding optimal ways that impact our ability to bring new medicines to patients. So, choosing a career in pharma was ultimately the right decision for me – there's no shortage of excitement or inspiration in this sector!

What inspired the launch of Ilya Pharma?

As a PhD student, I was tasked with developing molecular tools to steer and record the behaviour of immune cells and subtypes in vivo. In one project, results showed that macrophages attain perivascular positions in injured tissue – helping to regulate blood flow and accelerate healing. It was at this time that our team also achieved great therapeutic findings using a gene therapy approach. We found that a chemokine, CXCL12, was able to elicit wound-healing effects in the skin and could have implications for disease areas where problematic and non-healing wounds cause a significant burden to patients.

The success we had was a key motivator for starting the business. We wanted to make this exciting discovery into a scalable platform and drug products that could be translated into real, tangible treatment option for patients. The desire to achieve these goals was the beginning of our journey in industry. We spun out of the University Uppsala and The Swedish University of Agriculture in 2016.

Since setting up the company, we have shown a wealth of clinical data to support the fact that the lead candidate accelerates healing and reduces scarring and fibrosis in the skin and also in the intestine. It was certainly an interesting experience transitioning from academia to industry – and one that continues to evolve.

What were the initial challenges you faced?

One of the biggest challenges we were confronted with was the different people and mindsets we encountered in our early days. Everyone has their own opinion on the way a business should run. At the time, it was challenging for me to navigate through them and make decisions that felt authentic to me and my goals for the company. Thankfully, with time, I've learned that, though others' perspectives can be useful also for your business, it's always important to stay true to oneself.

That said, I've had some wonderful speaking-partners who have helped me in both academic and industry settings. Some of our senior investors and advisors, especially, Ingemar Kihlström, our current Chairman of the Board, have been bold enough to work with developing the pipeline and company long-term – sharing their experience and advice and always putting the company first. So, I suppose finding the people with the right experience and a vested interest in your success is one of the most important lessons any business person can learn.

What will the next five years bring for the advanced therapy sector?

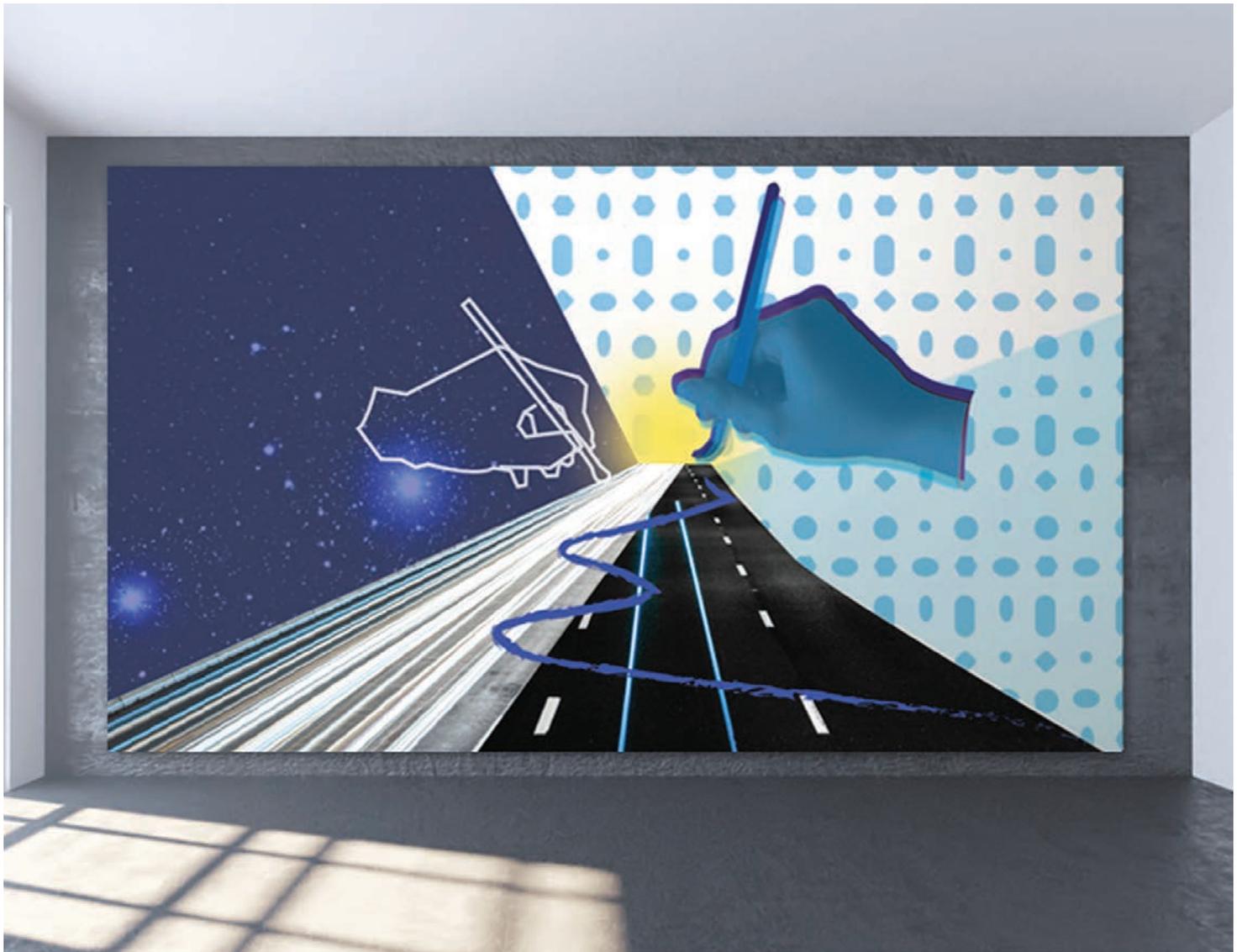
I predict that therapies also using parts of the microbiome for their mechanism of action will take center stage in the coming years. There are many companies in this emerging sector that are currently developing robust pipelines of therapies. With the strength of the current product offerings, it's certain that we will see more approvals as pharmaceuticals in the coming years.

Regulators like the FDA are also building their teams and understanding of the area, which will make all the difference in getting these products to market. As these regulatory teams continue to develop their expertise with the number of projects emerging, we should expect microbiome and other live therapeutics to become as regulated as pharmaceuticals similar to more straightforward cell and gene therapies. The more clearly defined the legislation and guidance, the better for all involved in the development and manufacture of this product type.

What are your goals for the rest of the year?

We're excited to start phase II trials for ILP100-Topical for post surgical- and non-healing wounds in obese and diabetic patients. It's an exciting step forward for us because, if successful, it will bring us closer to addressing an important area of unmet need. We have several other products in our pipeline including ILP100-Oral for which we also want to start clinical trials in different enteropathies.

Other than that, I am just excited to grow and scale the company with our projects and to see how the industry will continue to evolve – particularly the cell and gene and microbiome therapeutics sectors. Only time will tell how well, and to what extent, areas of unmet need will be served by these emerging advanced treatments. For now, we can only hold our collective breath in anticipation and enjoy the scientific discoveries and milestones in the field.



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