Seeking Solutions in Biopharma

Experts discuss how to tackle biopharma's need to move fast – and how integrated solutions can help

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Faster Than Ever Before

By bringing new vaccines to market in less than 12 months, the pharma industry has not only achieved what some thought was impossible – but also opened the door to a new era of medicine

By Stephanie Sutton, Editor of The Medicine Maker

The pharma industry rarely wins accolades for speed! Traditionally, it takes a decade or more to bring a new drug from discovery to market – and there are many scientific, manufacturing, and regulatory hoops to jump through. We all know that regulators have to be strict to ensure the highest levels of patient safety, but such high requirements – coupled with the high costs of development – mean that drug manufacturers tend to be cautious in everything they do, including the adoption of new technology.

The COVID-19 pandemic has initiated what could be a revolutionary shift in the industry. At the start of 2020, the outlook was uncertain. There was a need for speed, but how fast could the industry realistically move?

Well, as it turns out, the industry is capable of moving at lightspeed when it has a united goal. Vaccine candidates were announced within months and the first emergency use approval came before the end of 2020. More approvals have come since and by the summer of 2021 over a billion people worldwide had been fully vaccinated. And though that's only 15 percent of the global population, it's still a remarkable achievement – particularly for an industry stereotyped as being rather slow.

COVID-19 has inspired unprecedented collaboration and funding, but it has also resulted in some therapeutic areas falling behind as resources pivot to the pandemic response. Certainly, we can't expect the industry to move this fast for every indication, but it is still inspiring and there are lessons that can be learned. In the future, I believe that we can expect greater efficiency in drug development and manufacturing. Even before the pandemic, the industry was working to accelerate its processes, with a number of vendors focusing on new technology releases specifically aimed at helping pharma companies to get up and running with manufacturing faster.

Perhaps the most intriguing aspect of the industry's pandemic response is that two of the approved COVID-19 vaccines – including the first vaccine to be authorized by both the EMA and FDA – was based on mRNA. Prior to this, no mRNA-based therapeutic had been approved anywhere in the world. The industry didn't just move fast in developing a vaccine; it moved fast developing a vaccine based on a new modality. Now, increasing numbers of companies are looking to explore the opportunities offered by mRNA and genomic medicine. We appear to be witnessing the start of a new era in medicine – and the onus will be on pharma manufacturers and their suppliers to realize its full potential.

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Built for Change

The rapid rise of new manufacturing modalities, such as viral vectors to mRNA vaccines, is coinciding with a digital revolution in how we work. Only a holistic approach will allow companies to overcome the challenges and seize the opportunities.

By Morgan Norris, Vice President of Marketing, at Pall

If there's one phrase I might use to describe how I feel about the industry today, it's "cautious excitement." Monoclonal antibodies are still king in biotech and remain the biggest selling drugs in the world. We also know a lot about them; we know how to design, develop, and manufacture them efficiently and they are not going away any time soon. But there are many diseases that monoclonal antibodies or even recombinant protein therapies are not well suited to treat – such as more severe diseases with very small patient populations. This is the space now being filled by gene therapy. We have seen some truly exciting successes and it's clear that viral vectors are also here to stay; however, there is a bottleneck in terms of manufacturing capacity that is limiting the development of gene therapies. How will the industry cope with the increasing demand given the relatively low process yields, high cost of goods, and suboptimal unit operations?

The trend towards more advanced manufacturing technologies has come hand-in-hand with the development of mRNA vaccines – from both Pfizer and Moderna as examples. The investment in this area has been enormous and the pace of development unprecedented, and it is serving to invigorate and inspire the industry. Many companies are thinking, "If we can do this, what else can we do?" Companies should also be thinking about the kinds of capacity and knowledge base they need to build as newer modalities continue to emerge. All too often, companies have to turn to academia to understand some of the technology.

When I was working in contract manufacturing – over two decades ago – it was difficult to make a monoclonal antibody because there weren't many people in the world who knew how to do it. We are now seeing a similar situation with viral vectors. There is a lack of experience. But we've been through this journey before and I firmly believe that the industry will find a way to move forward. Two decades ago, we were all asking how we would be able to meet the high demand for monoclonal antibodies because it seemed that there wasn't enough raw material in the world to bring these therapies to patients. But we did it. And we will also figure out the challenges in viral vectors and other emerging modalities; not just the manufacturing hurdles, but also the challenges associated with the supply chain. The early stages of the COVID-19 pandemic illustrated the importance of supply chain redundancy, which will continue to be key as long-term demand trends upwards.

Despite analogies with monoclonals, I think it will take significantly less than two decades to overcome current issues; first, because we have past lessons to learn from, and second, because there is so much attention and investment being poured into the field.

And it isn't just new modalities that companies must be ready for; we must also cope with new ways of working. We've all had to adapt to virtual working, for example. Now, the challenge is finding the right balance between virtual and in-person work. We've been hearing from customers, especially bigger companies, how difficult it was to coordinate globally and realize tech transfer at all their manufacturing sites across the world – even in the same country. Prior to COVID-19, companies were sending armies of people to various sites to help implement new technologies and processes – clearly, expensive and time consuming. Today, virtual technologies – especially augmented reality – allow some aspects of tech transfer to happen remotely. And though travel will return to everyday business life, perhaps we don't need to send 20 people across the world; companies can choose to send a handful of project managers while everyone else works virtually.

The benefit with change can often be increased efficiency, which at the end of the day will help the industry to bring drugs to market more quickly. We'll be able to respond to demands faster and reduce lags in approvals. Tasks that used to take two years are going to take six months. It's exciting, but companies must be ready for the change or risk being left behind.

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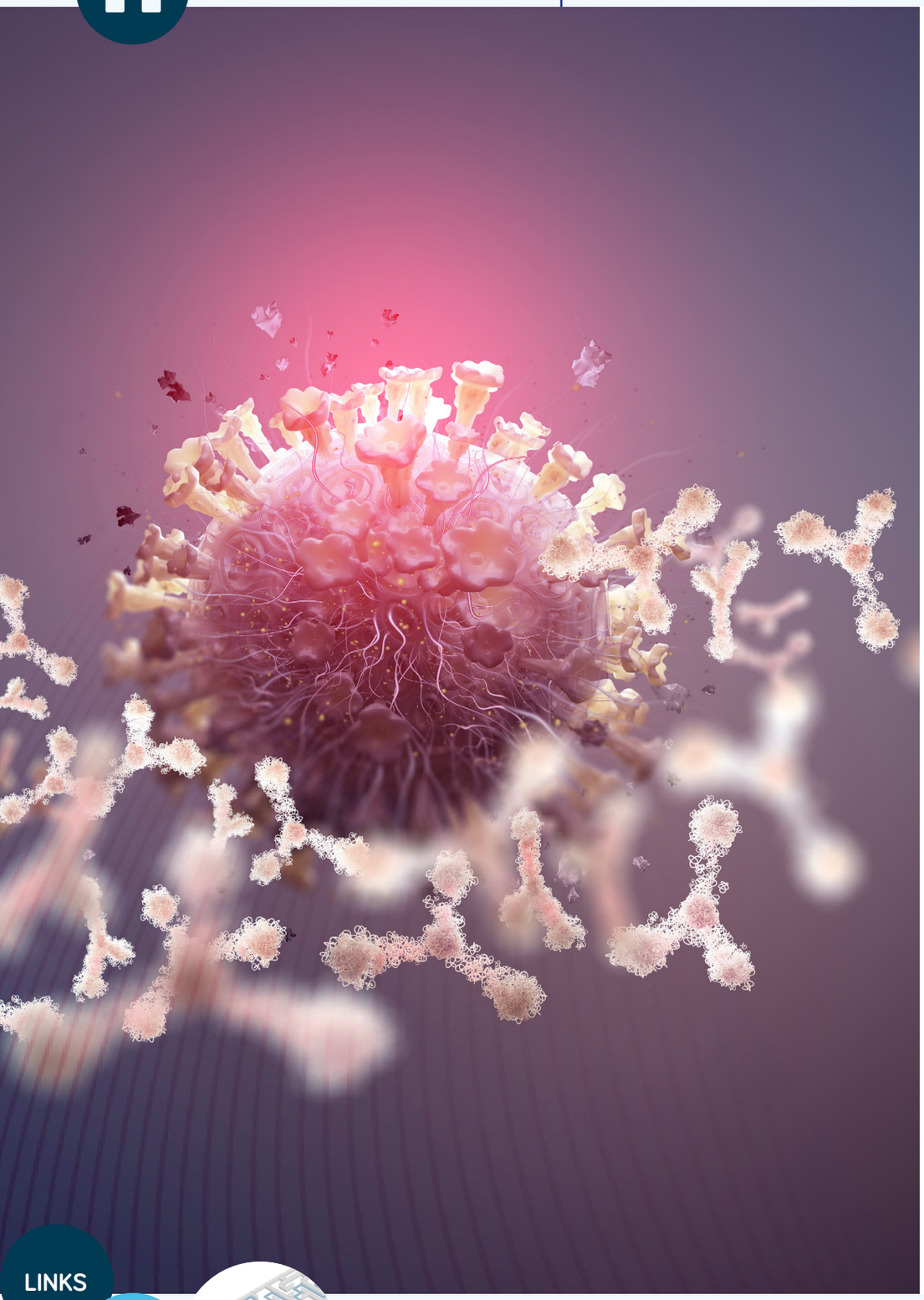

Staying one step ahead

How is Pall keeping pace with biotech's shifting tides? We continue to develop our equipment platforms in numerous ways, including making them easier to integrate. And that means more standardization of components and systems, as well as the use of automated platforms. We want our process engineers spending more time on process engineering and less time on working out how to get all the pieces of the puzzle to fit together, which allows us to spend more time with customers to help them understand their process and ensure it is reliable, sustainable, and efficient.

We will continue to invest in process development services to help customers, which in turn will also help us understand how customers are using our systems – and what new systems they need. We also want to continue to build our team of field scientists, which brings us even closer to our customers.

At Pall, we have learned to adapt to change. Pall was acquired by Danaher in 2015. Such a big change can bring uncertainty and potential upheaval, but I am excited to see how Pall is integrating Danaher's rigor and market knowledge into processes. Danaher acquired a high-performing organization in 2015, but now we can be totally sure that we're going in the right direction – reading the market correctly, developing the right products, and running plants as efficiently as we can. Ultimately, we can offer our customers even more value.

When we bring a product to market, our customers can be assured that we haven't just developed a really interesting new piece of technology for its own sake; there's a certain quality and reliability built into the product from the very beginning. For example, we will do all of the necessary work to ensure the supply chain can support the new product, and we will have all the documents the customer needs to support validation and to get the product into the process. This information is all accessed very easily via a portal, as opposed to sending dozens of emails to different people to obtain the information.

We've also applied that rigor all the way through the customer process to ensure the right training materials are available, and that we have the right people to ease the process and support the implementation of the product for our customers. I think what the customer starts to see is a much more robust interaction with Pall across the entire lifecycle of the product. We've done all the work up front so customers can spend their time focusing on building up their processes – without any surprises!

Of course, there's more change coming with Cytiva joining Pall under the Danaher umbrella. Fortunately, we're both very customer focused organizations – in fact, I worked for the company that became Cytiva before joining Pall, so I understand both companies. We're already figuring out how to put Pall and Cytiva systems together to create more complete solutions to support both traditional biopharma and the new modalities that are fueling intense activity in the industry. Both companies have tremendous bioprocessing expertise, so that's really exciting.

And there's still more great news coming out of Pall. Towards the end of 2020, we started building a new manufacturing facility in South Carolina; it's almost fully functional and it will bring a lot of single-use capacity online. We've also acquired a manufacturing venture in China, as well as adding a substantial facility in the US. You may be surprised to know that we are approaching four times the total capacity that we had this time in 2020!

For Pall to exist as a real driving force in a rapidly evolving industry, we recognize we have to think about the whole ecosystem. We can't fully support a customer if we're focused solely on the supply chain or building the next new product. A holistic end-to-end view is crucial to ensure the customer is supported at every step.

Morgan Norris in the Vice President of Marketing at Pall. He is responsible for the strategy, outbound marketing, branding and product portfolio for the business unit. Morgan is a respected leader in the biopharmaceutical manufacturing space with over two decades of experience in biotech and pharmaceutical manufacturing. Morgan's experience spans originator companies, contract manufacturing and suppliers with roles in technical, strategy, product management, marketing and business leadership. When he is not working or traveling Morgan enjoys spending time on the water, and at home with his young family.

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Transforming Scientists into Drug Developers

Companies like Pall, Cytiva, and Precision NanoSystems – one of the newest additions to the Danaher Life Sciences portfolio – can provide all of the technologies and expertise necessary to manufacture a drug. All scientists need to focus on is discovery.

Featuring Clive Glover, General Manager, Gene Therapy, at Pall, and James Taylor, co-founder and GM, Precision NanoSystems

What is the story behind Precision NanoSystems?

Taylor: My educational background is a combination of an engineering physics degree with a PhD in genetics. After my PhD, I co-founded the company with Euan Ramsay, and two professors: Dr Carl Hansen and Dr Pieter Cullis, who is a world-renowned professor and industrialist in the area of lipid nanoparticle delivery systems. The company was formed around the promise of new therapeutic modalities, such as RNA, and the challenges of enabling and delivering these as therapeutics. Over the years, we have put together the full technology stack to make what we call genomic medicines. This includes manufacturing technology, such as continuous flow manufacturing for making nanoparticle RNA delivered drugs and lipid nanoparticle delivery systems. We also offer services to clients and work with drug developers to help them get their genomic medicines to market.

How did Precision NanoSystems come to join Danaher Corp's Life Sciences Platform?

Glover: James and I have a history; we did our PhDs together in the genetics program at the University of British Columbia, Vancouver. Then, we headed off our separate ways. My PhD focused on advanced therapies, such as cell therapies and gene therapies. I was very interested in how to manufacture these therapies and I have built my career around developing tools and technologies to help bring advanced therapies to market.

Today, I run the gene therapy business at Pall Corporation where there is a strong focus on large-scale viral vector manufacturing, which is the primary method of delivering genetic material both *in vivo* and *ex vivo* at this point in time. However, there are also alternatives to viral vectors. While exploring these alternatives, I bumped into James at a conference and he told me about the work Precision NanoSystems was doing. I instantly saw that there was great synergy between his company and what Pall was doing with gene therapy manufacturing.

Everything progressed from there. In June 2021, it was announced that Precision NanoSystems would join Danaher's Life Sciences platform, complementing the portfolios of Cytiva and Pall. Now, the companies are getting to know each other in a more meaningful way – discovering how our combined expertise can help drug developers get exciting genomic medicines to patients.

What trends are you seeing in the industry right now?

Glover: Today, we have so many options for tackling disease. The pharma industry started off with small molecules and then graduated to proteins (primarily monoclonal antibodies), and now we are seeing the rise of cell and gene therapies, which are tackling unmet needs that neither small molecules or proteins have been able to address. Cell and gene therapies are a long-term driver of change within the industry, but COVID-19 has also accelerated change by bringing viral vectors, and specifically mRNA, to the forefront. mRNA therapeutics have been in development for many years, but COVID-19 has been a tremendous catalyst for the field. We now find ourselves at a really exciting time; when we start thinking about new or unmet clinical needs there is a wider range of tools and technologies that can be applied. Both Pall and Precision NanoSystems can support large-scale manufacturing for many different kinds of therapeutics.

Taylor: I am really excited by the possibilities of genomic medicine and its continued clinical validation. There are many tools in the genomic medicine toolbox that allow us to manipulate disease-causing genes in all the various ways required to treat disease. As a few examples: Small interfering RNA (siRNA) allow us to silence disease-causing genes. Whether it is a rare disease, whereby the patient inherits a gene that expresses a problem causing protein, or in a cancer, whereby the patient's genes mutate to express proteins that drive the cancer, silencing these disease causing genes can have significant impact on the patient. Messenger RNA (mRNA) allows us to express proteins that are missing or not working, or in the case of vaccines we can teach the immune system to recognize pathogens. mRNA COVID-19 vaccines are the tip of the iceberg on the impact mRNA will make in vaccines and the treatment of many diseases. New gene editing technologies, like CRISPR, allow us to fix genetic problems directly in a patient's genome. Gene editing technologies are enabled by delivering an RNA guide strand and an mRNA that expresses the

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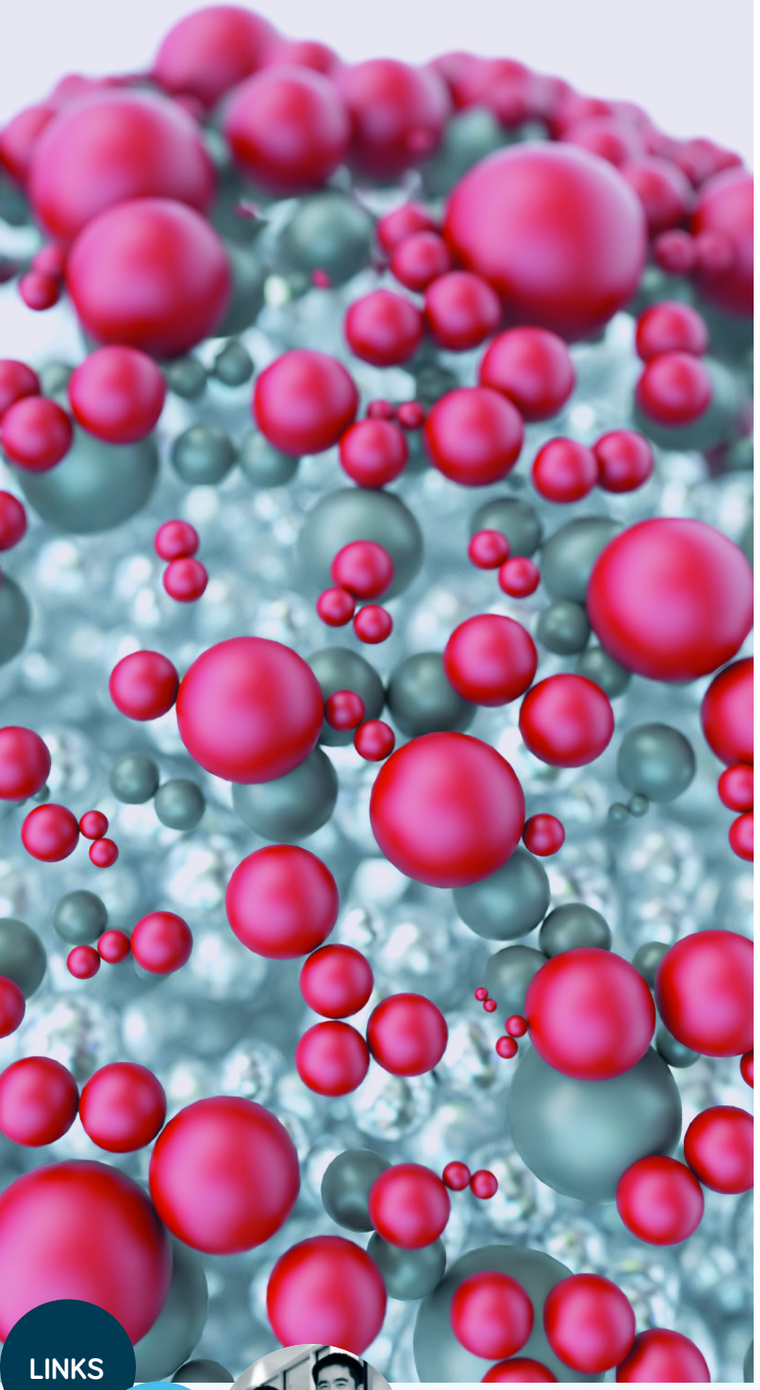

endonuclease to enable sequence specific gene editing. Similarly, there are wide range of other genetic modulators, like epigenetic regulators, that can be expressed in cells via delivery of mRNA, creating a completely new era of what is possible in molecular medicine.

The power of genomic medicine is immense – and the industry is now recognizing the massive impact it can have on society and the human condition.

How do you work with customers?

Taylor: We support innovative drug development by helping our clients to make their next big therapeutic and we have developed solutions across the full drug development paradigm. At Precision NanoSystems, we typically work with clients from the ideation of their drug project through clinical development. Our benchtop equipment, such as our NanoAssemblr Ignite system, is often one of the earliest "employees" in a startup, and represents the start of a multi-year partnership with our clients!

We are developing the full stack of technologies required to make genomic medicines and provide these to our clients across the full drug development process. Our platforms include manufacturing technologies, delivery technologies, and the expertise needed to help these companies move forward with their drug candidates. We support our clients from early stage discovery, through clinical manufacturing, and all the way up to the commercial stage. We're now reaching the stage with genomic medicines that once you know how you want to manipulate a disease-causing gene, you can create the associated genomic medicine candidate within days for pre-clinical testing. Through our platform, we enable any scientist to be a genomic medicine developer. I believe we are at a tipping point where the broader scientific community is realizing how accessible these technologies are and we will see a significant acceleration of innovation in medicine as a result. Now that we are part of the Danaher group, we are working with our colleagues to develop truly comprehensive, end-to-end drug development and manufacturing solutions.

Glover: Companies like Pall, Precision NanoSystems, and our sister company Cytiva have significant experience, particularly on the manufacturing side. A fantastic example of the value Pall can bring as a manufacturing partner is seen in our work with AstraZeneca and the University of Oxford on their COVID-19 vaccine. They partnered with us early on in the process and we contributed our expertise on how our equipment could be used to manufacture viral vectors on a large scale. We designed a manufacturing process and deployed it to a particular contract manufacturing organization within eight weeks. I don't think anyone in the industry compiles records, but I'd like to bet that is a record timeframe!

Precision NanoSystems strengthens our know-how further by adding more biological expertise. Together, we are a powerful force that can help companies to bring therapeutics to market faster and with more likelihood of success.

How do you expect the field to evolve?

Taylor: In genomic medicines, new types of modalities are being invented, discovered, and developed every day. mRNA is in the spotlight right now and it is very useful for vaccines for expressing antigens, as well as in other areas such as where an expressing protein is missing or not working properly, but there are many other tools in the genetic medicine toolbox. I think genomic medicine will become the largest class of therapeutics in the not-so distant future – and it will be accessible to all scientists, similarly to how easy it is to make a software app today.

In the future, I believe that every country will have the ability to efficiently set up in-country manufacturing of genomic vaccines and therapeutics. This will increase the security of supply, allow nations to more rapidly respond to future pandemics, and enable countries to treat their citizens more effectively. I also believe that we will reach the stage where bespoke genetic medicines can be designed for the molecular basis of an individual's disease, and single drug batches can be manufactured for patients. We are heading towards new therapeutic paradigms that were simply not possible before, and this is happening faster than most people realize.

Glover: Some people say 2021 will be the year of mRNA; others say it will be the year of the lipid nanoparticle. mRNA therapies have been in development for many years, but delivery was always a challenge. We now have a solution – and Precision NanoSystems has been a real pioneer in this area. As Pall, Cytiva, and Precision NanoSystems come together, I'm really excited about how we can deliver mRNA factories to the field as quickly as possible and work with clients on ground breaking new medicines.

Dr Clive Glover is the General Manager, Gene Therapy at Pall and leads the cell and gene therapy business. His work has been published in numerous scientific journals, and he has presented at many conferences. Previously he was responsible for driving product development efforts around cell therapy at GE Healthcare and has also held positions in marketing and product management at STEMCELL Technologies. Clive holds a PhD in Genetics from the University of British Columbia. When not at work, Clive spends a lot of time singing in Welsh choruses and hiking the Welsh hills.

Dr James Taylor is a Co-Founder and General Manager of Precision NanoSystems, and the leader of the company since invention. James holds a B.A.Sc. in Engineering Physics from the University of British Columbia (UBC), Canada and a PhD in genetics from UBC and the Institute for Systems Biology in Seattle, Washington, USA. James worked at the Seattle-based venture capital firm, Accelerator Corporation, concurrent with his PhD, and the Centre for Drug Research and Development in Vancouver, British Columbia, following. James has extensive experience in the science and commercialization of microfluidics, nanotechnology and systems biology.

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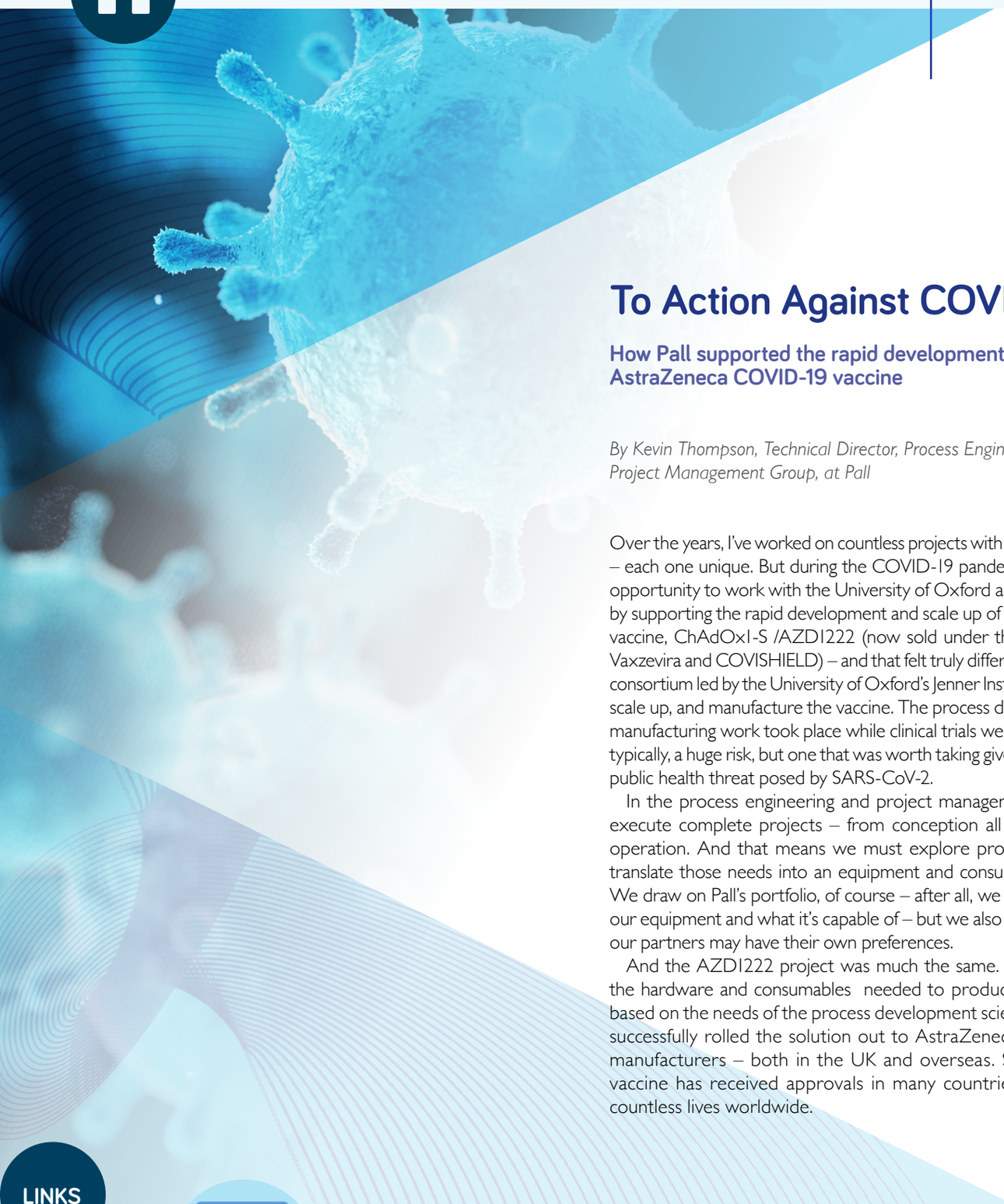

To Action Against COVID-19!

How Pall supported the rapid development of the AstraZeneca COVID-19 vaccine

By Kevin Thompson, Technical Director, Process Engineering Project Management Group, at Pall

Over the years, I've worked on countless projects with many customers – each one unique. But during the COVID-19 pandemic, we had the opportunity to work with the University of Oxford and AstraZeneca by supporting the rapid development and scale up of their COVID-19 vaccine, ChAdOx1-S /AZD1222 (now sold under the brand names Vaxzevira and COVISHIELD) – and that felt truly different. We joined a consortium led by the University of Oxford's Jenner Institute to develop, scale up, and manufacture the vaccine. The process development and manufacturing work took place while clinical trials were still ongoing – typically, a huge risk, but one that was worth taking given the significant public health threat posed by SARS-CoV-2.

In the process engineering and project management group, we execute complete projects – from conception all the way to full operation. And that means we must explore process needs and translate those needs into an equipment and consumables solution. We draw on Pall's portfolio, of course – after all, we fully understand our equipment and what it's capable of – but we also understand that our partners may have their own preferences.

And the AZD1222 project was much the same. We engineered the hardware and consumables needed to produce the vaccine, based on the needs of the process development scientists, and then successfully rolled the solution out to AstraZeneca and contract manufacturers – both in the UK and overseas. Since then, the vaccine has received approvals in many countries – and saved countless lives worldwide.

Learning to move fast

The AstraZeneca vaccine uses a chimpanzee adenovirus vector to deliver a portion of the SARS-CoV-2 spike protein into the recipient, triggering an immune response and producing antibodies against the virus. The traditional development and manufacturing process for an adenovirus-based vaccine takes time and involves many steps. For example, a typical project would begin with a feasibility study and an initial reach out; we would then deliver a basic proposal. The CAPEX would be approved and the customer would perform a vendor capability assessment. From there, there is a lot of process development work, including budget approval and approval of the final specs. All in all, it takes anywhere from three to ten years.

Clearly, such timelines were unacceptable during a global crisis, so processes had to be accelerated. For the AstraZeneca vaccine, additional speed was gained by performing work in parallel. The University of Oxford presented us with a 3 L manufacturing process that they had developed but, as is typical with lab-scale processes, it was not optimized or easily scalable. There were several aspects that needed simplifying to enable the process to work at larger scales. We streamlined the process and scaled it to 50 L, and then 200 L. While our process development scientists were working on scale up, other groups within Pall were working on visualizing the production environment. What equipment was needed? What utilities?

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What type of cleanroom space? What consumables? And where should all of this be sourced from?

We produced a mass balance detailing how the process worked – as well as a process flow diagram. The process flow diagram is essential because it shows exactly how the vaccine moves from one process step to another, including what tubing and manifolds are required for interconnectivity, allowing you to plan your equipment and consumables needs. Typically, it takes time to bring together all of the equipment and consumables required for a process. But with time of the essence, we looked back at a previous kaizen brainstorming event for a 2000 L mAb process, during which we had created an "a la carte menu" of standard consumables that would allow for rapid deployment. In biopharma, most customers have their preferences and nuances with equipment and processes, so there is always a need for specialized parts and customization; however, it is faster if you pick from a pool of more standardized options that can be preordered; it also reduces the need for new validation. At Pall, we're also fortunate in that many of our standard systems are flexible enough to be used across different platforms. In short, we looked at our menu of standard consumables and asked, "What is the quickest way to deploy this COVID-19 vaccine?"

There was no question about using single-use technology for the project; single-use systems are manufactured in a cleanroom and gamma irradiated so they are ready to deploy as soon as you receive them, and as they are disposed of after use there is absolutely no chance of batch contamination.

Although some modifications were made, the vaccine manufacturing process was largely designed around standard equipment. We not only standardized unit operations, but also single-use manifolds. And the first CMO was up and running with a 200 L scale process in just eight weeks – a remarkable achievement!

It was also important to ensure standardization between manufacturing sites; each site/CMO manufacturing the vaccine was using the same consumables. The huge benefit to this is that if one site runs short of a certain consumable, they can ask another site for assistance – in fact, the sites have been doing this using overnight couriers. The collaboration has been fantastic to see! In my view, even outside of pandemic times, there are enormous advantages to deploying standard technology to all of your sites globally, rather than having the chaos of working with dozens of different suppliers who need to develop different parts to your different sites or CMOs.

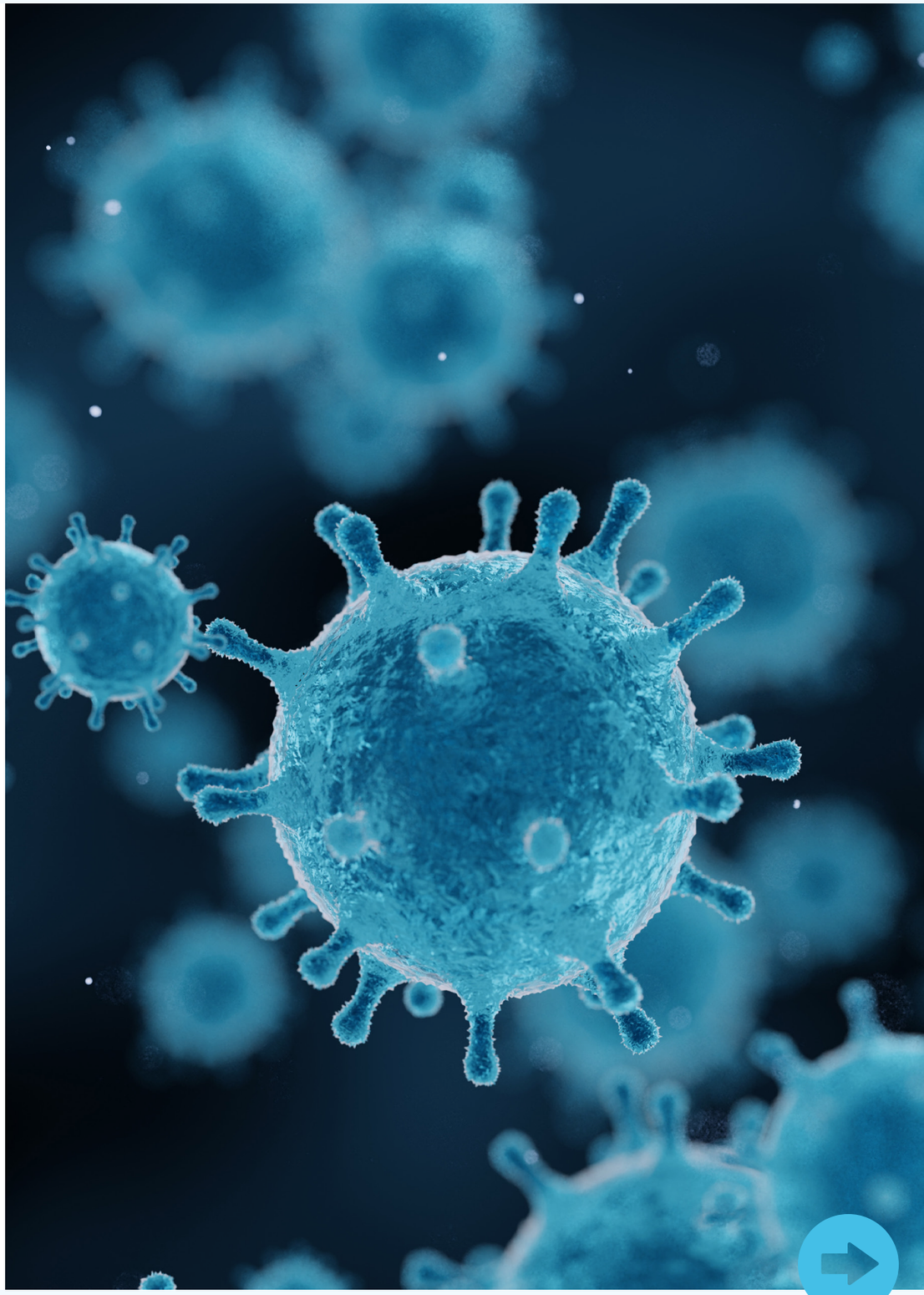
United against a common enemy

Throughout this particular project, collaboration and discussion were crucial. We've had to collaborate with dozens of external stakeholders, as well as different departments across Pall to ensure that we had the equipment and consumables ready to deploy quickly – and guarantee that we would be able to continue to supply consumables to avoid manufacturing delays. In some cases, we asked customers if we could redeploy their ready-to-ship orders for COVID-19 – if it wouldn't affect their own projects, of course – and customers were very generous in their response. Everyone was keen to play their part in the fight against COVID-19. And that freed up a lot of equipment to use for the AstraZeneca vaccine, from tangential flow filtration systems to pumping systems and more.

We were also moving fast in other ways; for example, we were deploying equipment without purchase orders – and anyone in the business will know that is completely unheard of! While still ensuring the process resulted in a safe, quality product, we cut out as many of the normal development steps as we could.

The COVID-19 pandemic is unprecedented and I think we all hope there is not another event like this in our lifetimes. However, there are lessons that can be applied to other areas of development and manufacturing. The process always has to come first; and sometimes your process will require very specialized equipment, but when there is the opportunity to choose from standardized components, it can lead to faster deployment of manufacturing and more reliable supply chains.

Kevin is a Technical Director within the PASS team at Pall - a customer-focused process engineering and project management team responsible for delivering integrated solutions to the pharmaceutical industry. He has spent the last 40 years in Engineering, starting in the UK's electrical supply industry, transitioning to Oil and Gas, followed by Chemicals and Polymers, with the last 22 years dedicated to Pharmaceuticals. He is located within our Center of Excellence in Portsmouth, UK, where he manages a group of project managers - process and commissioning engineers supporting global projects. His team was dedicated to the Astra Zeneca/Oxford COVID-19 vaccine project where their involvement started in the early process development phase, through to delivery.



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The True Spirit of Collaboration

We work closely with customers to bring speed and agility to process development – and to get crucial therapies to patients faster

By Benben Song, Global Product Manager, Technical Services, at Pall

The journey to commercialization for any therapeutic – whether small molecule or biopharmaceutical – has many twists and turns. And there are almost always challenges when it comes to simplifying and optimizing lab-scale processes to meet the more complex requirements of cGMP. For the new and rapidly evolving field of gene therapies, the road is even more complex, with very specific challenges. In some cases, developers may struggle to decide on the best equipment for the job and many others will not have extensive expertise in house.

The solution? Working with manufacturing partners that offer process development services. Choosing an experienced partner who understands the ins and outs of gene therapy can make a huge difference to the success of your project while helping you meet the needs of patients faster.

The expertise and engineering know-how of a competent process development team can be called upon to clearly define a project right from proof-of-concept down to its final stages. My advice is to identify a good partner early on so that you can lay the foundations for success from the very beginning. Every project, however, will have very different manufacturing requirements, so it is important to find a partner who actively listens to your needs and who can suggest appropriate approaches and craft solutions to meet the challenges. An experienced team can also offer unique insight into the various aspects of process development and help predict and iron out issues before they become significant (and expensive to fix).

Listening and adapting

At Pall, we understand that the journey to commercialization is a joint venture with our customers. Indeed, customers must be valued as an essential and equal part of the team for a smooth, problem-free manufacturing journey. And that's why open communication that encourages collaboration is at the heart of all of our relationships.

Though pandemic travel restrictions may have hindered face-to-face communication throughout 2020 and 2021, virtual technologies mean there is no excuse for not sustaining and maintaining customer interactions! We have still been working extremely closely with our customers through regular meetings where we gain their views on ongoing lab processes and change the scope of projects based on these interactions. This flexible approach is extremely important and there must always be room to incorporate changes into processes as a project evolves. For example, our recent collaboration with AstraZeneca resulted in the development of a successful end-to-end process for their COVID-19 vaccine, which is now used to prevent infection by the virus worldwide. The processes we designed have since been tech transferred to over 30 companies, including Cobra Biologics, Oxford Biomedica, and HALIX. Crafting both the upstream and downstream processes took a mere eight weeks, a testament to the importance of open dialogue between partners.

Customers can rest assured that our team – with a wealth of experience in gene therapy processes – can review your current manufacturing approach, help optimize and define your end goals, and prove process reproducibility. We understand that you may not have the expertise to achieve scale-up alone, so we have extensive tech transfer and proof-of-concept capabilities that can help make your journey a success. During the early stages of a production process, we can help control costs using our modeling services, which adapt to any changes that may happen under development. As we reach the end stages of process development together, our specialist operators can make on-site visits to support your manufacturing needs and provide training to your wider teams.

The gene therapy sector growth shows no signs of slowing – and many promising products are expected to be commercialized in the near future. This growth isn't limited to the EU or US; there are huge opportunities for new players to enter the market from across the globe. Our process development support services are here to help as this sector continues to expand and reach new heights.

Dr Benben Song is the Global Product Manager for Services at Pall. She is globally responsible for product management of Accelerator℠ Process Development Services, Accelerator Validation Services, the Accelerator Documentation Center and Training Services. Benben joined Pall in 2015 and has held multiple roles in leading the extractables and leachables validation studies on Pall products to ensure compliance with the latest regulations and evolving expectations for drug safety purpose. Prior to joining Pall, she managed government contracts on drug cardiotoxicity evaluation at the Stanford Research Institute. Benben holds a PhD in Biochemistry from Stony Brook University and has many years of experience in biotech. She has published over 18 articles in scientific journals and has been invited to present her work at many conferences. When not at work, Benben likes to spend time reading, hiking and participating in outdoor activities.

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Winning the Long Race

For long-term manufacturing success, you need to look beyond the process and account for an amalgamation of many important factors

With Ruta Waghmare, Vice President, Scientific Affairs and Laboratory Services, at Pall, and Deen Harman, Vice President of Pall's biotech operations.

It's often said that the product is the process – and it follows that a good process is essential if you want to manufacture a good product. And that's why it is industry best practice to incorporate quality by design from the very beginning. But long-term success cannot stop at the process. For Ruta Waghmare, Vice President, Scientific Affairs and Laboratory Services at Pall, scalability is also crucial and must not be ignored. After all, a perfect process at small-scale may not be suitable for large-scale production.

"Your process will go through many different phases, and it needs to be scalable throughout, or you will incur additional challenges and costs. My advice is to get your operations team involved from the start so that they have their say on the process and can use their experience and insight to make it as robust and as scalable as possible," says Waghmare. "Oftentimes, a molecule may also transfer between sites or different companies as it moves through different phases of clinical development, so you need to ensure your process is transferable."

However, outside of the process itself there are many aspects to consider. As a starting point, Deen Harman, who is responsible for Pall's biotech operations as Vice President, highlights the importance of the workforce itself. "You need a strong management team who truly act as a team, but you also need an engaged workforce overall. It goes without saying that workers need to know what they're doing, but they must also understand why they're doing what they're doing. Not every manufacturing run is identical – problems will inevitably arise and your people will need to think on their feet. Only a highly engaged workforce can become self-sufficient and able to make the right decisions under variable circumstances."

Harman explains that it is important to spot the small problems before they turn into big problems. And when a problem does arise with, for example, a piece of equipment, there needs to be a strong critical spares program in place that includes appropriate contracts with reputable equipment suppliers. "Then there's the material flow through the factory – everything must be as streamlined as possible so that the product reaches the customer quickly and effectively," says Harman. "All of these factors must be overseen by a strong team of managers and planners who can ensure everyone is able to adapt to changing circumstances with quick changeover capabilities."

An eye on supply

One particularly critical factor for long-term manufacturing success is supply-chain redundancy. "We've all had to deal with force majeure situations, whether it be a hurricane, the recent Texas freeze, or the blocking of the Suez Canal. Or sometimes freight goes missing and is never recovered!" says Harman. "However, it's fair to say that nothing has quite compared to the impact of the COVID-19 pandemic. The sudden increase in demand was unprecedented and freight reliability plummeted. Biopharma could not have asked for a harsher lesson on the necessity of building redundancy into the supply chain."

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To deal with the fallout, Pall expanded all of its facilities in the biotech space to ensure they could operate 24/7. "We wanted to get the most out of what we already have, but we also fitted out a brand new factory, which we brought online at record pace. We're also in the process of opening another factory too," says Harman.

Pall's investment in supply chain redundancy now sits at around 20 times what it was before the pandemic. The company also holds a good level of stock to buffer supply chain issues, including both finished products that are essential to customers and raw materials, which are held at vendors but underwritten by Pall.

"We have strengthened our strategic sourcing capabilities, while ensuring we have more people available to work closely with our vendors and identify where investment is required," says Harman. "This means picking up the phone and asking whether a given vendor is able to cope with the capacity, and then working with them to understand their bottleneck constraints. This allows us to create an underwritten plan that delivers what both Pall and our customers need. We also continue to use chartered planes for air freight products rather than the normal freight market."

Waghmare adds, "You must not forget that supply chain management is not independent from other areas of the manufacturing process – particularly quality. You might be under the impression that your supply chain is in a good state, until a quality issue with a component is uncovered, which leads to product recalls. This illustrates that your lifecycle is only as strong as its weakest link."

Both Harman and Waghmare stress that relationships with vendors are a significant factor in long-term manufacturing success. A biopharma manufacturer needs to trust its vendors, and feel comfortable talking with them when needs change. "The sooner you let your vendor know about potential problems or changes in supply demand, the better," says Harman. "Your orders might make up 10 percent of a vendor's capacity, so any unexpected increase in demand can be a problem. The earlier you let them know about problems, the better. At Pall, we ensure we keep our vendors informed of our ongoing needs."

Lifecycle support

To support customers over the entire manufacturing lifecycle, Pall has a dedicated team of over 300 scientists and engineers located in over 35 countries around the world. "The idea is to provide technical support from preclinical development to full-scale manufacturing, upstream bioreactor work to final filtration and even tech transfer between customers in different geographies, regulatory consultation and process validation support," says Waghmare. "The team spans multiple platforms, such as monoclonal antibodies, recombinant proteins, gene therapies, vaccines and so on. Outreach educational activities are another important part of what the lifecycle support team does. For example, last year our team worked on over 150 thought leadership activities, including conference presentations, publications, and posters."

Pall also works closely with customers on manufacturing challenges. There are several common challenges that arise. "For example, in gene therapy, the recoveries of products are often low (a well-known challenge in the industry), but we have several tried and tested strategies to help overcome this," says Waghmare. "Another example is the high concentration required at times for monoclonal antibodies with subcutaneous applications, over 200 mg/mL, which can be very challenging. In both of these examples, our scientists work with customers to improve yields and recoveries. Similarly, when molecules are moved across different phases of development there can be challenges with scale up, but our teams are ready to support customers in any way that they can."

Overall, there's more to manufacturing success than the strength of the process itself. The process must be underpinned by experts across multiple areas, including but not limited to regulatory, quality, and supply chain. And the organization must understand how all of the moving parts fit together and ensure they are all working towards the same goal. It isn't easy to tick all the boxes in-house, which is why working with a trusted partner to troubleshoot issues as they arise can be helpful.

Dr Ruta Waghmare is Vice President of Scientific and Laboratory Services at Pall. She is passionate about using science and engineering to enable the development of life-enhancing drugs, and leads a team of around 300 scientific experts. Ruta previously held senior positions at Millipore-Sigma/Merck including Senior Director for Marketing and Sales, Director of Emerging Biotechnology, Regional Sales Manager, Head of Chromatography (Americas), and Group Manager for Process Development Sciences. Ruta completed her post-doctoral research at the NIH (National Institutes of Health, Bethesda, Maryland) on protein purification and crystallization. She holds a PhD in Chemical Engineering from Iowa State University. Ruta has co-authored over 65 publications and conference presentations. She also served as an officer (including Chair) for Manufacturing Sciences and Engineering section for AAPS (American Association of Pharmaceutical Scientists) from 2012-17. In her spare time Ruta enjoys practicing yoga and is a qualified children's yoga instructor.

Deen graduated from University of Portsmouth with a BA in Business and Computer Studies and over his 38 years tenure at Pall Corporation has had responsibility for European logistics and for multiple manufacturing sites around the world. Now Vice President of Operations at Pall Corporation, Dean is helping Pall to meet the rapidly growing supply chain challenges the industry is facing.

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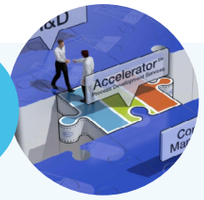

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Converting Customer Need into Speed

Introducing Integrated Solutions to accelerate time to market

By Renaud Balsse, Biotech Integrated Solutions Manager, at Pall

The market for gene therapies is becoming more competitive as companies recognize the opportunities to deliver new therapeutics to patients. Amidst this competition, developers need access to more efficient manufacturing operations that can cut time and costs. Conventional biopharma processes rely on multiple unit operations and are often not suited to producing the doses required for a gene therapy; some therapies require very few doses and, therefore, small batch sizes; others may require many or much larger doses and therefore larger batch sizes. Flexibility is important – but there is also room for improvement in terms of establishing consistent, scalable production processes.

Gene therapies can have a significant impact on patients – in many cases, treating previously intractable conditions. Developers are keen to accelerate time to market, but engineering expertise is required to overcome manufacturing sticking points. Pall offers integrated solutions that bring together various processes into a single, coordinated, and controlled environment. This approach should enable the medicines of the future to reach patients faster by trimming the excess off manufacturing protocols.

A guided journey

Our integrated solutions rely on engineering expertise and a diverse portfolio of established, scalable single-use and hybrid platforms that provide a simplified, low-risk option for cGMP manufacturing. Single-use technology is now well-established in the industry and has numerous advantages, including decreased cleaning time and validation, reduced contamination risks, and faster implementation times compared with investing in stainless steel.

For our customers to reap the benefits of our integrated solutions, we first help them define their individual needs and then visualize the end-to-end services required to industrialize a therapy. We then discuss how to customize the manufacturing parameters to meet the specific production needs of the therapy. For example, we can optimize mass balance for improved product yield, and design pertinent equipment based on requirements. We work closely with our partners at every stage of the journeys, bringing experience and process insight to meet the unique requirements of every project. Most importantly, we ensure there is a solid plan before we move forward!

Process flow diagrams can be produced to allow customers to visualize and improve processes. We can also take a digital approach to process visualization; for example, using 3D modeling software to create a digital version of a facility. Mirroring the equipment, resources, and consumables of real-world plants, these digital representations allow our customers to actively engage with the optimization of their processes and suggest adjustments based on their experiences. Virtual reality technologies further enrich the experience by allowing customers to participate in walkthroughs and to test the ergonomics of manufacturing equipment. Automation options can also be selected.

Support for all

And once the plan is set? We understand it can be challenging to move ahead with implementation, but our customers do not have to face these challenges alone. Our engineers are always on hand to test and validate equipment. From the point of installation and throughout the manufacturing process, our team provides onsite and online training for our customers' teams. They are also available to service equipment – replacing parts and providing emergency intervention when necessary.

With locations across the US, EU, and Asia, Pall's Global Centers of Excellence are there to make sure that regulatory and customer expectations are not only met – but exceeded. We hold regular workshops to ensure the smooth running of our customers' operations. Notably, each center has access to the same level of expertise, so whether a company is developing a therapy in the US or China, they can expect the best support possible from our team. Tech transfer is simple too, which allows our partners based across multiple regions to duplicate their platforms quickly.

Wherever our customers are based, our goal remains the same: to deliver the best, most cost-effective solutions to fit project scopes and timelines. In short, we understand our important role in allowing patients to reap the benefits of next-gen therapies sooner rather than later.

Renaud holds a Master's of Science in Biotechnology and has applied this foundation throughout his 20 year tenure at Pall. Over much of this time Renaud has focused on the implementation of upstream technologies to help drug developers and manufacturers optimize bioreactor productivity. Now he now applies this knowledge and deep understanding of the bioprocessing challenges to create cost effective 'end-to-end' integrated bioprocessing solutions that help manufacturers simplify and accelerate their journey from process design to manufacturing readiness. Outside of work, Renaud enjoys spending time with his family and is a keen mountain biker.

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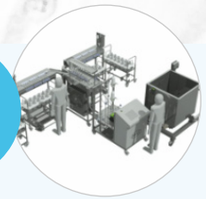

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Seeking Continuous Improvement

Though process intensification has obvious benefits for companies striving to improve efficiencies, it can be challenging to implement. What steps should companies take as they move towards more modern operations?

By Marc Bisschops, Senior Director, SLS - Integrated Process Solutions, at Pall

Now that continuous manufacturing is well established in small molecule circles, conversations have turned to continuous bioprocessing and bioprocess intensification. But some manufacturers are resistant to change. Here, Marc Bisschops, Senior Director, SLS - Integrated Process Solutions at Pall, explains why companies should be considering continuous for faster, more efficient routes to market.

Why is continuous bioprocessing so important?

Put simply, continuous bioprocessing falls under the umbrella of process intensification, which is about improving performance to gain higher titers – and that's always important! When I started my career in the industry 20 years ago, titers were around 0.1–0.2 grams per liter. Now, we can consistently produce 5-10 grams per liter titers for monoclonal antibodies – around 100 times more product! Any technology that saves money and time, streamlines processes, and improves efficiency has got to be seriously considered.

A lesser discussed benefit of a fully continuous plant is the need for significantly fewer interstage product hold tanks and buffer tanks, which contributes to the more compact nature of these sites. Consider this: liquid standing still is liquid that is not working for you!

Process intensification can also help support pharma as it evolves and explores new therapeutic avenues. Advanced medicines are taking the biopharma industry by storm; more complex therapeutics than ever before are under development. Typically, biopharma manufacturing facilities require large, resource-intensive facilities that need to be built very early on in the process to ensure that products are ready for the market as soon as they are approved by regulators. And that requires large capital investment before companies have final clinical trial results – and, crucially, before they can be sure that they will recover their investment.

Intensified and continuous bioprocessing reduces the upfront investment and drives flexibility, allowing us to respond to changing market conditions in ways that wouldn't have been possible before.

Are continuous systems difficult to implement?

There are many differences between a conventional manufacturing facility and a continuous manufacturing facility. It goes without saying that some companies will find the use of continuous approaches to be more complex than traditional batch methods. But in other cases, companies are simply resistant to transitioning towards any new approach.

I believe that a continuous system doesn't have to be perfect for efficiency and productivity gains to be realized; for example, continuous can be used to simplify certain processes, such as chromatography or filtration, to make them viable options for a broad spectrum of businesses.

Despite the benefits of continuous, the perception exists that adoption comes with big risks. But new ideas are often hotly contested – mainly because the industry is so tightly regulated (though regulators are often keen for change!) In the past, we debated whether single-use systems would ever compete with stainless steel units, but today the benefits of single-use are well known, and many former skeptics rely on them within their operations. Similarly, I expect that many of the individuals and companies who are wary of continuous

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Continuous bioprocessing: Increasing productivity through process evolution

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bioprocessing will eventually come to realize its potential. In the meantime, we must address their concerns; we work with our customers to examine the risk profile of continuous and discuss how challenges can be mitigated.

What do companies need to consider when it comes to continuous manufacturing and digital technology?

The drug manufacturing process results in an archipelago of information islands. And though different systems create the data, it must ultimately come together in the form of a batch report. A drug substance can't be released without this information – they go hand in hand. Today, the industry has a data problem. And process intensification, which is made up of many moving parts – from primary process flow bioreactors to closed chromatography, will produce even more data and at a higher velocity. Companies will have to sift through more information than ever before to produce robust reports, and so data management will become even more important. Digital platforms offer the industry an opportunity to better engage with the masses of data it creates by providing tools that can help analyze and simplify the information. Digital platforms ultimately enable companies to demonstrate their ability to produce consistent, reliable data and extrapolate meaningful insights from it. This is a piece of the process intensification roadmap that is not always visible, but it should not be left behind.

I think it would be wonderful if we could use digital tools across the industry in a more harmonized way. Right now, every company has its own protocols, which makes it very hard to standardize. I believe there is room for more training and uniform technical advancement – and that these will be essential if we want continuous processes to reach their full potential.

At Pall, we're working hard to dive deeper into the digital space. Not only do we offer customers access to digital twins and virtual reality platforms so that they can adapt and adjust their facilities to meet their changing needs, we are also using digital technologies to ensure that our customers' operations run efficiently and without hiccups. These objectives are now more important than ever before; the pandemic has proven that the industry must remain agile to respond to crises.

How else can Pall help?

We offer a broad range of support services. The field is still growing and as new platforms and technologies come to light, we aim to guide our customers through the options. From process development all the way through to clinical and commercial manufacturing – our team can help customers define the right process parameters and conditions, and then support them with scale-up within cGMP facilities and finally onto market success. When problems arise, our engineers are on hand to troubleshoot any queries our customers might have.

We also help our customers with regulatory applications. The labyrinth of legal requirements can be daunting to face alone. Many companies face the same hurdles and therefore, come to us with similar questions. And although most regulatory bodies are supportive of the industry's transition to continuous, it can still be challenging for companies to produce applications and provide the right supporting materials for their products. We've developed a toolbox of regulatory support and knowledge to help simplify the process. Our team can guide companies through risk assessments – making sure they can answer any questions in ways that satisfy regulators.

We want our customers to feel totally confident in their ability to manage their operations so that the next generation of drugs is produced to the same high quality expected by patients.

Dr Marc Bisschops is the Senior Director of Integrated Process Solutions at Pall. Marc leads the development of the regulatory support initiative for continuous bioprocessing. He is responsible for field support activities related to continuous bioprocessing, cell culture and single-use technologies. Marc is one of the leading scientists in this area. He has completed over 250 continuous chromatography and continuous downstream processing projects, authored 15+ continuous publications, and invented eight continuous bioprocessing patents. Marc won the Machevo Award (NLD) for Innovative Separation Equipment developed during PhD research, and is a guest lecturer at various post-graduate courses in Europe. Marc holds a PhD in Biochemical Engineering, Delft University of Technology (NLD). Prior to joining Pall, Marc was CSO at Tarpon Biosystems, the company that developed the continuous chromatography technology. Marc held several scientific and management positions in process development departments in Batavia Biosciences, Xendo. Mark enjoys photography and visiting the theater with his four daughters, including two sets of identical twins.

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