MAY 2021 # 75

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Simplifying Progress

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Thank You, Single-Use Plastics

Amongst the global negativity towards plastics, we shouldn't forget how single-use plastics are saving lives

If you were to Google "single-use plastics" (SUPs), you could scroll through thousands of unflattering opinions about the dangers of our "global plastic addiction(s)" and the impact on the environment, wildlife, and human health. I don't discount those concerns. But, lost in the chatter, is the fact that hundreds of polymeric products allow us to live safer, healthier, longer lives.

Nowhere is this more evident than in the use of single-use technologies (SUTs) in COVID-19 vaccine research, manufacture, and fill-finish operations… SUTs have (almost) single-handedly reduced the typical vaccine development timeline from nine years to nine months, allowing "warp speed" delivery of vaccines and vaccinations. Now, as we contemplate a need for 10-14 billion doses of vaccine, conversations around safe, fast and flexible vaccine production – and the need for supporting polymeric devices – have become even more urgent.

However, the "anti-plastic" drumbeat continues – and has gone global. At the time of writing, the government of Canada is contemplating the declaration of plastic as a "toxic" material, proposing bans on straws, stir sticks, food containers, food packaging, six-pack rings, and plastics cutlery. Though these single-use "consumables" are items we can live without, the designation of plastics as "toxic" is unprecedented, and it unfairly portrays plastic as "problematic" with little context of the beneficial flip side, which encompasses a universe of good. All SUPs are not created equal, but public perception is pulling us in that direction.

Just as we have employed SUTs to beat back the SARS-CoV-2 virus with polymeric-based vaccine-manufacturing tools and technology, our SUP friends have been there too: ventilator tubes, BP cuffs, hoods, shoe covers, gowns, goggles, face shields, treatment tents, mattress covers, face masks, and blood and saline bags are all in the COVID-19 fray as frontline defense tools – and they have saved lives. By design and definition, these "single-use" items ensure sterility and safety to patients and staff.

When it is your time to sit for a COVID-19 vaccine administered by a masked health care professional, remember to say, as the needle sinks into your arm, "Thank you. And thank you single-use plastics."

Kevin D. Ott

Executive Director of the Bio-Process Systems Alliance (BPSA) and the Flexible Vinyl Alliance (FVA). Both are SOCMA Affiliates, based in Arlington, Virginia, USA.

BPSA is the international industry association that represents the suppliers and users of single-use bioprocessing systems. www.bpsalliance.org. FVA is a coalition representing the business interests of the flexible-PVC value chain www.flexvinylalliance.com. Both organizations are SOCMA affiliates based near Washington, DC: www.socma.org.

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On the Cover – Credit Gavi/2021
On 26 February 2021, a plane carrying 504,000 doses of COVID-19 vaccines distributed by the COVAX Facility landed in Abidjan

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Change of address info@themedicinemaker.com
Hayley Atiz, The Medicine Maker, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
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Upfront

Research
Trends
Innovation

Food for Thought

How a Russian culinary staple inspired a new approach to drug delivery


Credit: Moszkvatér Bistro

Proving that inspiration can come from the most unlikely of sources, researchers at Skolkovo Institute of Science and Technology (Skoltech) in Moscow, Russia, have developed microcapsules inspired by pelmeni – a type of Russian dumpling. The team found that the unconventional shapes of their biodegradable pills were more effective for targeted drug delivery than traditional capsules (1).

Gleb Sukhorukov, Professor at Skoltech's Center for Neurobiology and Brain Restoration and lead author of the study, explains that he drew on his cooking experience to design the microcapsules. He says, "I remember helping my grandmother make pelmeni. You need a sieve large enough to accommodate one pelmen, similar to each microwell on the template surface. Each layer of pasta used is like a hydrophobic thin film, and the meat, a protein or bioactive."

The approach led the team to develop microcapsules with pyramidal or rectangular shapes that could encapsulate a variety of substances, including small, water-soluble molecules. Sukhorukov explains that this was important because the capsules retained the loaded molecules for several days – proving their capacity for controlled release. "Many drugs fail because they are unable to effectively deliver the right dose over long periods. Our approach may help solve this problem," he says.

Sukhorukov and his colleagues now plan to apply the technology to various polymers used shell components and assess their behaviors in vivo.

Reference

1. *GB Sukhorukov et al, Materials and Design, 202, 109527 (2021). DOI: 10.1016/j.matdes.2021.109527.*

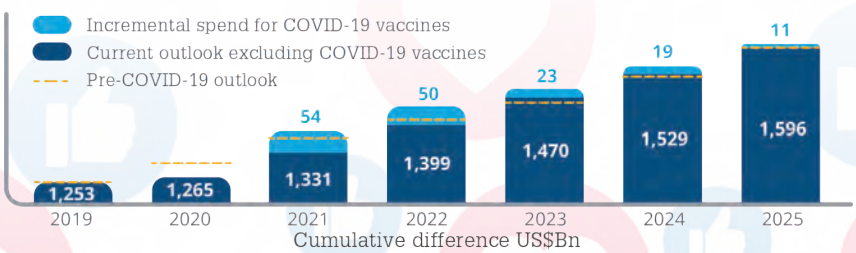
INFOGRAPHIC

What's Trending?

A snapshot of how the industry may change over the next five years

COVID-19 CRISIS

★ Global spending on COVID-19 vaccines is expected to reach **$157 billion** by **2025**



BUSINESS IN BRIEF

Patent waivers, reviews, and revenue forecasts... What's new in business

- The European Commission has announced its readiness to participate in a COVID-19 vaccine patent waiver – opening the doors for worldwide production. Ursula von der Leyen, president of the commission, expressed that they were prepared to discuss "any proposal that would tackle the crisis in an effective and pragmatic way." The news came a day after the Biden administration in the US announced its support for proposals to suspend intellectual property rights for coronavirus vaccines. The statement has prompted a fall in shares in major pharmaceutical companies. Some industry associations, such as EFPIA, have also spoken out against the move, claiming it could put hard-won progress in the fight against COVID-19 "in jeopardy."
- Forecasts suggest that Pfizer will rake in US$26 billion dollars in 2021 sales of its COVID-19 vaccine. The company expects to produce up to 2.5 billion doses in 2021 and continues to sign new contracts. It is also waiting to hear from US regulators on whether the vaccine can be expanded to children aged 12 to 15 years. "Based on what we've seen, we believe that a durable demand for our COVID-19 vaccine – similar to that of the flu vaccines – is a likely outcome," Pfizer's CEO, Albert Bourla, reportedly said during a conference call with investors.

- Gavi, the Vaccine Alliance, has signed an advance purchase agreement with Novavax for 350 million doses of its NVX-CoV2373 COVID-19 vaccine candidate for the COVAX Facility. Supply of the vaccine is expected to commence in Q3 2021, as soon as the vaccine has received regulatory approvals.
- The EMA has started a rolling review of Sinovac's COVID-19 vaccine. Though the vaccine is currently available for use in China, Indonesia, Brazil, and Turkey, it has yet to be approved in Western markets. The decision to start the review process was as a result of preliminary results from laboratory studies and clinical studies.

A Sticky Situation

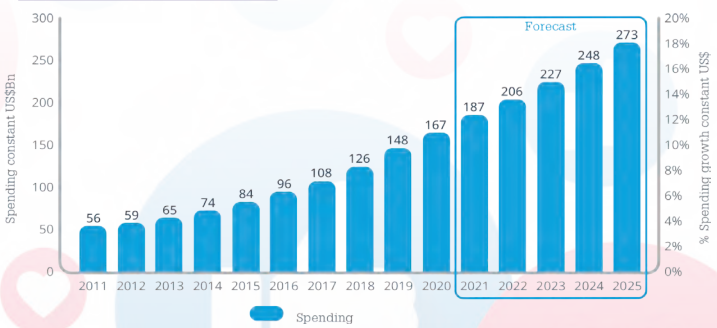
Exploring the importance of viscosity in pharmaceutical product design

Measuring particles' viscosity can offer drug developers important information on pharmaceutical products. As the stickiness of particles changes throughout reactions, important data – including reaction yield and the quantity of remaining reactants – can be gathered. But how easy is it to measure? Though sluggish rheometers make measurement challenging, researchers at The University of Queensland have now developed an optical tweezer approach that allows for accurate and rapid evaluation of viscosity.

"We developed optical tweezers that can track microparticles down to one femtometer (a millionth of a billionth of a meter) during a one-second measurement," says Warwick Bowen, professor and lead researcher on the project. The tweezers' design enabled them to measure viscosity four orders of magnitude faster than previously recorded – allowing more precise results.

Bowen says, "This could open the door to improved yield and quality control in the production of pharmaceuticals. It could also allow measurements of the active dynamics of living cells after a pharmaceutical is administered – providing a new level of detail on the effects of pharmaceuticals on the human body at the single-cell level."

CANCER CARE



- ★ CAGR of **9-13%** by **2025**
- ★ Over **100** oncology drugs expected to reach the market by **2025**

AUTOIMMUNE DISEASES

- ★ Spending predicted to increase by **63%**
- ★ **10%** CAGR by **2025**

Source

1. *IQVIA (2021). Available at https://bit.ly/2RqERDJ.*

Digital Coordination

An industry partnership is working to ensure the distribution of COVID-19 vaccines across Africa

As global COVID-19 vaccine campaigns continue, Vodacom and AUDA NEPAD – the African Union's development agency – have partnered to rollout mVacciNation, an interoperable, digital platform to help distribute vaccines across Africa and coordinate vaccine scheduling (1). The digital toolkit, launched as part of a continent-wide digital transformation partnership, consists of two core components and a control tower: a supply chain component that provides real-time information for health workers on the availability of vaccines and other medical equipment; and a beneficiary management component that allows individuals to register on the platform and assigns people to vaccine service points on a specific day and time.

"mVacciNation allows for the orchestrated distribution of stock to vaccination centers and temperature-controlled supply chain facilities," says Peter Breitenbach, Head of Product and Strategy for Vodacom subsidiary, Mezzanine. "An additional benefit is that, each time someone is vaccinated, their digital record is updated – and, if a further dose is required, mVacciNation automatically schedules and sends a follow-up date via SMS. Once vaccination is completed, the individual will receive electronic certification." The platform can also be linked to countries' vaccination travel passport platforms.

Though there are challenges in its implementation – particularly in rural areas where access to mobile devices may be limited – mVacciNation is already being used to manage COVID-19 vaccinations in South Africa, where over 300,000 people have been vaccinated to date. The platform also has applications beyond Covid-19. The Ministries of Health in Tanzania, Mozambique, and Nigeria have used the platform to improve immunization rates for childhood vaccines successfully in the past. Breitenbach adds, "Once installed, the mVacciNation platform will remain in place to help countries better manage future pandemics and other large-scale health programs. By agreeing to roll out mVacciNation, countries will be creating digital health infrastructure for the long term."

Though mVacciNation is the collaborative team's first joint venture, they plan to continue working together to create other digital tools. "Connecting everyone on the continent to the digital economy and ensuring that no one is left behind remains the seminal challenge of our time," Breitenbach says. "To do this, we must accelerate digitization efforts through the right public-private partnerships and expand regional cooperation – because we cannot achieve this in isolation."

Reference

1. *Vodaphone (2021). Available at https://bit.ly/3vLdHX3.*

Growing Popularity

What factors influence the public's perception of the pharmaceutical industry?

Pharma's reputation is improving, according to a report published by RepTrack. The annual report, which assigns a score to different industries based on public opinion, showed that the sector improved on its 2020 ranking by more than three points pushing its score to 72.8 out of 100 – giving it a "strong" reputation according to the company's scale.

The improved scoring left the pharmaceutical industry ranked eighth for public approval, ahead of the consumer service, transport, retail, media, and financial service sectors. The document also suggests that the industry's management of the COVID-19 pandemic, as well as its approach to environmental, social, and corporate governance, have helped change perspectives on the sector as a whole.

But RepTrack's study showed that the increased trust in the pharmaceutical industry wasn't universal. Though the industry received high scores in the EMEA, APAC, and LATAM regions, individuals in North America gave the industry average scores.

Access the full report at https://bit.ly/3ui8c1D.

IMAGE OF THE MONTH

A Winning Combination

DNDi along with partners from 26 African research institutions have launched the ANTICOV trial to determine the efficacy of a new drug combination in patients with mild to severe cases of COVID-19. The study will assess the antiparasitic drug, nitazoxanide, along with the steroid, ciclesonid.
Credit: Xavier Vahed - DNDi

Would you like your photo featured in Image of the Month?
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QUOTE of the month

"People want to end the pandemic, get the economy back on track and make healthcare more affordable. Instead, House leaders have introduced the same old divisive drug pricing proposal that will put more barriers between patients and their medicines. It will also destroy jobs, cede our leadership in life sciences, and stifle the development of new treatments, while failing to address the broader challenges facing patients."

Stephen J. Ubl, President and CEO of Pharmaceutical Research and Manufacturers of America. https://onphr.ma/3h4E7i4

Putting the Brakes on Inflammation

Can a new approach halt retinal degradation for good?

Geographic atrophy (GA) affects millions of patients worldwide and is characterized by the degradation of the retina following inflammasome-mediated events in the eye. Despite the challenges the disease presents, treatment options are scarce. But new research points to Kamuvudines – molecules that inhibit the inflammatory behavior of the innate immune system – in preventing retinal degradation in GA patients (1).

"Kamuvudines are modified derivatives of nucleoside reverse transcriptase inhibitors (NRTIs) – a class of anti-HIV drug," says Jayakrishna Ambati, co-founder of Inflammasome Therapeutics and senior author of the study. "They block retinal cell death mediated by amyloid beta molecules." Kamuvudines are less toxic than traditional NRTIs, making them suitable for long-term use.

The team is also exploring the potential of Kamuvudines in treating other inflammasome-mediated conditions, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease. Ambati says, "Kamuvudines have broad applications. Using them, we have an opportunity to make a difference to the many patients who live with debilitating diseases that have previously been difficult to treat."

Reference

1. *S Narendran et al, Signal Transduction and Targeted Therapy (2021). https://doi.org/10.1038/s41392-021-00537-z*

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In My View

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

Smooth (Transfer) Moves

Technology transfer is full of risks. But risks can be mitigated with the right strategy – and a little help from digital technologies.

By Alan Steven, Senior Principal Scientist at CatSci

Generally speaking, technology transfer is the culmination of scale-up from pilot plant facilities to a site capable of supplying the necessary volumes for commercial supply. However, technology transfer can also occur because of a need for extra manufacturing capacity to satisfy growing commercial requirements. Thirdly, it takes place when a maturing product is moved from its launch facility to make room for newer products.

Differences in product from manufacturing campaign to campaign within the same site are inevitable. Where such a change is deemed to be statistically significant, however, a pause in manufacturing is likely, threatening the supply of a medicine to patients. The risk of such a change in quality is even greater with a change of manufacturing site, and may be attributed to scale effects, new sources of raw materials and reagents, or differences in manufacturing equipment. In my view, communication, risk management, and digital technologies all have an essential role to play in identifying and addressing the impact of these changes, and hence ensuring the success of technology transfer.

Technology transfer involves the exchange of technical knowledge, data, or procedures, and, therefore, can be considered a subset of knowledge transfer. Being inherently "sticky," knowledge must successfully flow during the technology transfer process – it cannot be simply thrown over an organizational wall between the donating and receiving groups!

My advice when planning a successful technology transfer is to work backwards from the envisaged end goals – putting together a knowledge transfer plan that outlines the scope, roles, responsibilities, and success criteria for knowledge transfer. As well as the procedures, samples and methods, the receiving site needs to understand the rationale behind the design of the process of manufacture and associated testing.

Having clarity over what is known and what is not known about a manufacturing process makes it easier to decide what can be changed as part of the transfer. Ideally, there should be a mechanistic or statistical understanding (or a hybrid of the two) around how variation in a process input attribute (whether process parameter, material, or facility) affects the overall process or product. The most important gaps in this knowledge can then be addressed using targeted labwork or simulations, ahead of selecting a receiving site for the transfer and agreeing the changes to the process that are in scope.

As part of this assessment of knowledge gaps, it is important to capture the intricacies of the equipment needs and wants of the process, so these can be weighed versus the equipment availability at any potential receiving site. This approach forces decisions around whether to invest in the kit at the original site or to modify the receiving site's protocols to suit existing equipment.

Technology transfer is being increasingly enabled by new technology, which can help reduce risk. For example, with mixed reality (where 3D content becomes an interactive part of the real world) scientists familiarizing themselves with the process being transferred can be granted an "I-see-what-you-see" perspective when they interact with scientists at the donor site. These experiences allow contextualized data to be shared in real time, and mediate the transfer of "tribal" knowledge that is not easily written down.

Models are another key technology; by modeling how inputs affect product

quality and process performance, the behavior of the process in the modified operating environment of the receiving site can be digitally tested from the comfort of an office workstation. If necessary, thousands of simulations can be run. Taking individual models further, digital informational constructs of physical systems can be used to mirror the behavior and dynamics of physical assets involved in a process. Such digital twins can also be used as a training platform for operators and engineers, as they provide feedback in real time.

As an example of the power of modeling, I was recently involved in the technology transfer of an anticonvulsant drug used as an adjunctive treatment for partial onset seizures. Whilst preparing for the transfer, digital simulations based on a kinetic model highlighted the risk of a change in the reaction profile, on transfer, due to the impaired ability of hydrogen to move from the reactor headspace to the catalyst surface in the reactor available at the receiving site. The issue was addressed by stipulating the need to operate under a high pressure of hydrogen gas.

The experimental verification of this hydrogenation model also initially showed unexpected behavior that was traced to more sodium salts being present in an alternatively-sourced input. And that led us to refine the model, which was later successfully verified. I believe this example beautifully illustrates the need for mechanisms that continually build on the corpus of knowledge about what affects product quality and process manufacturability over the entire lifecycle of a product.

Since 2011, the FDA has openly advocated using a lifecycle approach to process validation. It's fair to say there have been different interpretations of what this should mean, but many in the industry are aligning around the need to use data-driven and risk-based approaches to build, rationalize, and maintain the manufacturing control strategy that articulates how a process should be implemented.

In my opinion, we must continually address gaps in knowledge around what delivers a product with the right attributes, and use this as a basis for controlling or accepting risks. When this approach is taken in the context of a technology transfer preceding a process performance qualification activity, there are likely to be fewer failed batches. In turn, this means the time and cost of achieving successful registration and manufacturing commercial product will be reduced.

Three in One

Why multilayer tablets, multiparticulates, and mini tablets could lead the way in patient-centric drug delivery

By Thomas B. Gold, Vice President, Pharmaceutical Development at Metrics Contract Services, North Carolina, USA

Today, there are more effective therapies for major diseases than ever before – and we now have a better understanding of disease comorbidities and the likely combinations of medications that patients may be taking. The efficacy of these therapies, however, can be limited by patient compliance challenges; the burden placed on patients who must take multiple tablets daily can limit the success of any treatment protocol.

One potential solution is to combine multiple APIs, or release profiles for the same API, in a single dose. In a survey of oral solid dosage developers (1), controlled release formulations and fixed dose combinations (FDCs) were identified as the technologies companies are most likely to use when formulating new products. In the same survey, however, 47 percent of respondents also said that controlled release formulations were their greatest challenge.

I believe that multilayer tablets, multiparticulates, and mini tablets (mini-tabs) have emerged as the most elegant means of delivering more effective and patient-friendly products. Each offers its own versatility when it

"Each offers its own versatility when it comes to controlled release profiles and the ability to deliver multiple therapeutic payloads in a single dose."

comes to controlled release profiles and the ability to deliver multiple therapeutic payloads in a single dose. Here, I dissect each option in terms of pros and cons.

i) Made up of two to four layers, the multilayer tablet allows for two or more chemically incompatible APIs with similar release profiles to be incorporated into a single tablet. Alternatively, they can be used to deliver two or more drugs with unique in vivo release profiles, or facilitate release of the same drug in two or more release profiles – offering both immediate and sustained release for an API for instance.

The challenge during formulation is that multilayer tablets must have adequate mechanical strength and hardness to endure processing, handling, packaging, and transport. Some of the common problems associated with the manufacture of multilayer tablets include delamination at the interface of the layers due to insufficient adhesion, incomplete segregation of layers, slower throughput, and relatively low yield compared with conventional tablets. There are also challenges in achieving the desired weight of individual layers.

ii) Multiparticulates are multi-unit dosage formulations that offer flexibility in target-specific delivery. They can be tailored for controlled and/or delayed targeted drug release depending on the polymer coating, and different polymer-controlled release profiles can be blended to achieve more sophisticated products. It's also increasingly common for inert cores to be coated with different APIs to create a FDC in a single capsule or tablet. For manufacturers, they offer a number of benefits when they have the experience and capability to handle multiparticulates.

Beads are usually 0.2–2 mm in size, and the spherical shape and compact structure allow for good flow behavior, making them easy to dose. Multiparticulates also disperse freely in the GI tract, which enables developers to achieve both the correct potency and controlled release

One of the challenges with multiparticulates, however, is gaining control over the size of the substrate sphere, so processing often requires tedious sieving. Some of those challenges can be overcome with the use of an extrusion-spheronization process, which gives manufacturers better control of the size of the multiparticulates as well as uniformity of drug loading.

Multiparticulates may also be compressed on a rotary tablet press to create substrates with different release profiles, and makes them easier to coat with technologies such as pan coaters and fluid-bed processing units. Other dosage form options include orally disintegrating tablets (ODTs), suspensions, sachets, and sprinkle capsules – giving developers significant flexibility.

iii) The small size of mini-tablets makes them ideal for children, the elderly, and patients who have difficulty swallowing – ultimately increasing safety, convenience of administration, and patient compliance. Mini-tablets typically have a diameter of 4mm or less and can be as small as 1mm. Their size, uniformity, shape, and mechanical strength allow them to be filled into a capsule or a sachet/stick-pack. They also provide similar filling flexibility to multiparticulates. A few typical approaches include dosing a capsule with two different minitablets containing chemically incompatible APIs, or dosing a capsule with minitablets containing the same API, but with different release profiles.

As with multiparticulates and multilayer tablets, immediate release, delayed release and/or extended release profiles can be dosed in one capsule to achieve the desired drug delivery. Mini-tablets can also be used to deliver two actives together in two separate tablets within the same capsule. In fact, approaches involving the combination of immediate release and sustained release mini-tablets in one capsule are becoming increasingly popular (2). The development of processing equipment that has the capability to deliver precise filling by counting the number of mini-tablets per dose has made mini tablets a more attractive option.

Offering versatility across varied patient populations and highly precise dosing options, these novel technologies are helping drug formulators bring the benefits of oral administration to molecules that previously had to be delivered by other routes. Reformulation of large molecules, that were previously injectables, into oral solid dosage forms is a growing trend in this space – Novo Nordisk for example is currently developing oral formulations of GLP-1 receptor agonists and insulin. With the right dosage forms, molecules can be protected from gastric acid allowing them to be taken in pill form. Given that patients invariably prefer oral doses over injections, these new forms have the potential to improve patient compliance. This and the sustained growth of these technologies are testament to their benefit in enhancing patient compliance and experience (3).

References

1. *American Pharmaceutical Review, "Oral Solid Dosage Trends," (2019). Available at https://bit.ly/3dMggRg.*
2. *P Priyanka, K Kumar, D Teotia, "A comprehensive review on pharmaceutical mini tablets," Journal of Drug Delivery and Therapeutics, 8, 382–390 (2018). DOI: 10.22270/jddt.v8i6.2060*
3. *KC Kwon, C Lee, "Analysis of Fixed-Dose Combination Products Approved by the US Food and Drug Administration, 2010–2015: Implications for Designing a Regulatory Shortcut to New Drug Application," Ther. Innov. Regul. Sci., 51, 111–117 (2017). DOI: 10.1177/2168479016663263*

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IMAGE

Two polymorphs of cholesteryl acetate recrystallised from the melt Gary Nichols, Materials Characterisation, Sandwich, UK.

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In with the New: Embracing Multicolumn Chromatography

Biopharma companies are rapidly making changes to their manufacturing strategies – and flexible downstream unit operation solutions that enhance process efficiency and reduce costs have a significant role to play

By Casey Mihal

Every manufacturer asks themselves the same question: how can we cut costs? In biopharma manufacturing, developers are always seeking to reduce the cost per gram of products, and by extension this also addresses one of the industry's most pressing issues – access to affordable medicine. If the cost of manufacturing operations could be reduced, it would influence the price of commercial drug products and allow more patients to benefit. However, for the industry to achieve its cost-cutting goals and more closely cater to patient demand, it must move away from traditional processes that come with low flexibility, high capital expenditure, and poor productivity.

Companies are already leaving conventional manufacturing practices behind and prioritizing the intensifying their downstream processes with next-generation technologies that can more effectively and efficiently manufacture the medicines of the future. These strategies are designed for intensified processing, with a focus on higher titers, smaller batches, and accelerated manufacturing. In the small molecule sector, there has been a huge uptake of continuous manufacture, which has led to a reduction in capital expenditure and the cost of drugs.

Having seen the benefits, drug developers want the same for biologics. When transitioning to an intensified process, it is essential to select the right hardware for the important manufacturing step of capture chromatography. This process provides the primary purification of a target molecule from a mixture – and it is also where a significant proportion of downstream processing costs are sunk. Traditionally, companies have relied on batch capture chromatography – an approach that employs a single column typically filled with costly affinity resins. This method pales in comparison to multicolumn chromatography (MCC), an approach that uses the benefits of parallel processing of smaller columns to greatly increase processing efficiencies. In fact, the use of MCC allows for a five-fold increase in productivity, which can be used to achieve up to 80 percent in cost saving on chromatography resin (1).

The superior bioprocessing power of MCC should be attractive to those manufacturers who are keen to transition towards newer, more efficient approaches. Let's look at the advantages in more detail.

Breaking down bottlenecks

Historically, manufacturers have had to strike a balance between operation cost and time due to the limitations of batch capture equipment. A company can use a larger chromatography column to boost processing speed or use a smaller chromatography column with more cycles to reduce operational costs. Traditionally, it is the norm to use large columns, which require larger capital and larger operational investments – not only in terms of the bigger columns themselves but also the huge volumes of chromatography resins required.

Higher upstream titers should be beneficial to businesses; however, increasing titers have put huge strains on the batch capture step, which has become a significant bottleneck. To remedy the issue, those companies still relying on batch capture have been forced to either use increasingly large columns to maintain process times or, to keep costs sustainable, use the same size columns and tolerate a slower process. Some companies have turned to mid-sized columns in an attempt to achieve a happy medium between process time and cost. Such hardware typically runs between three and four cycles but these mid-sized columns struggle to keep up as titers increase; more cycles are needed, which results in companies frequently exceeding their allowable operation times. Moreover, finding the right balance between speed and cost is sometimes subject to other factors; for example, if a product is relatively unstable in the clarified matrix, the capture process must be completed quickly to avoid product degradation.

MCC has emerged as a powerful solution to overcome manufacturing bottlenecks, and it has the added benefit of doing this within a small footprint. The technology enables customers to process higher titers without increasing the process time or the consumables cost. MCC leverages two simple concepts. Unlike batch chromatography, it makes full use of the capacity of its columns through controlled overloading – a process that allows the breakthrough of one column to flow onto another, rather than down the drain. It also eliminates idle volumes in packed beds by dividing a larger column into smaller sections that can be processed quickly and independently. As a result, up to 80 percent less resin is used (2). By improving resin capacity utilization, higher titers can be processed without affecting set manufacturing times while still significantly reducing resin costs. Notably, reduced resin usage is also a significant advantage in clinical development, where expensive affinity

chromatography resins are purchased for very specific projects and not used to expiry. If a molecule fails or the batch sizes are small, the significant capital spent on the partially used resin is lost.

Changing the narrative

From a regulatory standpoint, many agencies are encouraging companies to explore process intensification options like MCC, and this helps to break down barriers for the implementation of the technology. The wide range of tools and modeling capabilities available today also means that the transition from batch to MCC is an easy process with relatively low development costs.

However, there are some perceived barriers to use that have made some customers hesitant to adopt the technology. For example, companies have expressed concern that MCC could make the cleaning validation process more complex. However, MCC is designed to overcome such challenges! Technologies, such as BioSMB, offer a gamma-sterile, single-use flowpath to eliminate the need for system cleaning and cleaning validation. There have also been concerns about the feasibility of scale up and the limitations of the equipment. MCC system platforms span process development to compliant GMP operations and the BioSMB, in particular, is very flexible as the modularity and 8 column positions mean that it can be adapted for most process demands, including batch and continuous manufacturing.

Finally, with any new technology there are always questions about how easy it is to use and how long it will take to train staff to use it correctly. Some customers have worried that the system may be complicated, but the software (Phase Editor) is designed to make recipe writing intuitive and quick, so it doesn't require specialized expertise to use. Ultimately, technology like this is designed to address the current challenges that arise in bioprocessing and help manufacturers make the switch to embrace next-generation processes. Manufacturers have already recognized the benefits of single-use systems when it comes to reducing operational time and costs, so the adoption of a single-use MCC solution should be a low-impact process for many customers.

MCC helps manufacturers work towards their goals of developing the facility of the future, and can accelerate processes and allow medicines to reach patients faster. I believe MCC is an emerging paradigm shift in downstream processing that will become a staple in next-generation facilities within the next several years because it provides a great entry point for the wider adoption of process intensification.

As the industry moves towards next-generation facilities, it will be crucial that they put in place the right technologies that can truly transform bioprocessing. The capacity of MCC to enhance productivity and improve resin use means that we can help our customers to make new and existing products more accessible – a goal that helps create a healthier future for us all.

Casey Mihal is a Chromatography Application Specialist at Sartorius

References

1. *Sartorius, "Continuous Chromatography Multi-Column Chromatography Solutions for Minimizing Costs" (2021). Available at https://bit.ly/3tMScnD.*
2. *Sartorius, "Why Multi-column Chromatography (MCC)?" (2021).*

The GREATEST MEDICINE MAKING CHALLENGE

How do we vaccinate billions of people? Nobody wins the race until everyone wins.

By Stephanie Sutton

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Employees packing boxes with COVID-19 vaccine at the packaging and dispatch department in Pune, Maharashtra, India, on Tuesday, Feb. 23, 2021.

The global population stands at 7.8 billion people. To vaccinate just 70 percent of the world's population requires around 11 billion doses, based on two doses per person (1). The scale of the challenge facing the world – and the pharma industry – is enormous.

This time last year, questions were raised about how quickly pharma could feasibly ramp up R&D to design and test vaccines against COVID-19. On that point, the industry has performed remarkably well. At the time of writing, three vaccines have been approved by the FDA and four by the EMA. And others are currently under review.

Discovery is the most high-profile and celebrated aspect of the pharma development process. Once an effective therapeutic or vaccine is discovered and found to be safe and effective in trials, it's "simply" a case of ramping up manufacturing processes to produce the amount needed. In reality, it means having the right equipment, capacity, packaging solutions, quality control processes, supply chains, workers, and more – and it's not easy to get everything aligned – especially for billions of doses. The current annual global demand for all vaccines pre-COVID-19 was 3.5–5.5 billion (2) – and the need for many of those vaccines isn't going to vanish because of COVID-19. In short, we need more vaccine manufacturing capacity.

For vaccines that use newer methodologies, such as those based on mRNA, processes had to be designed from scratch. But there's no time for new, purpose-built facilities; companies have needed to adapt existing capacity or seek CMO partners. In an unprecedented move, we're also seeing other big pharma stepping up to offer their manufacturing expertise to rivals; for example, Sanofi has offered its assistance to both Pfizer and J&J.

So far, over 929 million doses of COVID-19 vaccines have been administered worldwide (3). It's a great start – but there's a very long way to go.

Manufacturing disruptions causing delays to COVID-19 vaccine supply have made frequent appearances in media headlines. In January, production issues at Novasep's Belgian site led to a significant decrease in the availability of AstraZeneca vaccines for the EU. EU member states were also unhappy when deliveries of the Pfizer vaccine were also delayed. Pfizer made changes to its manufacturing processes to increase production, but there were temporary delays while the upgrades were underway. Reportedly, the upgrades were set to reduce production time of a vaccine batch from 110 days to 60 days (4) – impressive, right? But some politicians in the EU did not think so, highlighting the challenge vaccine manufacturers face in ramping up production while not falling afoul of politics...

In April 2021, manufacturing issues at Emergent BioSolutions' Baltimore plant led to contamination of millions of doses of Janssen's COVID-19 vaccine. According to media reports, ingredients for the AstraZeneca vaccine were mixed into vials of the J&J vaccine. Subsequently, J&J took over its own production and AstraZeneca was forced to shift production elsewhere.

Aside from manufacturing issues, the pandemic has also highlighted one of the ugliest aspects of human nature: selfishness. Many individual countries are ruthlessly pursuing aggressive immunization campaigns for their own populations, with seemingly little thought for other countries. According to the United Nations Programme on HIV/AIDS (UNAIDS), rich nations vaccinated one person per second in March 2021, but some low-income countries did not receive any vaccines at all (5). UNAIDS also claims that it is likely only 3 percent of people in poorer countries will be vaccinated by mid-year, and only one fifth (at best) by the end of 2021.

COVID-19 is a global challenge and vaccinating wealthy countries is not enough. The longer SARS-CoV-2 circulates, the more it will mutate – and we've already seen the emergence of several concerning variants. As an industry that claims to put patients first, pharma also has a moral duty to ensure that its efforts reach patients everywhere.

In this feature, we examine different facets of the world's greatest drug manufacturing challenge – from the challenges of mRNA vaccines, to supply chains, packaging, and ensuring patient access. As a sidenote, this is the longest feature we have ever published in The Medicine Maker – and we're still only scratching the surface of the problem.

References

1. *Nature, "What it will take to vaccinate the world against COVID-19," (2021). Available at https://go.nature.com/3v03BB8.*
2. *IFPMA, "Towards Vaccinating the World," (2021). Available at https://bit.ly/3sCPkZE.*
3. *Bloomberg, "More than 925 Million Shots Given: COVID-19 Vaccine Tracker" (2021). Available at https://bloom.bg/3sFDCgJ.*
4. *FiercePharma, "Pfizer to nearly halve COVID-19 vaccine production timeline, sterile injectables VP says," (2021). Available at https://bit.ly/3asvkCF.*
5. *UNAIDS, "Rich nations vaccinating one person every second while majority of the poorest nations are yet to give a single dose," (2021). Available at https://bit.ly/3v5Fh0E.*

CHALLENGE: ACCESS

Delivering Vaccines to the World

"Nobody wins the race until everyone wins."

While certain higher-income countries squabble over vaccines supplies or boast about having inoculated huge proportions of their populations, lower-income countries have been left in the dust. Gavi, the Vaccine Alliance and the World Health Organization have stepped in to even the playing field.

COVAX is co-led by the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, and the WHO. UNICEF is also working as a key delivery partner. COVAX was set up to accelerate the development and manufacture of COVID-19 vaccines, and to guarantee fair and equitable access for every country in the world. As part of this mission, it has established a global procurement mechanism: the COVAX Facility, which pools purchasing power from all countries participating in the COVAX initiative.

According to Gavi, "Developing a vaccine against COVID-19 is the most pressing challenge of our time – and nobody wins the race until everyone wins."

A spokesperson from Gavi tells us more about COVAX.

How was COVAX – and the COVAX Facility – set up so quickly?

At an early stage during this pandemic, it quickly became apparent that to end this global crisis we don't just need COVID-19 vaccines, we also need to ensure that everyone in the world has access to them. This triggered global leaders to call for a solution that would accelerate the development and manufacture of COVID-19 vaccines, as well as diagnostics and treatments, and guarantee rapid, fair and equitable access to them for people in all countries.

COVAX was conceived at the World Economic Forum Annual Meeting in January 2020, when the scale and severity of COVID-19 was only just becoming known. Today, it is one of three pillars of the Access to COVID-19 Tools (ACT) Accelerator, which was itself launched in April 2020 to provide innovative and equitable access to COVID-19 vaccines, therapeutics, and diagnostics.

Today, COVAX is the only truly global solution aimed at ensuring equitable access to COVID-19 vaccines, regardless of a country's wealth.

What key successes and milestones has COVAX seen so far? And what challenges lie ahead?

COVAX has enlisted the support of over 190 countries and economies, making it one of the largest multilateral initiatives of the 21st century. It has secured access to over 2 billion doses of vaccines and is in the process of completing its first round of allocations to 146 participating economies, having crossed the 100-economy threshold in early April 2021, less than six weeks after the first international delivery was made to Ghana.

Currently, 191 countries and donors are part of the COVAX Facility, including 92 lower-income economies whose vaccine doses are being funded through COVAX's Advanced Market Commitment (AMC) mechanism.

We aim to deliver at least 1.3 billion doses – and possibly as many as 1.8 billion in 2021 to AMC economies. Something like this has never been attempted before. You can find more information on how vaccines are being rolled out to countries in our first round allocation at https://bit.ly/3gxKaLX.

But our work is only just beginning. In addition to needing to secure more doses and more funding, complexities that lie ahead, such as regulatory approvals, readiness and capacity, supply fluctuations, delivery and logistics, are all urgent challenges that need to be addressed by Gavi and its COVAX partners. Most importantly, the world must continue to work together and refrain from vaccine hoarding, vaccine diplomacy, and further bilateral procurement, if we are to end the acute stage of this pandemic as rapidly as possible.

Why is vaccine hoarding dangerous?

We created COVAX because we wanted to avoid a repeat of what we saw with H1N1 in 2009, where a few wealthy countries tied up global vaccine supply and left the vast majority without access. Without COVAX, most countries, from the wealthiest to those with the least resources, have little hope of getting rapid access to doses of a safe and effective COVID-19 vaccine.

If that happens, large reservoirs of disease will continue to circulate and the world. The pandemic will continue to impact the global economy, trade, tourism, and travel. Furthermore, if large parts of the developing world have delayed access to vaccines, this could deepen socioeconomic inequalities, on top of the devastating impact the pandemic has already had.

How can pharma companies help?

In a highly volatile global supply environment, it is crucial that the international community, vaccine manufacturers, and other stakeholders continue to work together to ensure as many doses as possible reach the countries that need them most. This will also require global manufacturers and higher income countries to remain committed to this vision of equitable access, and to prioritize supply to COVAX. The dangers of not doing so – for the entire world, given the effect of this pandemic on public health, economies, trade, travel, communities and individuals – are clear.

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A batch of 14,400 COVAX-funded COVID-19 vaccines landed at Chisinau International Airport on 4 March 2021

Lessons From COVAX

The COVAX model could potentially serve as a model to help achieve the Sustainable Development Goals (SDGs) set by the United Nations General Assembly in 2015. In a recent webinar, Seth Berkley, CEO of Gavi, Jay Collins, Chairman of Citi, and Gayle Smith, former President and CEO of the ONE campaign, and newly appointed coordinator of the global COVID-19 response and health security to the US Department of State, discussed how learning from the COVAX partnership could be applied to other global challenges.

Find out more at https://bit.ly/3xtHq8y.

With strong commitment from vaccine manufacturers and the right level of backing from donor governments, we can ensure global access to doses in a timely fashion for all countries, not just those able to pay their own way. Working together, we can further our work to secure at least 1.3 billion fully-subsidized donor doses for the lower-income countries eligible for support under our COVAX Advance Market Commitment (COVAX AMC), and ultimately bring an end to this crisis.

What key lessons must the world learn from COVID-19?

One year ago, we could have barely imagined that the world would have not one but several successful vaccines to combat COVID-19 – all developed to the same rigorous and exacting safety and efficacy checks. With these vaccines entering wide circulation, we have our best shot at ending this pandemic, and it is vitally important that this message is delivered loud and clear to people from all groups and ages.

This unprecedented international collaboration in terms of technological innovation, funding for vaccines, and new models of public-private cooperation to enable rapid roll-out of vaccines once doses are delivered is going to be a valuable learning for future pandemics.

Though we have started delivering the first doses – and this is already faster compared with the H1N1 pandemic experience – our work is not done and the world must continue to work together if we are to successfully deliver on our mission.

When considering the complexities that lie ahead – from regulatory approvals to readiness and capacity, supply fluctuations to delivery and logistics or funding – COVID-19 has taught us that the scientific and medical community must all work together if we are to successfully deliver on the largest global vaccine rollout in history.

For One and All

How can pharma ensure equitable access to COVID-19 vaccinations worldwide?

We wanted to know more about the disparities that have arisen as vaccine rollout campaigns continue, so we spoke with two experts from the Access to Medicine Foundation – Claudia Martinez, Research Programme Manager for the Access to Medicine Index, and Fatema Rafiqi, Research Programme Manager for the Antimicrobial Resistance Benchmark.

Top: Claudia Martinez
Bottom: Fatema Rafiqi

What challenges are affecting vaccine rollout?

Fatema Rafiqi: There are several challenges for us to resolve. For example, there are well-documented logistical issues surrounding delivery, transport, and storage, as well as how to organize and staff the drive to administer vaccines to ensure timely, safe and efficient distribution without wastage. Each country, with its own health system and infrastructure, faces a unique set of hurdles. The priority should be to ensure equitable access to COVID-19 vaccines worldwide. Currently, the total demand for vaccines exceeds supply; however, in some high-income countries, the reverse is true, while low- and middle-income countries are reliant on donations and the COVAX program coordinated by the WHO.

Are initiatives like COVAX enough?

Rafiqi: There are between 2 billion and 5 billion people in low- and middle-income countries who are still awaiting COVID-19 vaccines. So far, COVAX expects to deliver 2 billion doses this year to 190 countries. To be able to close the gap with demand, more manufacturers and more sources of vaccines must be secured, which will require support and action from governments and the industry. There is still untapped manufacturing capacity and opportunities to use licenses, share data and expertise, and partner with manufacturers to increase supply. Achieving global access to COVID-19 vaccines is critical for saving lives, jobs, global economic security, and minimizing the time for mutations to set in and enable the virus to evolve and evade the vaccines.

What can pharma do now?

Claudia Martinez: A core issue highlighted by the pandemic has been the need for expanded capacity for vaccine manufacturing and distribution networks locally, as well as the importance of having robust supply chains to ensure uninterrupted supply. There is huge untapped manufacturing potential in low-and-middle-income countries. Pharmaceutical companies can and should support initiatives aimed at strengthening and building local capacity for the manufacturing of vaccines, and support the deployment of vaccination programs. The 2021 Access to Medicine Index highlights how companies can enter into technology transfer agreements with local manufacturers to expand medicines supply locally, as well as engage in voluntary licensing to enable generic versions of their products to be manufactured (1).

What role can local manufacturing hubs play in improving access?

Rafiqi: Local manufacturing hubs mean shorter distribution chains for the finished product. They are also able to tap into local knowledge about specific needs and conditions on the ground for transport and storage. And that reduces transport obstacles by making the best use of cold-chain capacity and preventing failures.

How can we best prepare for future pandemics?

Martinez: Action is needed on multiple fronts. The 2021 Access to Medicine Index found that R&D targeting coronaviruses surged in 2020, from zero projects in 2018 to 63 projects, reflecting a clear

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Employees packing boxes with COVID-19 vaccine at the packaging and dispatch department in Pune, Maharashtra, India, on Tuesday, Feb. 23, 2021.

and vigorous response by pharma to the COVID-19 pandemic. However, a further 15 emerging infectious diseases (EIDs) that pose a risk of a pandemic receive very little R&D attention. But the industry cannot be caught out again with empty pipelines. More R&D needs to go into EIDs. Pharmaceutical companies can also share compound libraries and similar assets for other EIDs so that they can be put to full use preparing for the next pandemic.

When it comes to patents, companies should either proactively engage in voluntary licensing to enable generic manufacturers to boost supply or publicly waive patent rights. We also saw a limited number of companies demonstrate the ability to react to and anticipate supply disruptions. Specialist teams dedicated to ensuring continuous supply in low- and middle-income countries should become standard in pharmaceutical companies' toolkits against pandemics, and we also need action to improve local availability through capacity building initiatives with local manufacturers.

What other challenges have been highlighted by the pandemic?

Martinez: The pandemic laid bare the global fault lines in our system for developing and delivering vaccines and medicines to our communities. For example, despite significant advances in driving down child mortality rates in recent decades, almost 5.2 million children under five – most of whom are in low- and middle-income countries – still die every year from preventable and treatable diseases. Far too often, the youngest members of society are at the back of the queue when it comes to receiving treatment because of a shortage of appropriate medicines. We just published an analysis of pharma's efforts to tackle this issue and found that just 7 percent of the pipeline specifically targets children under 12 (2).

The pandemic must be grasped as a wake-up call for the pharmaceutical industry; though there are medicines for children moving through pipelines, the selection of drugs is limited. We also have to ask ourselves whether they will be accessible to those living in low- and middle-income countries. Pharma must now use its learnings from the pandemic and apply them to ensure consistent medicines access for us all.

References

1. *Access to Medicine Foundation, "Access to Medicine Index 2021" (2021). Available at https://bit.ly/32Ssr9R.*
2. *Access to Medicine Foundation, "Handful of new children's meds on the horizon. But will they be accessible to children in LMICs?" (2021). Available at https://bit.ly/3voB9cj.*

mRNA: The New Kid on the Vaccine Block

Exploring the manufacturing challenges of mRNA vaccines

Pharma has been investigating the potential of mRNA-based therapeutics for years but, prior to the pandemic, none had ever reached the market. The COVID-19 vaccines developed by BioNtech/Pfizer and Moderna both use mRNA – and moved from idea to commercialization in less than 12 months. Amélie Boulais, Head of Market Entry Strategy, Viral Based Therapeutics, Sartorius, gives the rundown on mRNA vaccine manufacturing, including how vaccines have been developed so quickly. But the biggest question is how much can the manufacturing process be scaled up? And are mRNA vaccines a viable option for vaccinating the world?

Were you surprised at how quickly vaccines against SARS-CoV-2 were developed and approved – particularly the mRNA vaccines?

Yes and no. When I first heard that the industry was aiming to develop and launch the vaccine in 12–18 months, I knew it would be challenging; the average time to develop a vaccine is 10 to 12 years – but we made it! The latest technologies combined with a willingness to collaborate were the keys to success.

Although mRNA vaccines are new, they have clear advantages as a platform technology. Manufacturers were starting with an unknown pathogen and, with mRNA, as soon as the sequence of the antigen was identified, developers were able to move forward quickly. With the mRNA approach, the process is the same for all potential indications, which makes it a true platform technology. For example, there is no did not need to find out how to produce the virus nor how to purify it. In fact, this platform is so efficient that BioNTech said they can produce a vaccine candidate against a new variant in just six weeks!

Another factor in the success of the mRNA vaccines was the speed at which companies could recruit patients and carry out trials, which is usually the most time-consuming stage of vaccine development. However, because COVID-19 was – and is – so prevalent, investigators were able to conduct trials much more quickly and were able to determine the efficacy within just a few months.

Pfizer and Moderna were also able to get ahead by initiating production of their vaccine before their clinical trials were complete, partnering with CDMOs to increase capacity and hasten delivery.

Overall, I am not surprised that the first approved vaccines were based on mRNA; as noted, mRNA platforms provide a clear advantage when it comes to development time. But viral vectors are also a promising platform – and they made it to the market very quickly, too, as we've seen with the Johnson & Johnson and AstraZeneca (originally developed by the University of Oxford) vaccines.

How does the mRNA vaccine manufacturing process work?

There are 3 steps in mRNA manufacturing. First, the target DNA sequence (coding for the antigen) is inserted into a DNA plasmid (pDNA). The production and purification of pDNA relies on E. coli fermentation, which is often outsourced.

Second, mRNAs are produced by an enzymatic reaction called in vitro transcription (IVT). Here, nucleotides, enzymes, and plasmid DNA (pDNA) that encodes the antigen are mixed together – the pDNA is used as a template, from which the mRNAs are produced. Then, the mRNA is purified to remove IVT reagents, pDNA, and other contaminants. These purification steps include a mix of chromatography, tangential filtration, and filtration.

Finally, the mRNAs are usually encapsulated into lipid nanoparticles – this allows mRNA to enter the cells once injected to patients while also improving stability) – which are also purified and concentrated using tangential flow filtration and chromatography.

What are the main challenges associated with mRNA vaccine manufacturing at large scale?

A common challenge for all vaccines is ensuring safety and efficacy at scale, but mRNA processes are very different compared with other vaccine types, and with that comes very specific challenges. First, these processes are very new and expertise lies in the hands of only a few players. Now that we are facing the need to produce billions of doses, partners need to rapidly acquire expertise.

Second, classical technologies used for vaccine production and purification are not always adequate for mRNA processes. What is most suitable reactor for the IVT? A bioreactor or a mixing bag? What about the purification steps? Chromatography or precipitation? And which type of chromatography matrices? What is the best analytical solution to characterize and monitor the process? These are still relatively open questions.

Third, the processes have been scaled up very quickly, which means they work but can be further improved. For example, choosing the right storage conditions for the lipid nanoparticles is a challenge we've heard from our customers. We also know that the productivity of IVT processes could be improved with a better understanding of the interaction between reagents. We also know that contaminants can interact and form stable aggregates, and some of these aggregates can bind to mRNA and interfere

Manufacturer	*Stability in frozen state*	*Stability at 2–8 °C*	*Stability at room temperature*	*Dose (injection volume); Dosing schedule*
Moderna	-20 °C, up to 6 months	30 days	Up to 12 h	100 µg (0.5 ml); day 1, day 29
Pfizer-BioNTech	-80 °C to -60 °C, up to 6 months	up to 5 days	Up to 2 h (up to 6 h after dillution	30 µg (0.3 ml); day 1, day 21
CureVac	<-80 °C, at least 6 monthss	At least 3 months	Up to 24 h	12 µg (no information); day 1, day 29

Table 1. The required storage conditions of the top three players on the mRNA vaccine market (1).

with purification. Our new colleagues from BIA Separations are working to address this challenge and we are learning from them as they develop solutions for these purification steps.

Why are mRNA vaccines so sensitive to storage conditions?

mRNAs are not stable molecules; they are very fragile and sensitive to degradation. Though a lot of work has already been done to improve their stability, there remains room for improvement. mRNAs are usually encapsulated as lipid nanoparticles to ensure entry into the cells, and this can also impact overall stability. Table 1 shows the storage conditions of the top three mRNA vaccine contenders.

New formulations and alternative excipients may improve the situation, but it simply wasn't possible to overcome the issues in 2020 given the time pressures. The main focus has been on safety and efficacy.

Could any shortages of raw materials delay the rollout of mRNA vaccines?

The most critical shortages have been related to the reagents used for the IVT. Also, lipid nanoparticles have never been produced at such a scale before, which has led to shortages. The quality of the raw material is critical, and lot-to-lot inconsistency and contamination make the purification process of mRNA much more complex.

There are also shortages of pDNA because. I noted earlier that it is used as a template for production of mRNA, but it is also used as a raw material for the production of viral vectors, which are used in cell and gene therapy; in fact, this is where pDNAs are used most often. The need for pDNA is increasing, and this is creating a bottleneck in the production of advanced therapies. The sudden needs in COVID-19 mRNA vaccine production is not helping!

What are the advantages and disadvantages of outsourcing vaccine production?

Much depends on the context. In the middle of the COVID-19 pandemic, there was no other choice; the companies licensing the vaccines do not have enough capacity to fill demand, nor the time to build new facilities. Outsourcing allowed them to ramp up production quickly. Another general advantage of outsourcing vaccine production is the reduced financial risk. Companies that outsource this step do not need to build a facility to produce their vaccine before they know it will be financially viable.

The disadvantage of outsourcing is the need to rely on a third partner and a loss of control over your process. Traditionally, CDMOs are not involved as much in vaccine manufacturing because the vaccines are all so specific and require a unique expertise. But mRNA and viral vector platforms are enabling companies to use CDMOs. And we will likely see CDMOs constructing their own mRNA platforms to support developers in the future.

For companies like Moderna, which have chosen to outsource their vaccine production, what are your top tips to ensure the relationship runs smoothly?

First, select a partner that has experience in the area they're being tasked with handling (whether it's vaccine production, packaging, and so on). Note that this first tip is general – and it is highly challenging with mRNA vaccines because no one has experience! Second, find out whether the partner is able to produce enough vaccine in time. Do they have all the equipment they need? Do they outsource some activities or perform everything in house? Companies must conduct a risk assessment. Third, verify their track record in vaccine production. Have they already been inspected by a major health authority? And finally, define the communication and project management needs upfront to avoid problems down the road.

Ultimately, the industry will have to produce billions – perhaps tens of billions – of doses of vaccine to tackle the virus across the planet. Broadly speaking, what will it take for this to happen?

It will take time. We are seeing some unexpected collaborations, like Sanofi partnering with Pfizer to help them produce their COVID-19 vaccine; but we're still not producing vaccines fast enough. We are also closely following the evolution of the virus and its variants, and we don't yet know how long the vaccine will protect us – and whether it will have to be a seasonal shot or not. There are many uncertainties!

Reference

1. *DJA Crommelin et al., "Addressing the Cold Reality of mRNA Vaccine Stability," J Pharm Sci, 110, 3, 997–1001 (2021). PMID: 33321139*

CHALLENGE: VACCINES

Where Did it All Go Wrong for AstraZeneca?

AstraZeneca turned down tens of billions in profits to develop a safe and effective vaccine that is already protecting millions from COVID-19. So how did it end up a PR nightmare?

By James Strachan

It was supposed to be pharma's crowning glory. The industry did what many thought was impossible: developed and approved an effective vaccine against COVID-19 in a matter of months. Perhaps even more remarkably, AstraZeneca did it all while pledging not to make a profit. While organizations such as Médecins Sans Frontières have requested transparency regarding the pledge (1), and the Financial Times reported that AstraZeneca has defined the pandemic period as ending on 1 July 2021 – potentially opening the door to future price hikes (2) – the AstraZeneca vaccine is currently considerably cheaper than alternative vaccines (3). But events over the past six months have dented the reputation of the company – and its vaccine. And public trust is waning.

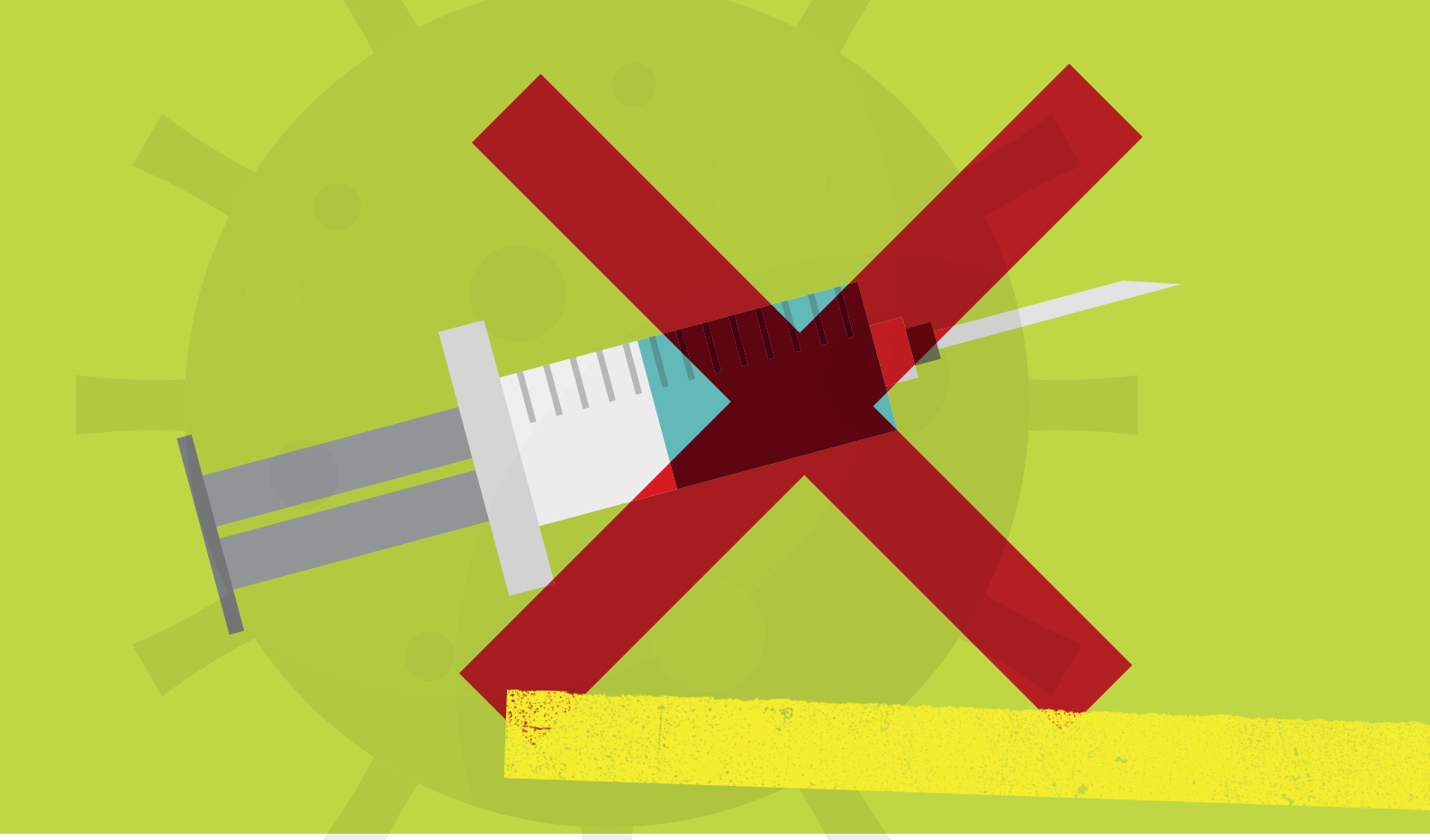
Communication problems arose in the development stages of the AstraZeneca vaccine. First, there were contradictions in how neurological symptoms in a patient in the vaccine clinical trial were described in the company's press statements, comments to investors, and internal documents. For example, CNN obtained an internal safety report that detailed how the participant "experienced confirmed transverse myelitis." The company's CEO, Pascal Soriot, then told investors in a conference call that the trial was stopped because a woman volunteering in the trial had symptoms consistent with transverse myelitis. But later that day, AstraZeneca released a statement saying that "there is no final diagnosis and that there will not be one until more tests are carried out" (4). The incident led to trials being put on hold. Then in November last year, AstraZeneca reported a 90 percent efficacy from their initial trial results, but it became clear that 2741 subjects in the trial had inexplicably received half the intended dosage. Contrary to best practice, the results of full-dose trial and the results of the half-dose trial were combined to give the headline figure (5), leading to bad press and erosion of confidence in the company.

And this was only the beginning of AstraZeneca's woes. In January 2021, AstraZeneca found itself in a very public spat with the EU after informing the block that it would be supplying considerably fewer doses of the vaccine than previously agreed. Soriot blamed "yield issues" at one of its manufacturing sites in Europe and cited a "best effort" clause in the contract, but the EU contended the company was contractually obliged to meet the scheduled doses. In the end, both parties published the contract online, with certain parts redacted. The row culminated with the EU publishing its Export Authorization Regulation – giving member states the power to block vaccine exports (6). Italy later exercised the new powers to block a shipment of the vaccine bound for Australia (7). AstraZeneca was also accused of stockpiling vaccines in the EU to export to the UK – and the company's CDMO partners were caught in the crossfire. Italian inspectors said they had found 29 million vaccine doses at a CDMO factory in Anagni. It was later revealed that 16 million doses were for the EU and the remaining doses were to be supplied to the COVAX program. At the time of the inspection, the vaccines doses had not even been through quality control. AstraZeneca released a statement to clarify the problem, stating: "It is incorrect to describe this as a stockpile. The process of manufacturing vaccines is very complex and time consuming. In particular, vaccine doses must wait for quality control clearance after the filling of vials is completed (8)."

"Quasi-ineffective"

AstraZeneca's vaccine has also faced criticism about its efficacy. French President Emmanuel Macron said – without evidence – that the vaccine was "quasi-ineffective" in people older than 65, despite the jab having just been approved by the EMA for all adults (9). And a German economic newspaper, Handelsblatt, reported that the vaccine was "apparently hardly effective in seniors." At the time, German regulators questioned whether there was enough data about how well the vaccine works in those over 65 and advised against approving the vaccine for older adults – although this decision was later reversed (9). In the US, the National Institute of Allergy and Infectious Disease (NIAID) warned that AstraZeneca may have used "outdated" data that provided an "incomplete" picture of its effectiveness. The company then released updated results from its US clinical trial, including more up-to-date data, showing that its vaccine is 76 percent effective (10). However, there are questions about whether this efficacy is maintained against variants (and the same questions are being asked of the other COVID-19 vaccines too).

More recently, the vaccine has faced another PR storm because of blood clots. But AstraZeneca is not alone in this issue; Janssen's COVID-19 vaccine is facing similar concerns. In March, a number of European countries suspended distribution of the AstraZeneca vaccine and the EMA subsequently determined that unusual blood clots with low blood platelets should be listed as very rare side effects of the



vaccine; however, they also noted that the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects (11). Despite this, Denmark has banned the use of the vaccine completely and some countries have introduced age limits for the vaccine. Italy, for example, has suggested that it will only use the AstraZeneca vaccine for those over the age of 60 and the UK will only use it in those over the age of 30. At the time of writing, AstraZeneca has yet to release a public statement regarding the blood clotting issue.

Disharmony among different national regulators and laxity on the part of politicians and journalists (whose comments were surely influenced by the politics of the situation) have only added to the confusion caused by AstraZeneca's communication issues – with regulators, governments and the public. Even before the issues with blood clotting came to light, there were problems with the uptake of the AstraZeneca vaccine in the EU. An investigation by a UK newspaper found that four in five doses delivered to the EU were not being used, as Angea Merkel admitted to an "acceptance problem" (12). It seems inevitable that the recent blood-clotting debacle will further dent the public's confidence in the vaccine. Indeed, a recent report found that up to 80 percent of people offered the AstraZeneca vaccine in Sicily refused it due to safety fears (13).

What can the industry learn from the debacle? The fact remains that the AstraZeneca vaccine is the most sought-after vaccine in the world, with over three-billion doses having been purchased worldwide – partly because it can be stored at normal refrigerator temperatures. It is also proven to be safe and effective, and it is already playing a pivotal role in the pandemic, with millions of people across the world already having been vaccinated. Yet, as Moderna expects to make $18 billion in revenue this year from their vaccine and Pfizer/BioNTech $15 billion, AstraZeneca's share price is down (14). Is AstraZeneca getting the credit it deserves for turning down huge profits and saving healthcare systems billions in the process?

Once the dust settles, let's hope that the lesson learned is about the importance of clear communication rather than questioning whether not-for-profit development is worth the hassle.

References

1. *BMJ (2020). Available at: https://bit.ly/2RRKPxz*
2. *The Week (2021). Available at: https://bit.ly/3avkPyy*
3. *The Financial Times (2020). Available at:https://on.ft.com/2RH3Gv1*
4. *CNN (2020). Available at: https://cnn.it/3aupwsh*
5. *BMJ (2021). Available at: https://bit.ly/3szopxM*
6. *The Medicine Maker (2021). Available at: https://bit.ly/3n1sn0Z*
7. *BBC (2021). Available at: https://bbc.in/2P2CS7w*
8. *AstraZeneca (2021). Available at: https://bit.ly/3ndKiBB*
9. *The Guardian (2021). Available at: https://bit.ly/3efGBaC*
10. *Fortune (2021). Available at: https://bit.ly/3n1oJnI*
11. *EMA (2021). Available at: https://bit.ly/3v5GpBk*
12. *The Guardian (2021). Available at: https://bit.ly/3dxCyao*
13. *France24 (2021). Available at: https://bit.ly/2QGEgNQ*
14. *The Guardian (2021). Available at: https://bit.ly/3n2sfOE*

CHALLENGE: DISTRIBUTION

Around the World

The challenges of transporting vaccines across the globe – and into countries with difficult terrain and weather conditions

World Courier has been delivering COVID-19 vaccines to various countries since the start of the pandemic – and even before then was a key courier for medicinal products. But even at the best of times, pharmaceutical logistics can encounter challenges. As one example, World Courier cites the unique challenges of distributing vaccines in Norway during winter months, when average temperatures drop to -7 °C, making the country's rugged terrain even more difficult to navigate (1). Jens Mattuschka, Regional Vice President of the Nordics, Central and Eastern Europe, and Marius Undlien, Norway country manager, both at World Courier (a part of AmerisourceBergen), tell us more about the challenges of distributing vaccines during a pandemic.

In terms of the global distribution of COVID-19 vaccines, when did the scale of the challenge really hit home?

Mattuschka: We realized very early on. In March 2020, we knew we would have to move quickly to maintain the pharmaceutical supply chain. Within a couple of months, as pharmaceutical manufacturers raced to develop safe and effective therapies and vaccines, we began engaging with partners across the supply chain to identify how we could best support distribution efforts. To put this distribution effort into perspective, countries around the world have ordered more than 9 billion vaccine doses. This rollout requires timely deliveries to all corners of the world – from large cities in the US to rural, remote islands in Norway to regions throughout sub-Saharan Africa. The immense scale of this effort is compounded by the fact that some of the vaccines need to be stored at frozen or deep-frozen temperatures throughout transport.

As such, there's a tremendous amount of work and collaboration required among government agencies, pharmaceutical manufacturers, and supply chain partners. Given the scope, and the urgent need across the globe, the entire industry needs to work together for the transport, storage and distribution of these vaccines.

We're supporting vaccine distribution efforts at various points around the world, including South Africa, Bulgaria, Germany, Lithuania, Finland, Sweden, and Norway. We're also playing a vital role in transporting active pharmaceutical ingredients and semi-finished products across the world, as well as the manufacturing samples for safety testing prior to vaccine batches being released.

What are the general challenges associated with transporting vaccines or medicines, particularly those with sensitive storage requirements, in "normal" times?

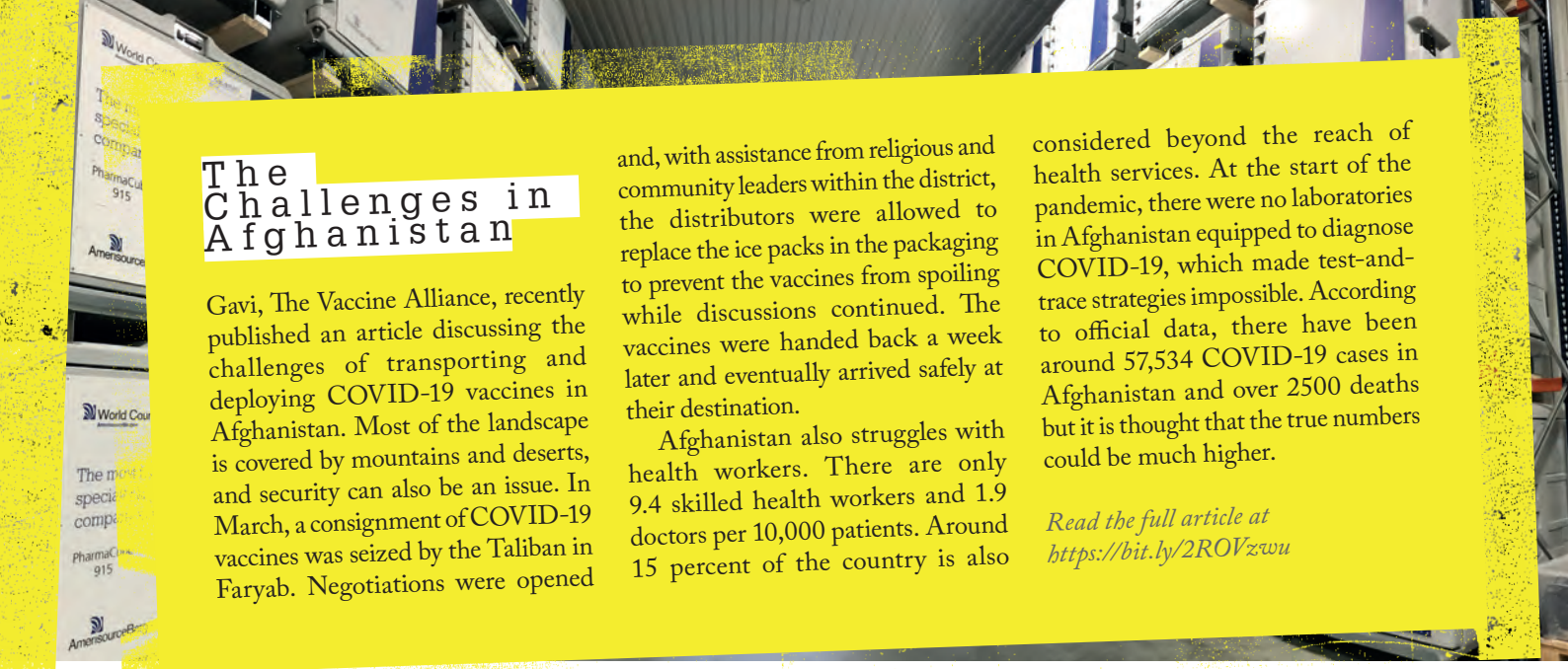
Mattuschka: Even before the pandemic, we transported complex pharmaceutical products, such as cell and gene therapies and highly temperature sensitive products, across the world every day. The products need to be delivered on-time, and in the right condition, so it's critical to design and execute a logistics plan that reduces the risk of temperature excursions. This can be particularly challenging when shipping products over long distances, and to regions with high heat or extreme cold. In the planning phase, it's important to identify the appropriate packaging solution and ideal transport route based on the product's specific needs. The right packaging solution can help protect product integrity, even when unforeseen factors arise. For example, a shipment sent in our Cocoon packaging container maintained its specified temperature range of 15 to 25 °C throughout a two-week delivery from Austria to Baghdad, Iraq, despite being stored in a desert warehouse for nearly 10 days with limited external temperature control!

Let's talk about Norway in particular – what are the specific challenges when it comes to supplying vaccines around the country?

Mattuschka: Norway's geography presents unique challenges. The country's rugged coastline, which is the second longest in the world, is broken up by fjords – large, narrow inlets of sea in deep valleys. About two-thirds of the country is mountainous, with nearly 300 mountain peaks topping 2,000 meters. Tens of thousands of small, remote islands also sit off Norway's coast, only accessible by boat or air. As such, ferry crossings are part of the daily life for the population in the coastal areas. In Norway's northern region, settlements are widespread, with large distances between the small towns and villages. Fortunately, we have a strong short-haul flight network in that area, so we are able to reach the small municipalities within a day from Oslo.

The challenging geographic conditions are exacerbated in winter months, when the country transforms into a snow-clad landscape and the average temperature drops to -7 °C. The weather conditions make it much more difficult to reach areas that are only accessible by ferry or crossing a mountain pass. During our planning process, we prepared for the potential for closed mountain passes and isolated islands, and identified alternate routes to ensure we could still deliver the vaccines to those regions.

Undlien: In Norway, we are supporting the distribution of all COVID-19 vaccines that have received authorization from the Norwegian Institute of Public Health (NIPH). The vaccines have unique time- and temperature-specific requirements, ranging from refrigerated (2 to 8 degrees °C) to frozen (-20 degrees °C), and deep frozen (-70 degrees °C). As such, there's no one-size fits all approach – plans must be tailored to the needs of each product, with specific packaging solutions and temperature monitoring systems.



The Challenges in Afghanistan

Gavi, The Vaccine Alliance, recently published an article discussing the challenges of transporting and deploying COVID-19 vaccines in Afghanistan. Most of the landscape is covered by mountains and deserts, and security can also be an issue. In March, a consignment of COVID-19 vaccines was seized by the Taliban in Faryab. Negotiations were opened and, with assistance from religious and community leaders within the district, the distributors were allowed to replace the ice packs in the packaging to prevent the vaccines from spoiling while discussions continued. The vaccines were handed back a week later and eventually arrived safely at their destination.

Afghanistan also struggles with health workers. There are only 9.4 skilled health workers and 1.9 doctors per 10,000 patients. Around 15 percent of the country is also considered beyond the reach of health services. At the start of the pandemic, there were no laboratories in Afghanistan equipped to diagnose COVID-19, which made test-and-trace strategies impossible. According to official data, there have been around 57,534 COVID-19 cases in Afghanistan and over 2500 deaths but it is thought that the true numbers could be much higher.

Read the full article at https://bit.ly/2ROVzwu

For example, to support transport at 2 to 8°C, we used a combination of Global Thermal Containers with phase change material and an active container, called PharmaCube. This is a custom-built container that performs like a mobile refrigerator. It is stored in a van and powered by the vehicle's battery.

How did you prepare and plan for vaccine distribution?

Undlien: As part of our contract with the NIPH, we have served as the country's distribution supplier in case of a pandemic since 2016. Each year, in collaboration with NIPH, we conduct a pandemic response training exercise that coincides with the annual distribution of seasonal flu vaccines, which we deliver to more than 400 sites across the country. During that two-week process – in which we are actually distributing the flu vaccine – we test our internal and external resources, capacity, packaging solutions, temperature monitoring capabilities, and overall distribution plan. The annual exercises help us to identify and eliminate gaps in our process and better position us to respond in a crisis.

Mattuschka: Months prior to the first COVID-19 vaccine authorization, we began working closely with the NIPH, manufacturer partners, and our suppliers to better understand the time- and temperature-sensitive requirements for each vaccine candidate. In collaboration with our partners, we built a supply chain strategy designed to protect the product integrity throughout transport, including when temperatures plummet in the winter. Our planning involved a number of components, including identifying the appropriate temperature-control packaging solutions and specific transport routes, as well as coordinating with the healthcare sites. In Norway, we're supporting 500 to 600 shipments each week, with deliveries to more than 350 sites across the country. Each shipment is equipped with smart-monitoring solutions, including sensors that track product temperature. To support our distribution efforts, we have also established a control tower in Lithuania. From there, a team of associates help to plan the shipments, set the orders, and then monitor the shipments, including the temperature, throughout the delivery.

The situation changes quickly during a pandemic – how can companies and governments make sure they are prepared?

Mattuschka: I think your question reinforces the importance of specialty logistics partners that have robust contingency plans in place that allow teams to mobilize quickly and, if needed, to take corrective measures. In some cases, teams may need to replenish a gel pack or simply replace a monitor with a low battery. In other situations, a storm may cause road closures or transportation issues that could cause shipment delays. In this case, a significant delay might affect hundreds of people waiting for a vaccine…

Undlien: I've said this often, but I'm proud of and extremely grateful for all of the work led by our teams on the ground to keep people across Norway safe! As just one example of how things can change and how we need to think on our feet; on Jan 20, 2021, one of the drivers was scheduled to deliver a shipment of vaccines to the islands of Traena and Lurøy. Generally, the ferry to the islands operates only once or twice per day, with the first ferry leaving at about 10 am. To avoid delays and provide timely access to the vaccines, it's crucial that our drivers take the first ferry. However, the first ferry was canceled that day and a severe storm threatened to cancel the second, which would have caused at least a 24-hour delay. Given the short shelf life of the products after thawing, it was imperative that these vaccines were delivered on time. The driver sourced different options before discovering a local shuttle boat in Sandnessjøen. After contacting the consignee to share the update plan, the driver chartered the local shuttle boat and set sail alongside the skipper at about lunchtime. They made the last delivery at about 2.46 pm, ultimately providing same-day delivery and ensuring residents had access to the vaccine.

Reference

1. *AmerisourceBergen, "Case study: COVID-19 vaccine distribution during the Norwegian winter," (2021). Available at https://bit.ly/3sBuXMh*

The Demand Rollercoaster

Consumer stockpiling led to an initial surge in demand for certain ingredients and experimental treatments also resulted in increased and unpredictable demand. How can companies keep up? Communication is the answer.

By Paul Smaltz, Vice President of Roquette's Pharmaceutical Global Business Unit

The pandemic may well prove to be one of the biggest challenges in modern history – especially from the perspective of the pharma industry and specifically with regard to how fast it could react to the outbreak and develop an effective vaccine.

In just over a year, the industry has reached impressive milestones in terms of vaccine development – bringing eight fully approved vaccines to market though vastly accelerated timescales. Key to this success are the extraordinary levels of collaboration between international governments and the global pharmaceutical community. We saw the pharmaceutical industry repurpose existing market-ready medications for experimental cures, and we continue to see research being conducted to find other novel solutions to COVID-19.

Impact on supply chains

One of the biggest challenges experienced by Roquette is the changing swing in demand for certain raw materials and products. In the early days of the pandemic, for instance, we saw a significant spike in demand for OTC products because of consumers stockpiling supplies. Raw materials, such as liquid polyols (used in cough syrups), were in very high demand during the first half of 2020. Due to the impact on the respiratory system by COVID-19, demand for powdered polyols – used in coatings for smoking secession gums – was also up, alongside tablet fillers, binders, and disintegrants that were being used in various experimental cures. However, if a possible new treatment was deemed ineffective, demand abruptly dropped. We've had to work very closely with our customers to ensure we could react to changing requirements.

The opposite was true for vaccine development. Here, there was a much more gradual increase in demand. But to be able to scale from small volumes for preclinical trials to very large volumes of raw materials needed for commercialization, it was crucial that we work closely with our partners to understand their needs and expand capacity accordingly. Today, we continue to see significant demand for our biopharmaceutical excipients, which can effectively stabilize vaccine formulations.

A further ongoing challenge is ocean freight. As demand for goods continues to experience unusual consumption patterns, there is a shortage of sea containers. With plants across the world, we've been successful in minimizing the impact on our customers to a certain extent. Although, in specific cases, ensuring on-time delivery has been almost impossible. The importance of keeping communication lines open to ensure customers know the exact status of their order has been amplified by the pandemic.

In such a highly regulated industry, change cannot happen without the necessary qualifications – which could take several months. To that end, any adaptations we made were mainly in relation to logistics and building stockpiles, including the adoption of air freight if delivery by sea freight meant that products wouldn't be delivered on time. Of course, this had greater cost implications, but the timely distribution of these materials is essential for many customers.

Seeing the good

Despite the tragedy brought about by COVID-19, the positive reaction by the pharma industry has been truly remarkable – with many companies demonstrating ingenuity and speed. We've seen many examples of pharma companies quickly reconfiguring their operations to start producing products that are in high demand. This ability to repurpose capacity provides a model for business agility going forward. In addition, the power of collaboration has been exemplified – partnerships forged across all areas of the supply chain enabled the industry to react as quickly as possible in unprecedented circumstances.

Will the industry go back to normal when the pandemic is finally over? It's likely that it has prompted a response from the pharmaceutical industry to re-evaluate business continuity plans for the better. Although the industry is largely risk averse, with many companies holding sufficient inventories in case of supply interruptions, the EU and some countries, for example, Canada, are already undergoing serious review of their drug manufacturing supply chains – assessing the risks and discussing what steps should be made to reduce those risks in future.

Working in this industry, you always have the notion in the back of your mind that your efforts are contributing to something bigger – that you're helping to sustain and save lives. The pandemic has emphasized this even more. Our team is proud to be able to make a difference – not only to helping family, friends, and loved ones, but also the rest of the world.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CHALLENGE: PACKAGING

Securing Supply Chain Integrity

Whitney Winters, Senior Director, Strategic Marketing, Containment Systems at West Pharmaceutical Services, discusses the impact the pandemic has had on the supply chain for primary packaging.

What different components typically go into a vaccine vial?

From a containment perspective, the system comprises a vial, elastomeric closure (stopper), and seal (crimp cap). Drug packaging must protect the drug product and help maintain safety and efficacy, without adding anything that could negatively affect the drug. Ensuring both consistent high quality and container closure integrity are critical to maintaining the sterility of the container system.

How has demand for vaccine vials changed – and what supply chain issues have arisen?

With COVID-19, there has been a large spike in demand for vials, elastomeric stoppers, and seals in a very short period. All the risk mitigation plans vaccine developers and suppliers have in place are now being tested and adjusted as necessary to meet the increased demand. Open communication has been critical! Supplier management teams have had to be proactive in communicating with key suppliers so that they can collaboratively establish risk mitigation plans for dual supply or multi-sourcing suppliers. Demand planning and sharing of both short-term and long-term forecasts has also been important.

Developing robust supply chains and working with trusted suppliers has become even more critical. Vaccine developers and their suppliers are all rapidly expanding capacity and building flexibility into their supply chains while maintaining the stringent quality requirements required in our industry. Safety stock of finished inventory and raw materials is being increased and many are looking for suppliers with global networks that can supply locally.

Do vials have to be made of glass? What different types of materials can be used?

The majority of vials used to package vaccines are glass vials, but there are alternative options, such as cyclic olefin polymer and cyclic olefin copolymer (COP/COC) vials. Polymer vials have good break resistance and low temperature qualities; however, they can present a greater likelihood of permeation. Some customers have been interested in alternatives to glass vials, but most have been looking at ways to maximize their supply of glass vials by using larger glass vials, for example. Larger vials allow manufacturers to include multiple doses within one vial to maximize the constrained quantity of vials available in the market.

Vaccine manufacturers should always evaluate their chosen container system to ensure that it is suitable for their specific product

The industry has had to move quickly; are there challenges associated with choosing primary packaging systems in haste?

Development and distribution of a vaccine for SARS-CoV-2 has presented challenges that are, without hint of exaggeration, unprecedented. And selecting a vial/stopper primary package system has been complicated greatly by the accelerated timelines for vaccine approval. A vaccine manufacturer wants to reduce risk as much as possible, as accelerated timelines do not permit standard evaluation of a drug product with a package system. Selecting proven components and systems is a good way to start. You can also leverage your supplier's technical data and material characteristics for the container system components.

It's also beneficial to identify suppliers with long-standing history of quality and reliability. Many vaccine manufacturers have chosen to partner with suppliers they are familiar with or have an established relationship with.

Have you had to make changes to keep up with demand?

The ability to access dependable transportation continues to be a focus for our logistics teams. We have partnered with top global logistic providers to prioritize the timely transportation of our product and to help accelerate the movement of equipment globally. Our suppliers, whether they provide equipment/services, materials, logistics and distribution, have been working hard to ensure they are delivering on their promises as they understand the impact they have on our ability to supply and assist with the overall global pandemic response.

Securing global capacity to meet supply remains a top priority. Our teams are working tirelessly with our customers to ensure we supply the right components and solutions to help address challenges presented by this pandemic. Again, communication is critical; we have to listen carefully to understand customers' progress, scale up initiatives, and other needs.

How do you think the current focus on vaccines will impact the industry's future?

The rapid development of COVID-19 vaccines will have long lasting effects on our industry. It has opened communication and collaboration among competitors, as we see multinational companies manufacturing their rivals' vaccines to increase output. We see customers being more agile with greater R&D flexibility, and supply chains with modular COE and shifts in locations. The rapid response to COVID-19 creates a model for new processes and quicker regulatory reviews moving forward. With the new technologies being used to create COVID-19 vaccines, we have a whole new set of tools to fight contagious diseases and other illnesses, which could lead to more effective vaccines in the future. As the industry innovates, primary packaging will also need to evolve and change to meet the market.

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CHALLENGE: PACKAGING

The Packaging Challenge

Billions of vaccine doses equate to a need for billions of primary packaging units – and glass vials are still top dog

By Fabian Stöcker, Vice President Global Strategy and Innovation at Schott Pharmaceutical Systems

With COVID-19, time is a luxury the world does not have. Perhaps one of the main differences compared with other drug manufacturing challenges is the starting point of commercial production; some COVID-19 vaccine manufacturing projects ran in parallel to phase III clinical trials to have sufficient volumes at hand as soon as official drug approval was granted. And the good news is that the pharma industry and its suppliers form well-integrated teams that can make use of well-established processes and technologies.

The demand for high-quality pharmaceutical glass and packaging has been steadily on the rise, even before the pandemic because of governmental initiatives in China and other territories for high-quality drug packaging. We actually set up an investment program in 2019, which enabled us to ramp up production in our global production network quickly and even speed up processes where possible. The timing was fortuitous. The investment program (comprising US$1 billion) in our pharmaceutical business is in full swing, despite the pandemic, and many new production lines are already up and running. By the end of 2021, we will have already implemented 50 percent of these projects.

The packaging currently in demand for COVID-19 vaccines is standard borosilicate glass vials ranging from 2 ml to 10 ml ISO formats, which is something that packaging suppliers produce millions of on a daily basis. Most COVID-19 vaccines are being packaged in borosilicate glass. This specialty glass was invented by Otto Schott in around 1890 and has since become the gold standard to package pharmaceutical drugs. The material is chemically inert, meaning it avoids interaction between the container and the vaccine, preserving the drug's effectiveness. Today, the pharmaceutical industry has a great deal of experience with this glass and knows how it behaves towards different drug formulas.

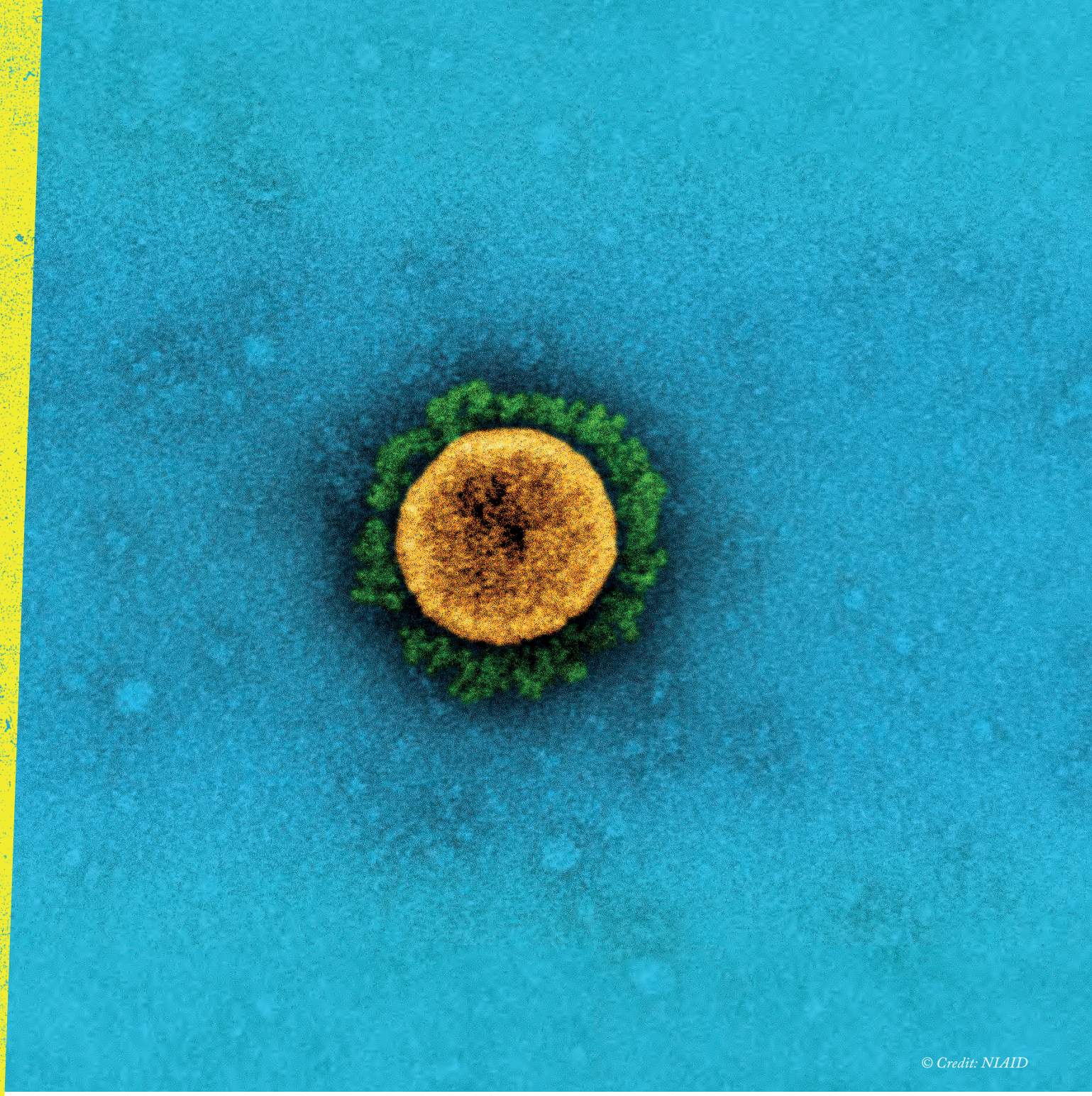
Following the approval of COVID-19 vaccines that must be stored well below freezing temperatures, there have been many discussions about ultra-cold storage requirements. The topic has also received further attention through cryogenics and cell and gene therapy, which require similar storage temperatures. The fact that borosilicate glass is able to withstand temperatures from -200 °C up to +500 °C makes the material highly suited for formulations with even the most demanding requirements!

The supply process for pharma vials itself has not changed and is based on standardized procedures. As a matter of fact, pharma companies often plan from the very beginning about how they want to package their drug. The respective suppliers get involved at a very early stage, well before phase II and III trials. As a packaging manufacturer, we know with several months' lead time how many vials to deliver and when to deliver them. And that gives us enough room to prioritize our production. Since we produce the pharmaceutical glass tubing for the packaging ourselves, we are also able to adjust the capacities for glass production in advance. It's also very important to maintain continuous contact and cooperation with customers to monitor market demand and container needs – even outside of pandemic times. Particularly throughout the last months, daily meetings and discussions with our customers played a key role in our efforts in the fight against COVID-19.

I can confirm that we are still meeting our supply agreements with pharma companies. Of course, this is only possible thanks to the immense work of our partners, suppliers and customers. With their support and collaboration, our production network was classified as system relevant by governments early on. This, and the fact that we set up a task force early last year and implemented numerous hygiene concepts at our sites, allowed us to continue production. But ensuring that there are enough vials for a global immunization campaign is a joint effort for the industry. The fact that all major glass and packaging providers made significant investments to expand capacity before the pandemic makes us optimistic that adequate supply with glass vials can be achieved. In other words, it is a stretch but if the industry pulls together, we are hopeful that worldwide demand can be met.

How many vials do we need to vaccinate the entire world? This is a complex question, as the vaccination programs of pharma companies show great variation. Some companies want to package a single dose in a small vial; others want to package five doses or more in a larger vial. Consequently, the mere number of glass tonnage or vials doesn't give much of an indication of the supply situation. And that's why we talk about vaccine doses rather than packaging units. If you add up all the COVID-19 vaccine projects we are involved in, we are supplying vials for around 2 billion doses. And just recently, we announced that we have already delivered vials to hold 1 billion doses. The delivery will take place in several project phases; this ranges from a few (hundred) thousand vials for the clinical trials, to industry-scale supply in the range of millions later on.

Manufacturing a vial takes a matter of minutes. Schott actually manufactures 30 million pharma containers (such as



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vials, ampoules, syringes, and cartridges) per day, adding up to 11 billion pharma containers each year!

It is possible that the pandemic will have a long-lasting effect on the pharma industry in the sense that vaccine booster shots will likely be needed every year. Hence, pharma companies will need to add another drug product to their manufacturing cycle. Naturally, the industry is currently highly focused on COVID-19. Yet all other life-saving drugs and treatments continue to play a big role in global health and require packaging solutions as well. This means that we are expecting growing demand for packaging due to COVID-19 vaccines, catching up on previously postponed life-saving drugs and treatments and the general market growth. Based on that, we are assuming that further capacity expansions will be needed to meet the need for pharmaceutical primary packaging in the future.

NextGen

R&D pipeline
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Future trends

Making Sense of Change

Why serological testing will play an essential role in COVID-19 surveillance and vaccine monitoring

By Andy Lane

As the number of cases of COVID-19 began to climb in late 2019, labs began collecting and sequencing patient isolates. Within weeks, the first draft sequence of the SARS-CoV-2 genome was published, opening the gates for a wave of early research (1). At the time, one of the major questions surrounding SARS-CoV-2 was its natural mutation rate. It has long been understood that viral genomes naturally mutate over time. However, the pace at which this occurs can vary significantly. Given how little was known about the new coronavirus in late 2019 and early 2020, scientists had no choice but to sit and wait.

Fortunately, by the spring, it had become apparent that SARS-CoV-2's genome was relatively stable. Like the SARS and MERS coronaviruses, the novel virus was confirmed to encode a proof-reading polymerase that limits errors during genome replication (2). The news was a relief to the scientific and public health communities. However, the threat of mutation was not a closed case. As the outbreak continued to grow exponentially through the spring of 2020, SARS-CoV-2 was given an ever-increasing opportunity to mutate. By the summer, multiple point mutations were repeatedly cropping up in genomic analyses – of which a large proportion occurred in the Spike gene (3). The significance of this was unclear at the time, but one mutant quickly gained widespread attention.

First identified in China in January 2020 (4), D614G seeded the early outbreak in Europe and rapidly proliferated – establishing itself as the global consensus (5). After the extent of its proliferation was recognized, it became a contentious point of debate, with multiple groups arguing that its success was either down to chance, or the result of a beneficial phenotype (6). Moreover, given that its Spike protein mediates a range of key functions, including host-cell entry and cell tropisms, changes in its gene sequence were understood to be particularly relevant to infectivity, clinical manifestation, and immune escape.

By late summer, it had become clear that D614G did not pose a significant threat. Though some mutations improved spike flexibility to facilitate stronger binding with the human ACE2 receptor (7), they only conferred a slight increase in affinity for it. What's more, it only resulted in an even smaller increase in infectivity. Given that the mutation does not occur in Spike's receptor-binding domain (RBD) – the region responsible for ACE2-binding and the major target of neutralizing antibodies – it fails to mediate resistance to host immunity.

The changing mutational landscape

Since the summer of 2020, the emergence of new mutations has continued to accelerate as global cases have risen at a near-exponential rate (8). This culminated in late 2020 when three new lineages were detected all within the space of a month: B.1.1.7 in the UK (9), B.1.351 (501Y.V2) in South Africa (10), and B.1.1.24 in Brazil (11) (see Figure 1). What's surprising about the emergence of these variants, in particular, is that each possesses a broad constellation of mutations not seen together before, marking a more significant leap in viral evolution.

Coinciding with their emergence, the countries that detected them witnessed surges in case numbers, potentially associated with increased variant infectivity (12). Given that the promise of vaccine-mediated herd immunity was still many months away, this didn't come as welcome news, and governments have since had to re-impose strict lockdowns and travel restrictions to contain variant transmission. As vaccination programs progress, transmission is expected to decrease. However, the proportion of vaccine coverage needed to achieve herd immunity is not yet clear, and the bar may rise higher and higher if new variants are more transmissible in naïve and immunized individuals.

To characterize the origin and impact of these mutations, the scientific community has been hard at work. So far, it appears that the increased infectivity of these variants is largely conferred by mutations in the receptor binding domain of their Spike proteins – most notably, E484K and N501Y, as well as the combinatorial N419K:E484K:N501Y, which have all shown to improve affinity for ACE2 (13). All three have emerged repeatedly and independently of one another, suggesting they are advantageous low hanging fruit for the virus to adopt, alongside a string of other, less significant mutations (14). In addition, Spike has shown a tendency to lose portions of its N-terminal domain (NTD) during replication, which, unlike point mutations, cannot be corrected by its proof-reading exonuclease. These deletions have also shown to reoccur and represent a viable means for SARS-CoV-2 to develop more drastic changes (15). The H69/V70 deletion found in the B.1.1.7 (UK) variant, for example, has shown to contribute to increased infectivity, as well as potentially reducing the sensitivity of PCR tests (16).

The second major area of investigation is immunity. As nearly all vaccines that are currently approved or under development target the Spike protein of the original Wuhan-Hu-1 strain, there is concern that mutations could render them less effective. This was first supported by early in vitro studies, showing that the mutations of some variants make them less susceptible to the neutralizing ability of specific antibodies, or are able to escape them entirely (13,17,18). Data from South African trials of the Novavax and Johnson & Johnson vaccines also showed slight decreases in vaccine-induced protection, likely due to the locally-circulating variant (19,20,21). Fortunately, as the majority of vaccines provoke an immune response to the entire Spike protein, it is expected that the antibody diversity elicited from vaccination will retain at least a moderate degree of protective efficacy, especially

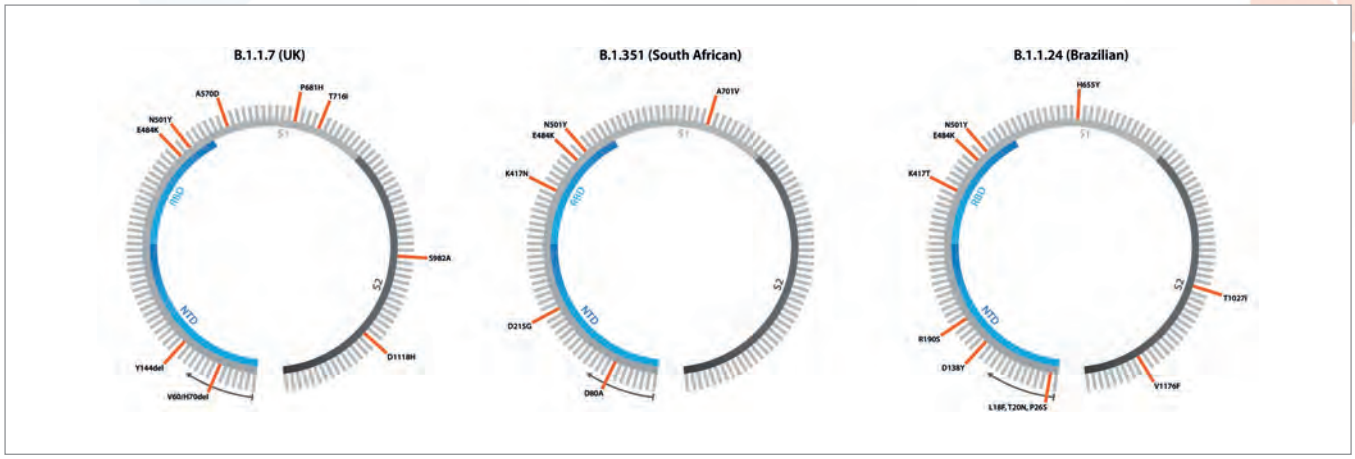


Figure 1. Spike gene sequences for the B.1.1.7, B.1.351, and B.1.1.24 variants, including both point mutations and deletions.

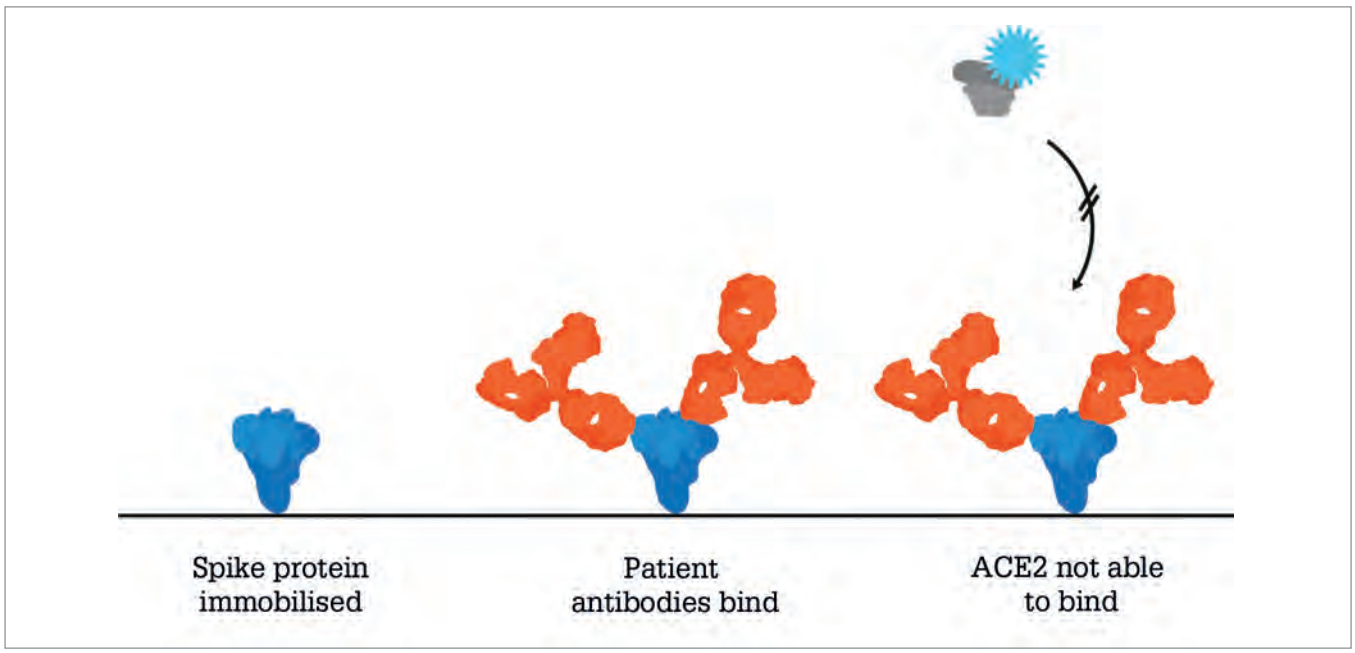


Figure 2. The basic mechanism of a competitive binding assay. If a patient produces neutralizing antibodies, they will preclude the binding of ACE2 with the label, resulting in a negative signal.

against severe COVID-19. The reason for this is because the reduced affinity for one antibody is often compensated for by antibodies that target other regions of the Spike protein, not to mention the oft-forgotten role of cell-mediated immunity. Finally, it's also worth considering that evolution tends to result in trade-offs, in which the enhancement of one trait, such as receptor binding, is negated by a loss of fitness elsewhere, which is exemplified by D614G being more susceptible to neutralizing antibodies.

Keeping Tabs

The emergence of new SARS-CoV-2 mutations in recent months has driven home the notion that viral evolution – which has otherwise had little impact on the COVID-19 pandemic – could yet result in some last-minute surprises. Mutations are a wake-up call for public health and require systemic surveillance, tracking, and post-vaccination studies. Next-generation sequencing is currently playing a crucial role in surveillance, helping to identify new mutations that occur and track their geographical spread. Supported by epidemiological modeling, NGS provides early indications of whether mutants are fixing in a population, and if they might be more infectious, virulent, or resistant to vaccines.

Prospective studies have also been

using techniques such as deep mutational scanning, in which every single possible point mutation is evaluated, as well as predictive computational simulations of binding interactions (21,22,23,24). However, as mutations are additive in their effects, experimental data is essential to inform any changes in the correlates of protection. Furthermore, the leading hypothesis for the origin of recent variants is that immunocompromised individuals incubated unusually long infections, producing low titers of narrow antibody repertoires, that allowed SARS-CoV-2 to mutate (25). It is, therefore, crucial to quantitatively and qualitatively assess the antibody profiles of at-risk groups who have developed natural and vaccine-induced immunity to determine the factors associated with patient-to-patient variation (16).

Neutralization assays have been key in assessing the protective efficacy of patient antibodies and can also be used in conjunction with serial passage to investigate selective pressures. To determine specific affinities and how mutations contribute to protein interactions, assays can be designed to investigate the binding of Spike, ACE2, and monoclonal or polyclonal antibodies. Competitive assays, for example, allow the simultaneous evaluation of seroreactivity against the binding affinity of Spike variants (26) (see Figure 2).

In the case that the protective efficacy of vaccines against moderate-to-severe disease is lowered significantly by new variants, there will be a need to reformulate existing vaccines. Longer-term, there has also been speculation around whether SARS-CoV-2 will become like the endemic coronaviruses that cause seasonal infections, similar to the flu. This may require the development of more broadly protective vaccine candidates de novo. However, in either instance, new multiplexed assays will be required that can quantitatively assess cross-protective efficacy. The scientific community is in a better position than ever before to address these problems if and when they arise.

Andy Lane is the Commercial Director at The Native Antigen Company.

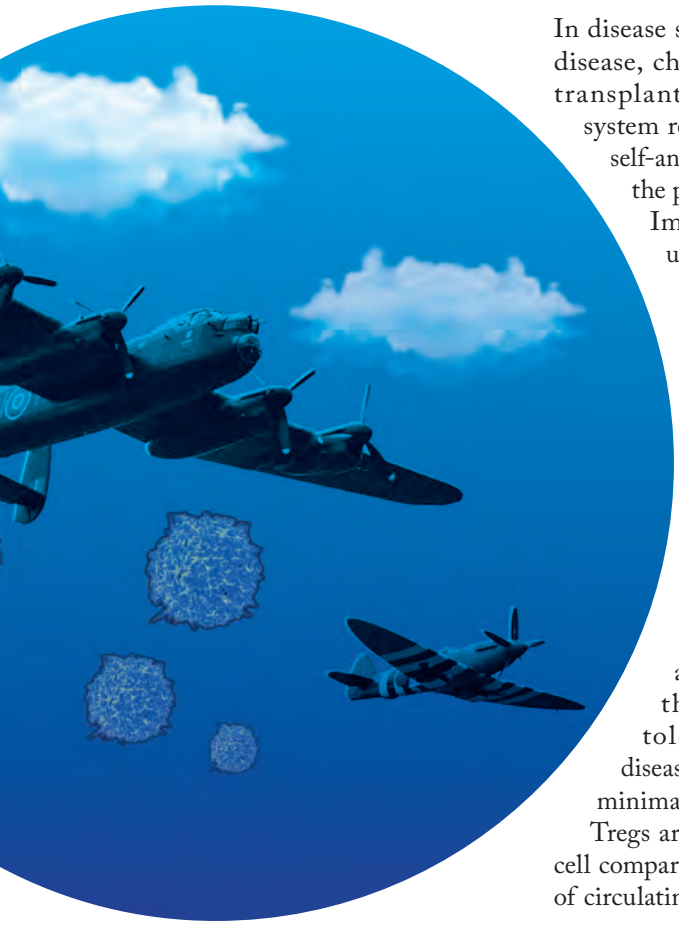
References

1. *Zhu et al., New England Journal of Medicine, 20, 382 (2020).*
2. *Robson et al., Molecular Cell, 79, 710 (2020).*
3. *Zhan et al., "Molecular Evolution of SARS-CoV-2 Strucutural Genes: Evidence of Positive Selection in Spike Glycoprotein," [Preprint] (2020).*
4. *Isabel et al., Scientific Reports, 10, 14031 (2020).*
5. *Yurkovetskiy et al., Cell (2020).*
6. *Korber et al., Cell, 182, 812 (2020).*
7. *Yurkovetskiy et al., "SARS-CoV-2 Spike protein variant D614G increases infectivity and retains sensitivity to antibodies that target the receptor binding domain," [Preprint] (2020).*
8. *World Health Organization Coronavirus (COVID-19) Dashboard. Accessed 2021: https://covid19.who.int*
9. *NR Faria et al., "Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings" (2021). Available at https://bit.ly/3fKr4Sh.*
10. *A Rambaut et al., "Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations" (2020). Available at https://bit.ly/3wyCZIT.*
11. *H Tegally et al., "Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa," [Preprint] (2020).*
12. *JF Cadena et al., "Detection of the new SARS-CoV-2 variant B.1.526 with the Spike E484K mutation in South America" (2021). Available at https://bit.ly/3moeVUH*
13. *Z Wang et al., "mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants," Nature (2021). https://doi.org/10.1038/s41586-021-03324-6*
14. *P Priya and A Shanker, Infection, Genetics and Evolution, 87 (2021).*
15. *KR McCarthy et al., Science, 371, 1139 (2021).*
16. *FDA, "Genetic Variants of SARS-CoV-2 May Lead to False Negative Results with Molecular Tests for Detection of SARS-CoV-2 - Letter to Clinical Laboratory Staff and Health Care Providers" (2021). Available at https://bit.ly/3eyPE7Q.*
17. *Z Liu et al., "Landscape analysis of escape variants identifies SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization," [Preprint] (2020).*
18. *WF Garcia-Beltran et al., "Circulating SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity," [Preprint] (2021).*
19. *Biospace, "Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial" (2021). Available at https://bit.ly/3mlSyPs.*
20. *Johnson & Johnson, "Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 ENSEMBLE Trial" (2021). Available at https://bit.ly/31QLEZi.*
21. *TN Starr et al., Cell, 182,1295 (2020).*
22. *AJ Greaney et al., Cell Host & Microbe, 29,44 (2021).*
23. *MH Cheng et al., "Impact of South African 501.V2 Variant on SARS-CoV-2 Spike Infectivity and Neutralization: A Structure-based Computational Assessment," BioRxiv (2021).*
24. *Sztain et al., "A glycan gate controls opening of the SARS-CoV-2 spike protein," [Preprint] (2021).*
25. *SM Kissler et al., "Densely sampled viral trajectories suggest longer duration of acute infection with B.1.1.7 variant relative to non-B.1.1.7 SARS-CoV-2," [Preprint] (2021).*
26. *JR Byrnes et al., Clinical Science and Epidemiology, 5 (2020).*

Cell Therapy for Autoimmune Disease: Armored Tregs to the Rescue

How Treg-cell therapy could transform the way we treat autoimmune disease and transplant rejection

By Raul Elgueta and Cristina del Carmen Rosello



In disease states such as autoimmune disease, chronic viral infection, and transplant rejection, the immune system responds inappropriately to self-antigens or doesn't resolve once the pathogen has been removed. Immunosuppressants may be used to reduce inflammation, but current biologic and small-molecule therapies must be administered over the long-term and can only alleviate symptoms. Regulatory T cells (Tregs) maintain a healthy immune response by suppressing inappropriate activation. And, in recent years, researchers have turned to Tregs to develop adoptive cellular therapies that can restore immune tolerance in autoimmune disease and transplantation – with minimal side effects.

Tregs are a subcomponent of the T cell compartment. Around five percent of circulating CD4+ T cells are Tregs, which can be identified by expression of the transcription factors FOXP3 and Helios, together with high expression of cell surface marker IL-2 receptor (CD25). In addition, the subunit α of the IL-7 receptor (CD127) is downregulated, which is inversely correlated to the suppression function of human Tregs (1). Lastly, the demethylation of the Treg-specific demethylated region (TSDR), an evolutionary conserved noncoding region of the FOXP3 locus, is the best marker for the stability of Tregs (2). Clinically stable Tregs are defined as a CD4+CD25+CD127low/- with over 80 percent of demethylation in the TSDR.

Once Tregs are activated via their cognate antigen, they suppress immune response by i) releasing inhibitory cytokines; ii) expressing suppressor cell surface molecules, such as CTLA-4, PD-1, Vista; and iii) depriving nutrients needed for T cell activation. These mechanisms block dendritic cell maturation and abrogate effector T cell proliferation and function. And that's why this subset of CD4+ T cells are showing promise in the development of

cellular therapies for autoimmune disease and transplantation.

Current state of play

Currently, three main Treg-cell products are being developed for adoptive cell therapy: polyclonal Tregs, antigen-specific Tregs and chimeric antigen receptor (CAR) Tregs (see Table 1). In clinical trials, polyclonal Treg cells isolated from peripheral blood tend to be used, as these cells can be readily expanded in vitro. Polyclonal Treg-cell therapy has been found feasible and safe in different clinical settings, including kidney transplant and autoimmune type 1 diabetes (3,4). However, these studies have failed to demonstrate efficacy – and this failure has been attributed to the low Treg specificity of the therapy.

In the context of transplantation, the second approach for adoptive Treg therapy is the use of antigen-presenting cells from donors to stimulate in vitro Tregs from recipients (5). This method provides greater specificity than polyclonal Tregs, but the yield of cells is very low in comparison, and it cannot be applied to expand Tregs from patients with autoimmune diseases. Therefore, this Treg product has not successfully moved forward into the clinic.

The third approach is the expansion of polyclonal Tregs genetically engineered to contain a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR) expressed on the cell surface to increase the specificity of the therapy. In recent years, CAR T-cell therapy has been successful in the oncology field, but has seen significant cytotoxic side effects associated with cytokine release syndrome and neurotoxicity. In contrast, CAR Treg-cell therapy would be expected to have the opposite effect and dampen down inflammation in autoimmune disease and promote transplant tolerance. Transgenic TCRs and CARs should play an important role in the future adoptive Treg-cell therapy clinical landscape, given the antigen specificity they are able to introduce.

Adoptive cell therapy	*Strengths*	*Weaknesses*
Polyclonal Treg therapy	• Easy to isolate and get a good cell yield after expansion	• No specificity • Low suppression capacity
Antigen-specific Tregs	• High specificity and suppression capacity	• Cell yield is low after expansion
Genetically engineered Tregs (TCR or CAR)	• High specificity and suppression capacity • High number of antigen-specific cells is obtained after expansion	• Cost of the therapy is elevated • Long waiting time
Allogeneic engineered Tregs	• Reduced cost and waiting time • Reduced variability across the process	• Risk of rejection
hiPSC-Tregs	• Limitless capacity for gene engineering • Rejuvenated Tregs • Universal cell line (GMP grade characterized cell line, edition of HLA)	• Lack of protocols to generate Tregs from hiPSCs

Table 1. Different adoptive regulatory T cell therapy strategies

What about allogeneic approaches?

Autologous adoptive cellular therapy is currently the most promising model of Treg-cell treatment, but there are challenges. First, the starting material required must be of high quality. In many cases, patients' T cells are exhausted and unable to be expanded or their numbers are too low for the manufacturing process. Second, engineering and expansion protocols are long and there is a risk of the patient deteriorating rapidly – shrinking the window of time where the therapy could be efficacious. Finally, the price per treatment tends to be high; for example, the cost of the CD19 CAR T-cell therapy for B cell lymphoma is currently around $475,000 (6). Thus, an alternative therapeutic approach is needed to reduce both the cost and time of the manufacturing process.

Allogeneic or "off-the-shelf" Treg-cellular therapy could be the answer. This approach involves generating CAR Tregs expanded from a bank of healthy donors with the best possible human leukocyte antigen (HLA)-match. In the short term, this may be sufficient to establish the suppressive environment in both autoimmune disease and in transplant tolerance. The isolation and preparation of Tregs from healthy donors is advantageous

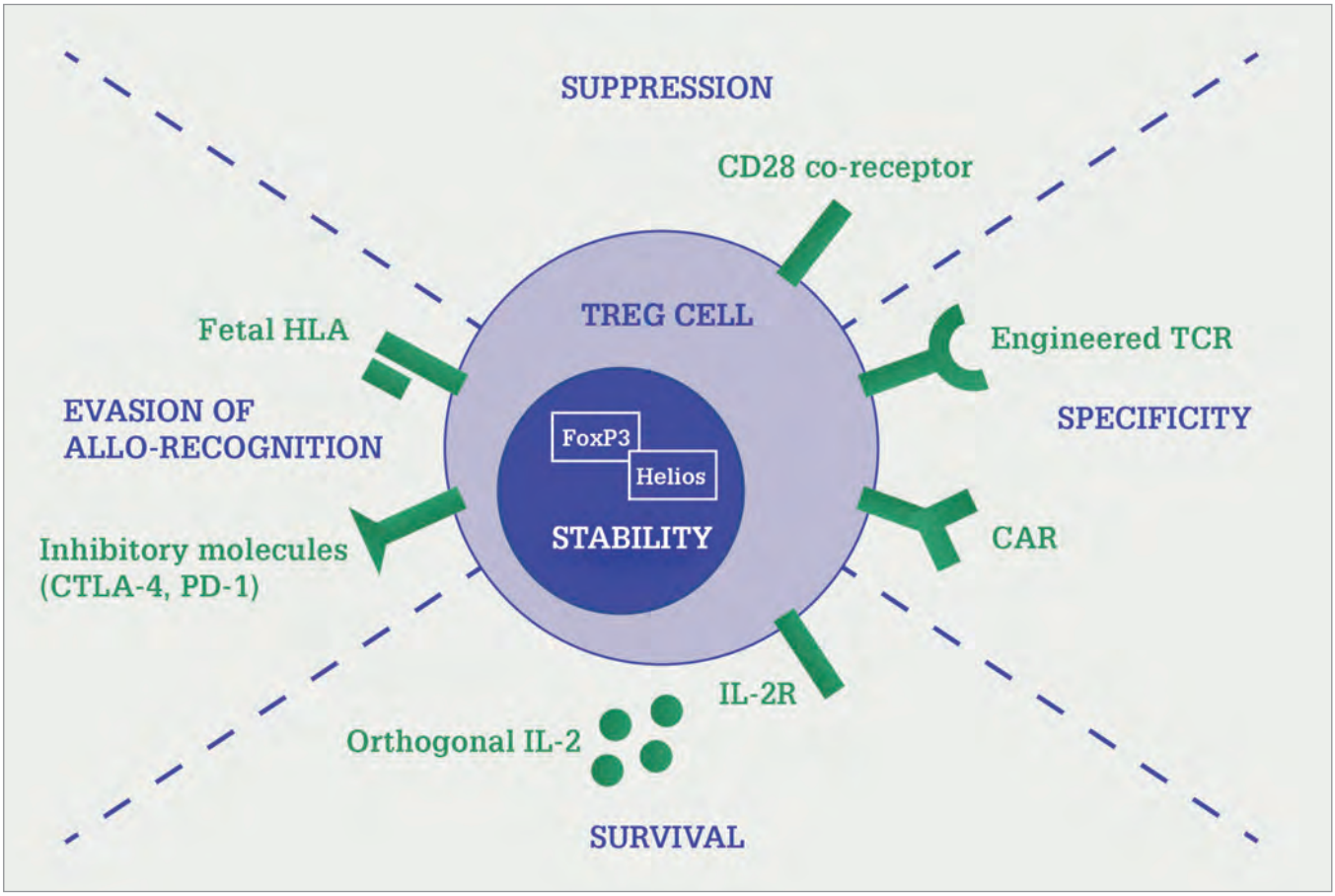
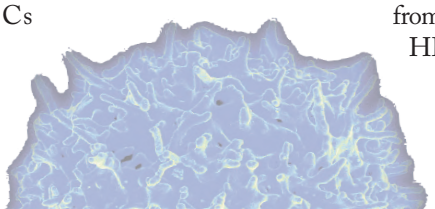


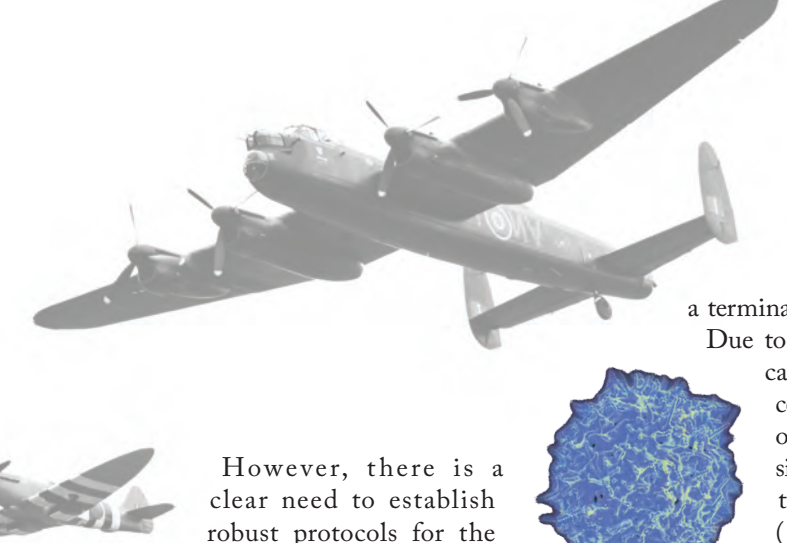
Figure 1. Summary of accessories that can be included in adoptive Treg therapy. These accessories will tailor the survival, stability, specificity, and evasion of allo-recognition of the therapy.

"As we've seen, there is room for improvement regarding the potency and efficacy of Treg-cellular therapies."

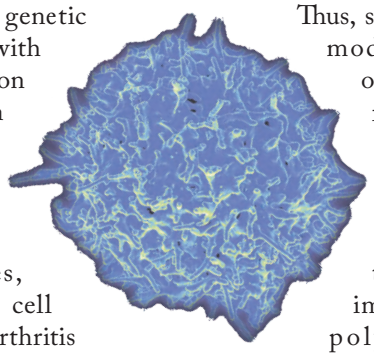
as it helps reduce variability in expansion, increases the quality of the starting material and reduces the treatment time. Nevertheless, this method is susceptible to host-mediated allo-rejection of the transferred cells, which will likely limit repeat dosing and long-term efficacy. Therefore, developing Treg cells that can evade host-mediated immune recognition will present exceptional opportunities in the creation of off-the-shelf therapies.

At this point, the use of human induced pluripotent stem cell-derived Tregs (hiPSC-Tregs) for allogeneic therapy appears an attractive alternative. hiPSCs can be expanded easily and could be an endless source of Tregs given that they are amenable to biotherapeutic manufacturing processes. Computational approaches to cell reprogramming are well placed to identify new genes needed to accelerate and improve the process of generating both consistent and well-characterized batches of hiPSC-Tregs (14). Importantly, hiPSCs would generate "rejuvenated" Tregs with longer telomeres which will improve expansion and prevent cell cycle exhaustion (7). Finally, the genome of hiPSCs can be routinely modified in the lab, bringing a wide range of possibilities: from adding CARs to editing HLA identity.





However, there is a clear need to establish robust protocols for the generation of Tregs from hiPSCs. Mohammad Haque and colleagues have developed a method based on the genetic modification of iPSCs with the FOXP3 transcription factor followed by in vitro stimulation with Notch ligand (8). The resulting Treg cells were able to produce suppressive cytokines, inhibit other immune cell activities and suppress arthritis development in an adoptive transfer context (8). Notably, this study was only carried out in a murine model, and efforts are now focused on unraveling how Tregs are developed in the human thymus and in defining protocols to generate phenotypically stable Tregs from hiPSCs. Here, the deployment of next-generation sequencing and gene regulator/epigenetic network data could play a key role. Through the systematic identification of gene regulators and soluble factors, we can expect to enhance the generation, maintenance and stability of hiPSC-Tregs for cellular therapies (14, 15).



Armoring allogeneic Tregs

As we've seen, there is room for improvement regarding the potency and efficacy of Treg-cellular therapies. And four promising avenues are emerging; namely, improving survival, stability, specificity, and evasion of allo-recognition (see Figure 1).

A major concern is the stability of Tregs, which means that Tregs are not in a terminally differentiated state. Due to their plasticity, Tregs can adopt an effector T cell phenotype depending on the environmental signals. Recently, several transcription factors (FOXP3, Helios, BACH2, NRP-1) have been identified as key to maintaining Treg stability. Thus, strategies to genetically modify the expression of these transcription factors and obtain phenotypically stable Tregs are being investigated. For instance, gene transfer of FOXP3 in immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) patient-derived CD4 T cells that generate potent suppressor T cells, which in turn sustain a regulatory phenotype in inflammatory conditions (9).

To promote Treg survival, some researchers have focused on precisely targeting IL-2 to guide cells to their target. Low dose IL-2 treatment has shown to increase Treg numbers in patients, but it is also able to induce proliferation of other proinflammatory immune cell sets. To address this problem, researchers are developing a human anti-IL2/IL-2 complex that preferentially stimulates Treg expansion over effector T cells or the combination of an orthogonal IL-2R engineered Tregs paired with an orthogonal IL-2 (10).

To improve the specificity of Treg therapies, the use of engineered TCRs and CARs are being widely explored. The most intuitive strategy to generate antigen-specific Tregs is to engineer them with a specific TCR recognizing a peptide of interest. Several approaches have been designed to promote

"To improve the specificity of Treg therapies, the use of engineered TCRs and CARs are being widely explored."

preferential pairing of exogenous TCR and avoid pairing with endogenous TCR (extra-disulfide bridges between TCR subunits, "murinization" of TCR constant chain, and so on). Promisingly, Theodore Roth and colleagues engineered primary T cells by replacing the endogenous TCR locus with a tumor antigen-specific TCR using a non-viral CRISPR-Cas9 genome-targeting system (11). This strategy should avoid off-target effects led by exogenous-endogenous TCR mispairing.

On the other hand, CAR constructs have the advantage of being independent of the HLA complex and do not require a co-receptor. Following CAR construct development in the immune-oncology field, CAR Treg-cell therapy has been evolving from simpler first generation to more complex third-generation CAR designs. Similar to CAR T cells, the inclusion of costimulatory domains in CAR constructs can enhance the suppression ability of Tregs. For instance, Nicholas Dawson and colleagues compared 10 different costimulatory domain CAR variants in gene-edited Tregs and demonstrated that the CD28 co-receptor intracellular domain was fundamental for a potent and stable immunosuppressive response (12). However, different studies have shown

discrepancies in their results, which highlights the need to standardize experimental settings and success criteria.

There have also been attempts to engineer cells to avoid allo-recognition; for example, deleting HLA class I or II molecules avoids allo-rejection of the transferred cells by CD8+ and CD4+ T cells, respectively. However, cells that do not express major histocompatibility complex molecules can be recognized and killed by natural killer (NK) cells. Here, inducing the expression of fetal HLA-E or HLA-G (molecules expressed during maternal-fetal tolerance) can lead to tolerance in NK cells (13). In addition, the expression of PD-1 and CTLA-4 could inhibit allo-activation of T cells, and the induction of CD47 expression – a "do not eat me signal" – will inhibit phagocytosis by macrophages. Thus, the combination of accessory proteins with a universal cell that can evade allo-rejection may provide off-the-shelf Treg cell therapy with the "armor" they need.

What does the future hold?

The successful validation of CAR T cell therapy in oncology has paved the way for Treg-cellular therapies for both transplant tolerance and autoimmune disease. So far, clinical trials and research studies have shown that adoptive Treg therapy is a safe and feasible approach, with plenty of room for improved efficacy via an evolution from polyclonal to antigen-specific approaches. The price and waiting times of these therapies present additional challenges, but off-the-shelf Tregs therapies may provide the solution. And if researchers can successfully tailor the survival, suppression, specificity, and stability of Tregs to each patient, while generating them from a universal and self-renewing source, the current shortcoming of the field should dissolve – a truly exciting prospect for patients.

"Clinical trials and research studies have shown that adoptive Treg therapy is a safe and feasible approach."

Raul Elgueta is an R&D manager and Cristina del Carmen Rosello is a scientist, both at Mogrify, UK

References

1. *W Liu et al., "CD127 expression inversely correlates with FOXP3 and suppressive function of human CD4+ T reg cells", J Exp Med, 203, 1701–1711 (2006). DOI: 10.1084/jem.20060772.*
2. *N Ohkura et al., "Development and Maintenance of Regulatory T cells", Immunity, 38, , 414–423 (2013). DOI: 10.1016/j.immuni.2013.03.002.*
3. *B Sawitzki et al., "Regulatory cell therapy in kidney transplantation (The ONE Study): a harmonised design and analysis of seven non-randomised, single-arm, phase 1/2A trials", The Lancet, 395, 1627–1639 (2020). DOI: 10.1016/S0140-6736(20)30167-7.*
4. *JA Bluestone et al., "Type 1 diabetes immunotherapy using polyclonal regulatory T cells", Sci Transl Med, 7, 315 (2015). DOI: 10.1126/scitranslmed.aad4134.*
5. *A Putnam et al., "Clinical grade manufacturing of human alloantigen-reactive regulatory T cells for use in transplantation", Am J Transplant., 13, 3010–3020 (2013). DOI: 10.1111/ajt.12433.*
6. *J Furzer et al., "Cost-effectiveness of Tisagenlecleucel vs Standard Care in High-risk Relapsed Pediatric Acute Lymphoblastic Leukemia in Canada", JAMA Oncol., 6, 3, 393–401 (2020). DOI: 10.1001/jamaoncol.2019.5909.*
7. *T Nishimura et al., ."Generation of rejuvenated antigen-specific T cells by reprogramming to pluripotency and redifferentiation", Cell Stem Cell, 12, 1, 114–126 (2013). DOI: 10.1016/j.stem.2012.11.002.*
8. *R Haque et al., "Programming of Regulatory T Cells from Pluripotent Stem Cells and Prevention of Autoimmunity", J Immunol, 189,3, 1228–1236 (2012). DOI: 10.4049/jimmunol.1200633.*
9. *L Passerini et al., "CD4+ T cells from IPEX patients convert into functional and stable regulatory T cells by FOXP3 gene transfer", Sci Transl Med, 5, 215, 1–11 (2013). DOI: 10.1126/scitranslmed.3007320.*
10. *JT Sockolosky et al., "Selective targeting of engineered T cells using orthogonal IL-2 cytokine-receptor complexes", Science, 359, 6379, 1037–1042 (2018). DOI: 10.1126/science.aar3246.*
11. *TL Roth et al., " Reprogramming human T cell function and specificity with non-viral genome targeting", Nature, 559, 7714, 405–409 (2018). DOI: 10.1038/s41586-018-0326-5.*
12. *NA Dawson et al., "Functional effects of chimeric antigen receptor co-receptor signaling domains in human Tregs", Science Translational Medicine, 12, 557, eaaz3866 (2019). DOI:10.1126/scitranslmed.aaz3866.*
13. *R Lanza et al., "Engineering universal cells that evade immune detection", Nat Rev Immunol, 19, 723–733 (2019). DOI: 10.1038/s41577-019-0200-1*
14. *(7) Rackham OJL et al. "A predictive computational framework for direct reprogramming between human cell types." Nature Genetics, 48, 331–5 (2016). DOI: 10.1038/ng.3487.*
15. *US Kamaraj et al. "EpiMogrify Models H3K4me3 Data to Identify Signaling Molecules that Improve Cell Fate Control and Maintenance." Cell Systems (2020). DOI: 10.1016/j.cels.2020.09.004.*

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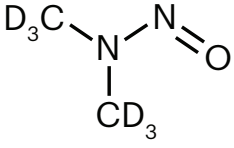


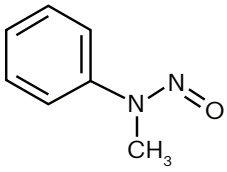
Molecular Formula: $C_2D_6N_2O$
CAS No: 17829-05-9
Uses: Internal standard for quantitative testing

N-Nitrosomethylphenylamine (NMPA)

Catalog #: 1466607

Category: USP impurity RS

Chemical Name: *N*-Methyl-*N*-nitrosophenylamine



Molecular Formula: $C_7H_8N_2O$
CAS No: 614-00-6
Uses: Impurity standard for quantitative analysis and other purposes by LC-MS and GC-MS

EXISTING NITROSAMINE IMPURITIES

Item #	Description	Item #	Description
1466641	N-Nitrosodibutylamine (NDBA) (1 mg/mL in methanol)	1466674	N-Nitrosodimethylamine (NDMA) (1 mg/mL in methanol)
1466652	N-Nitrosodiethylamine (NDEA) (1 mg/mL in methanol)	1466685	N-Nitrosoethylisopropylamine (NEIPA) (1 mg/mL in methanol)
1466663	N-Nitrosodiisopropylamine (NDIPA) (1 mg/mL in methanol)	1466696	N-Nitrosomethylaminobutyric Acid (NMBA) (1 mg/mL in acetonitrile)

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Is It Time to Onshore Your API Supply?

COVID-19 has thrown the spotlight on the weaknesses of today's highly dispersed, globalized pharma industry, prompting many companies to consider onshoring their API supply

By Ben Wylie

Given what we know now, who can deny the fragility of the industry's supply chains? As the demand for sterile manufacturing capabilities rose during the pandemic, we saw many companies struggle to source the ingredients they needed to operate, resulting in shortages of vital medicines – both prescribed and over-the-counter – around the world (1). The sudden and extended lack of drug substance and other ingredients needed to manufacture drug products can be traced to two issues. Firstly, the additional strain on global healthcare systems quickly consumed supply capacity. Secondly, and most crucially, the economic lockdowns that paralyzed much of the world throughout the first six months of 2020 led to the closure of key factories that were producing vital pharmaceutical ingredients.

The problem was most acute in China – now one of the world's leading suppliers of basic raw materials and APIs – where a number of factories closed as part of efforts to prevent the spread of COVID-19 during the first quarter of 2020. In fact, the pandemic restricted global ingredient supply right at the point when demand peaked in the second quarter. Media around the world carried images of pharmacy shelves empty of over-the-counter painkillers and other treatments.

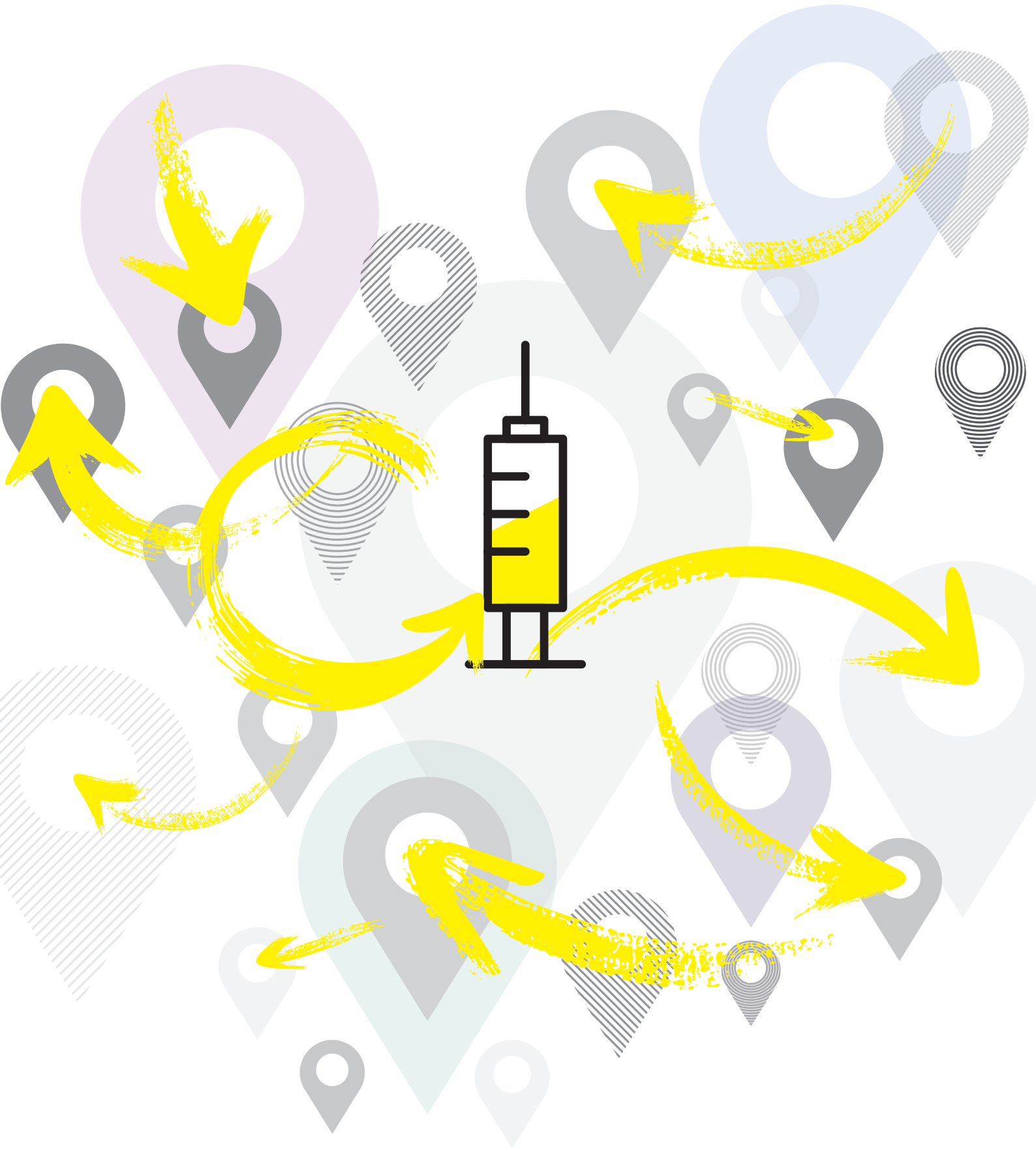
Bringing API supply home

As a result, pharma is now rethinking its supply chains in a bid to reduce reliance on any one single market or source and to demonstrate that they have strong and robust business continuity plans in place to prevent a repeat of the events back in spring 2020. Some companies are in the process of switching their ingredient supply to manufacturers that are geographically closer to home to help guarantee they have the materials they need to meet future spikes in demand (2).

But this recent move towards onshoring pharmaceutical ingredient supply is not driven by companies alone. Recognizing the national security implications of a disrupted pharmaceutical industry, governments around the world are encouraging (or toying with forcing) drug companies to localize their supply chains. For example, lawmakers in the US have openly discussed legislation that would mandate the production of APIs on America's shores – a costly move for the industry. This "Buy American" order would exempt the import of drug ingredients if they are already in abundant supply or if their procurement from within the US would increase costs by more than 25 percent. This is a move that the pharmaceutical industry has significant reservations about (3).

Similar moves are happening in India. Pre-COVID-19, the nation's pharmaceutical industry relied on Chinese suppliers for as much as 70 percent of its required APIs. Responding to the disruption at the beginning of the outbreak, the Indian government set aside a fund of $1.2 billion to support the sector. It also announced the creation of a new production-linked incentive scheme designed to encourage the development and expansion of homegrown API and ingredient suppliers. The government hopes these steps will play a key role in ending the dependence of India's pharmaceutical sector on Chinese suppliers (3).

The relatively new demands for onshoring are already having an effect on pharmaceutical companies worldwide. We are witnessing greater investment in local manufacturing sites for API production in a number of markets – either by existing manufacturers or newcomers moving



into the ingredient supply space. And that will have significant consequences for the industry in the future. A greater prevalence of local suppliers will shorten supply chains for many manufacturers, militating against the impact of border closures or economic lockdowns overseas.

Not only does a move towards onshoring provide new opportunities for manufacturers to expand and grow within individual markets, but it will also help to build more robust supply chains in future – protecting the sector from spikes in demand and regional manufacturing disruption.

Meeting the onshoring challenge

There are downsides to the localization of the supply chain; for one, it may well lead to higher production costs, as companies select suppliers based on their location rather than price. For many North American and European manufacturers in particular, it could be considerably more expensive to work with local suppliers compared with former partners in Asia. The potential added cost needs to be weighed against the benefit of sourcing locally before any decision about onshoring supply is made.

And though the move to localize ingredient supply offers plenty of exciting opportunities, it poses other challenges. Companies establishing new facilities or expanding existing sites for API production must achieve effective and validated containment and sterile transfer where required – a challenge in today's complex pharmaceutical manufacturing environment, where ingredients often pass through multiple production lines and manufacturing facilities before they become the finished drug product.

Those companies seeking to establish new partnerships with local suppliers must be confident that their new ingredient providers are compliant with stringent local regulations governing sterile and high potency pharmaceutical production. A failure to do so will likely undermine their efforts to attract new customers within their local market. Moreover, if API suppliers want to benefit from renewed and increased demand from local customers, they need to ensure they have the capacity to deliver reliable supply – after all, that is the crux of the trend. For many, this will mean not just investing in new production equipment for their existing facilities, but the acquisition of new sites as well. To maximize the return on this investment, manufacturers need to carefully select the right equipment to optimize productivity – while maintaining the highest quality and safety standards, of course.

For example, the transfer of APIs and other materials from one manufacturing process or facility to another can waste time and cause delay, as well as being a point where line operatives may be exposed to potent and hazardous APIs. However, this can be avoided – while also increasing productivity – through the careful selection of the right process components. Valves specially designed for containment can support the efficient and rapid transfer of powders into and out of process equipment, while protecting operatives from exposure. Manufacturers can also opt for single-use valves, bags, or other equipment, which offer flexibility as well as access the highest level of sterility assurance, while reducing time spent cleaning and validating equipment.

Thriving post-COVID-19

The events of the past 18 months have highlighted the weaknesses and vulnerabilities of today's globalized industry. If we are to prevent similar issues arising during a future pandemic, companies need to learn lessons from COVID-19 and take steps to de-risk their API and ingredient supply.

Onshoring supply chains to more local providers can help achieve this goal, safeguarding operations from future global manufacturing disruption. At the same time, companies should ensure their supply isn't too heavily dependent on a single market – even if it is local – to reduce vulnerability to supply shocks. Indeed, companies must strike a balance between localization and supply chain diversity if they truly want to ensure their operations are resilient.

Whatever the future brings, API manufacturers worldwide should take steps now to prepare for changes in demand.

Ben Wylie is Senior Product Manager at ChargePoint Technology

References

1. *S Romano et al., "Time-trend analysis of medicine sales and shortages during COVID-19 outbreak: Data from community pharmacies", Res Social Adm Pharm, 17, 1, 1876-1881 (2021). PMID: 32482587.*
2. *Pharma Manufacturing, "Bring It Home" (2020). Available at: https://bit.ly/3asqXaT*

2021 PDA EUROPE HIGHLIGHTS

Advanced Therapy Medicinal Products
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Universe of Pre-Filled Syringes and Injection Devices
OCTOBER 2020

Biomanufacturing
SEPTEMBER 2021

Aseptic Animal Health
OCTOBER 2021

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21-22 JUN 2021	2021 PDA Virus Conference	Online
23-24 JUN 2021	2021 PDA Advanced Therapy Medicinal Products Conference	Online
14 -15 SEP 2021	2021 PDA BioManufacturing Conference	Berlin, Germany
16-17 SEP 2021	2021 PDA Pharmaceutical Freeze Drying Technology Conference	Berlin, Germany
05-06 OCT 2021	2021 PDA Universe of Pre-Filled Syringes and Injection Devices Conference	Gothenburg, Sweden
26-27 OCT 2021	2021 PDA Aseptic Animal Health Conference	Online

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Sitting Down With… Anne Phelan,
Chief Scientific Officer at BenevolentAI,
London, UK

Did you always want a career in pharma?

As an undergraduate, I was entirely unfamiliar with the pharma industry. I had never given any thought to where medicines come from or how they work, which feels ridiculous now! My fundamental interest in science and problem-solving led me to a PhD in genetics, after which I planned to pursue a career in academia.

For my first postdoc, I worked at the MRC Institute of Virology in Glasgow with John Barklie Clements. We were investigating HSV-1 viral host interactions – a very competitive area of research. We needed to make every experiment count. It was a steep learning curve, but it instilled a sense of care and precision in my work.

But nine years of postdocs – though interesting from a pure research perspective – taught me that publishing in peer-reviewed journals and securing grants was not sufficiently fulfilling. I wanted the research I engaged in to have a more practical and tangible outcome – seeing new medicines reach patients and treat the conditions they lived with. I made a career shift from academia to industry 20 years ago and have never looked back.

You spent many years in big pharma before moving to smaller companies. What are the biggest differences?

In a large company, there is an enormously sophisticated infrastructure of support and domain area expertise for every element of the drug discovery process. This enables the most comprehensive discovery programs to be funded and delivered, which is obviously satisfying, but can also be slow and cumbersome. A small company, on the other hand, brings with it a greater sense of autonomy and decision-making, but you have to learn to deliver without the safety net of the pharma support network – and fast. New skills have to be learned quickly and multitasking is essential for delivery, but it is a pace I personally find compelling.

The sheer volume of biomedical literature and the complexity of human biology is an unfathomably difficult area for even the most gifted scientists to traverse unaided. The industry needs the capacity to interrogate and interpret the vast amount of data at its disposal. Well-trained artificial intelligence and machine learning models thrive on this information and clearly represent the potential for a step-change in the way we think about drug discovery and the delivery of drugs to patients.

I joined BenevolentAI in spring 2018 because I was intrigued by the possibility of doing drug discovery differently. Expensive failures in clinical drug development have cost the industry and the patients waiting for these treatments dearly. Now is the time to define a new era in R&D. Using an integrated knowledge graph, as well as machine learning and AI tools, BenevolentAI is working toward discovering the best therapeutic targets, drugs, and treatments for patients – something I'm thrilled to be a part of.

What projects with BenovolentAI are you most proud of?

Back in January, a Benevolent team of researchers – made up of a pharmacologist and a handful of data scientists – used our biomedical knowledge graph to identify approved drugs that could stop the progression of COVID-19, inhibit the cytokine storm, and reduce the inflammatory damage associated with the disease.

Using our predictive tools, they narrowed down the therapeutic options until baricitinib became a clear favorite. The drug, developed by Eli Lilly, is used to treat rheumatoid arthritis. We alerted the company and published our findings in several medical journals. Within a matter of weeks, the drug was administered to patients, including a large global trial by NIAID and Eli Lilly. Baricitinib has since been used in investigator-led trials as a therapy in more than 800 hospitalized patients, with the NIAID trial's latest data showing that baricitinib in combination with remdesivir reduces the recovery time in hospitalized patients with COVID-19.

Though I was impressed by the speed with which the team were able to identify baricitinib, I was not surprised. We would never have discovered this without the years of investment and building our biomedical knowledge graph, which underpins everything we do.

How do you think AI will change pharma's future?

Traditional drug discovery was, and to an extent still is, siloed into specialist therapeutic areas – looking to find the next best target or drug in a predetermined domain. There is little cross-fertilization of ideas or information-sharing, which stifles creativity and limits discovery.

AI, on the other hand, can be integrated from early discovery to clinical testing to remove data silos, and biases and allow for better-quality hypotheses. New technologies can integrate and interrogate data at scale across any given therapeutic area and drug modality. Working in this disease area-agnostic forum, where the mechanistic signature of disease can be evaluated and extrapolated across multiple areas of high unmet clinical need, is liberating for scientists, and will help accelerate discoveries.

Overall, I believe that the partnership of AI and scientific expertise will result in a faster, more cost-effective, inclusive, and efficient drug discovery and development model and expand the search for treatments in typically neglected disease areas.

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