JANUARY / FEBRUARY 2021 # 72

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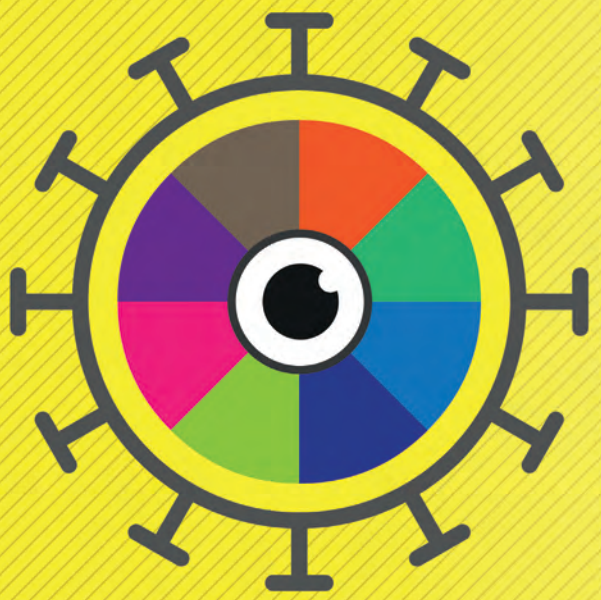
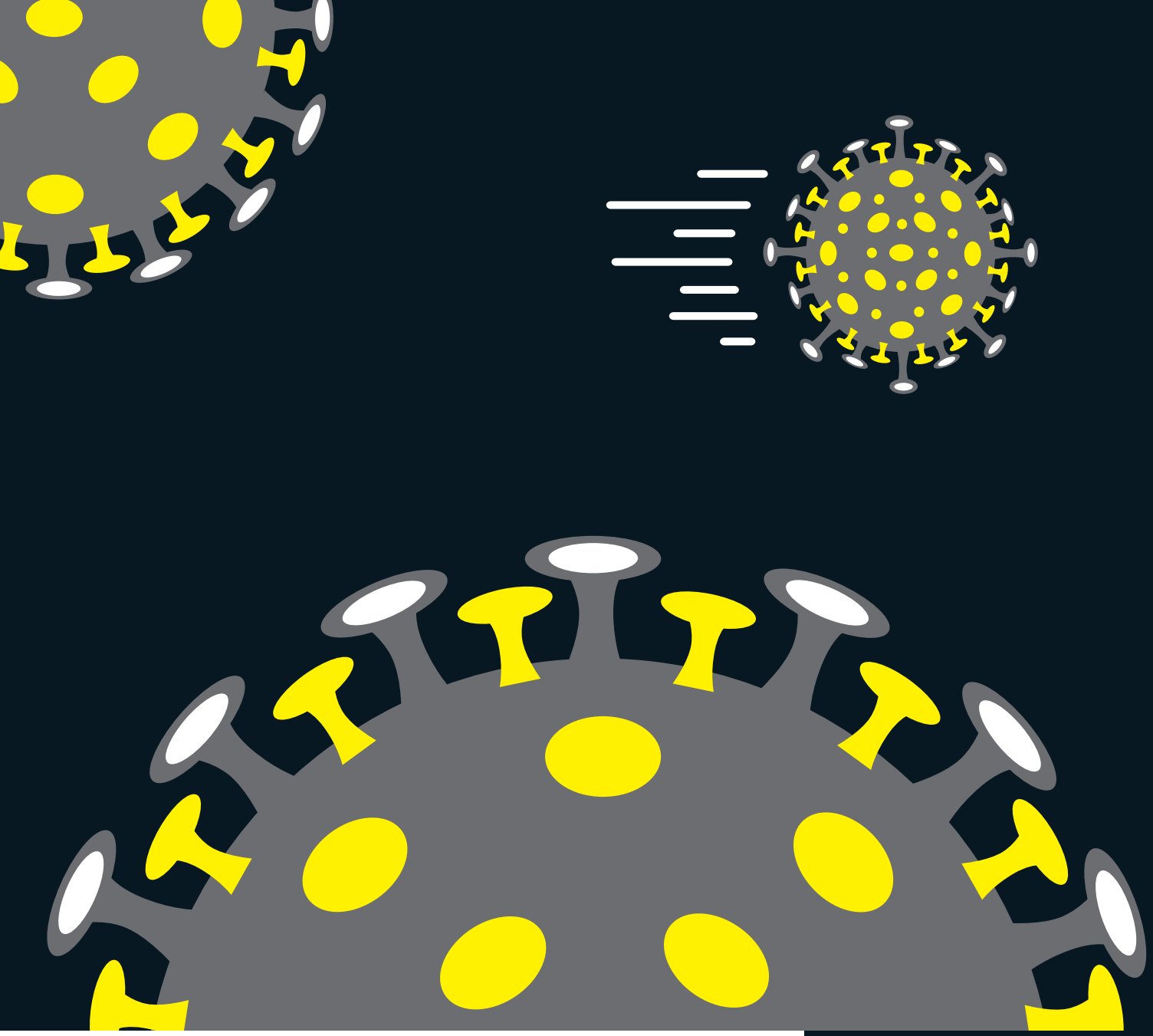


COVID-19 Perspectives

Was the industry equipped to deal with the global challenge of COVID-19? And what lessons must be taken forward?



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Simplifying Progress

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What's Fueling Your Research Engine?

How to add value and reduce risks with ethics

Certain events – the COVID-19 pandemic being a very good (or bad) example – can shift research from steady and paced to a sprint. As a researcher running that sprint (and proudly donning the corporate branded apparel), there is no time for a mistep; the whole world is watching this high-stakes race (1, 2). Additionally, thousands in society will join in as research participants testing new vaccines and therapies.

It's no secret that the word "ethics" can result in rolling eyes, as well as visuals of hurdles, red tape, and barricades. Admittedly, the good of ethics is tarnished by too many negative experiences with research ethics committees or institutional review boards – who may move at a snail's pace, staffed by volunteers who are sometimes working beyond their scope. And though that area of ethics surely needs remedying, let us turn to another area of ethics that researchers and corporations can control: their own ethics and integrity.

Robust research is more than a green light from a regional research ethics committee. The pharma industry is responsible for its organizational ethics – this means ensuring that they operationalize their mission, vision, and values in the research setting. The "corporate branded apparel" mentioned earlier is akin to the set of values internalized and functioning in each researcher (and each corporate leader) every day; these must align to qualities of robust research (for example, honest and truthful data collection, analysis, and reporting; admission of errors; protection of research participants). Without this operationalization, ethics is merely an affirmation poster or Code of Ethics – documents that "tick the box" for the compliance team.

Robust research must be viewed with a lens that is focused on more than compliance. This is because a company/employee can be legally compliant but still be behaving unethically. The results of unethical behavior can be harmful to research data, research participants, employees, shareholders, the organization, and the public. Ask yourself, as a researcher, and as a company, what have you poured into your research engine? A few policies? Some checklists? An online training quiz with too-obvious answers? Are you compliant or are you ethical?

The stakes are high and compliance is not enough for robust research. Society wants ethical research and, if you can provide it, you are providing value in your research outputs and setting the tone of trustworthiness for your brand and image.

Katrina Bramstedt

Head of Advisory and Training for Your Call Whistleblowing Solutions, Melbourne, Australia

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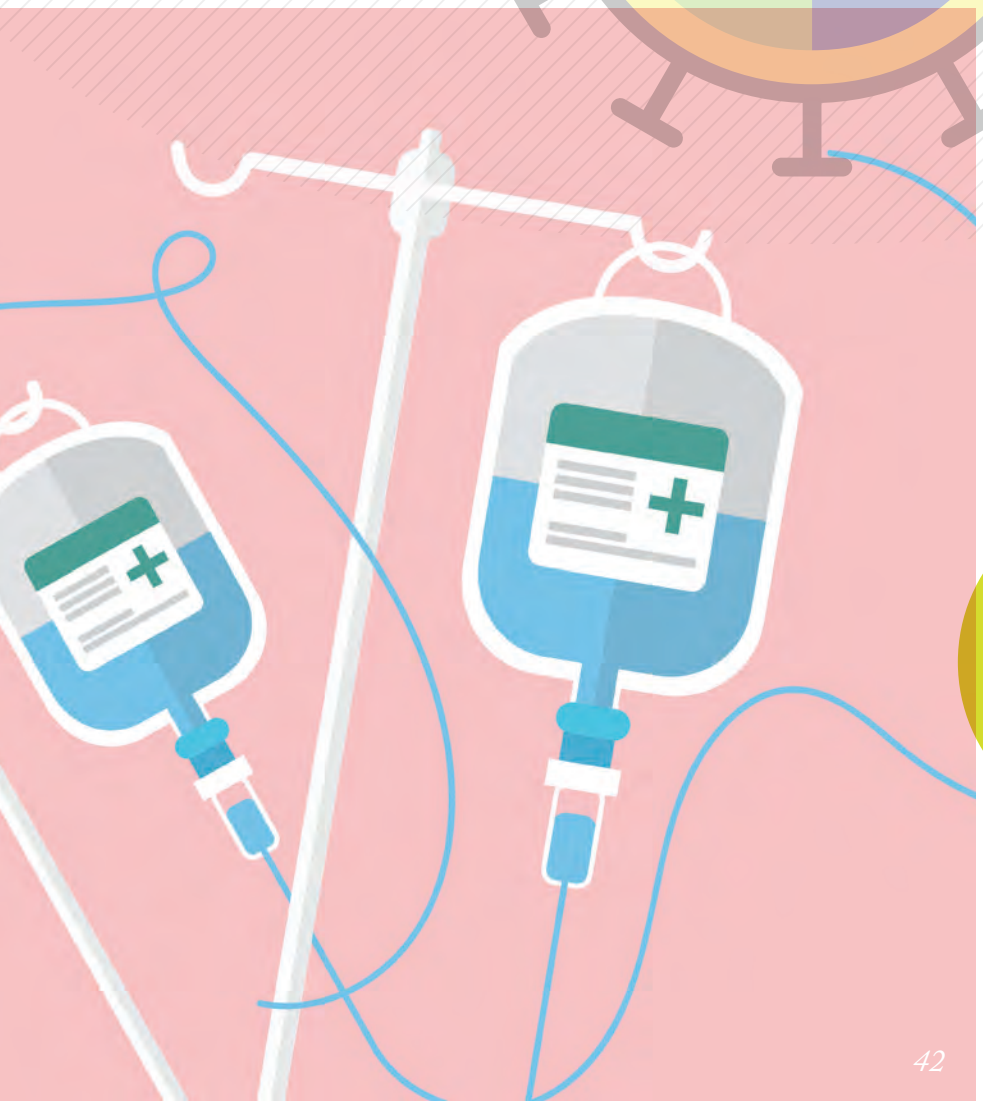

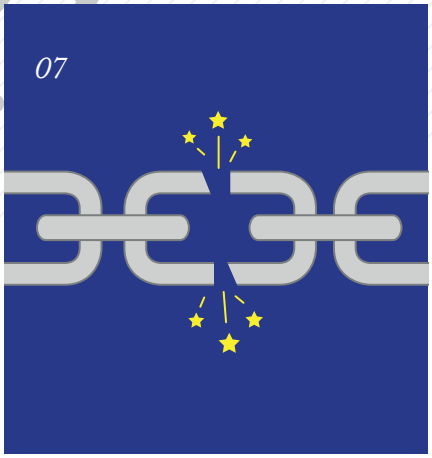

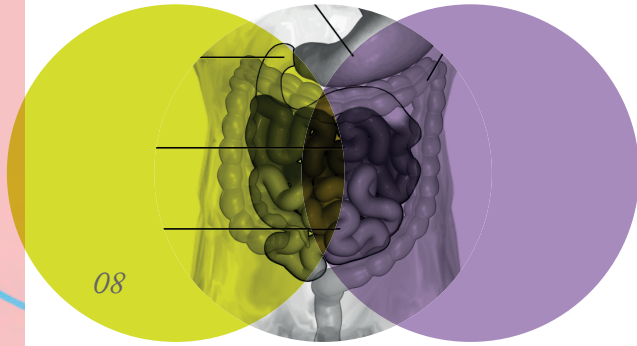

On The Cover

What has the pharma industry learned from the COVID-19 pandemic?

Feature

Best Practice

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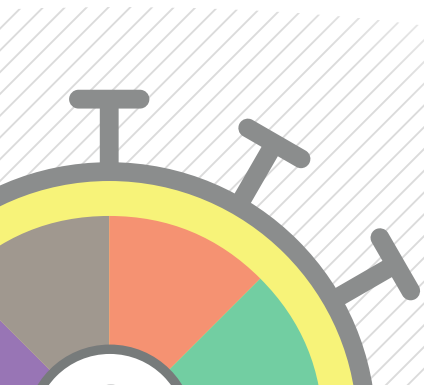
Reports

Sitting Down With



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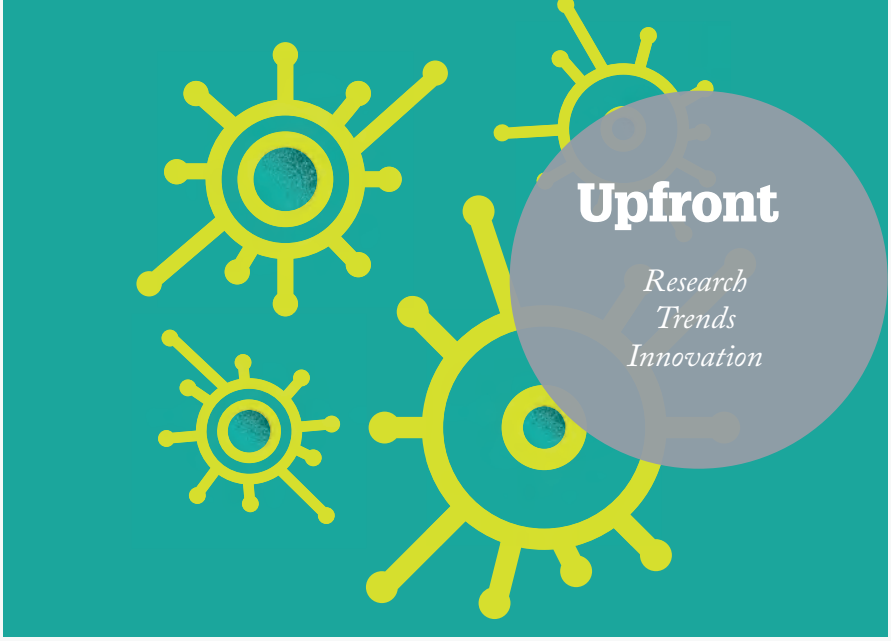


Advanced Therapies: New Year, New Challenges

We posed one big question to a selection of speakers at CAR-TCR Summit Europe 2021: what is the single greatest challenge facing the cell and gene therapy industry in 2021?

A major theme emerging from speaker responses was expanding the current advanced medicines technology – particularly engineered cell therapies – to solid tumors and beyond.

"Engineered cell therapies can bring hope to patients who lack good alternatives. The major challenge we face is to extend their promise by expanding their utility to new indications and to populations that have not yet had access to these therapies," says James Trager, CSO at NKarta Therapeutics.

But Nina Worel, Medical Director of Tissue & Cell Collection & Processing Facility at Medical University of Vienna, is keen to point out that, although cell and gene therapy is already established for lymphoma (and ALL), success rates are still below early expectations. "Industry has to come up with solutions to optimize these expensive treatment options to allow the cure of more than 40 percent of relapsed/refractory patients." She also raised the ongoing challenge of COVID-19 and its impact on patient access. "For CD19 CAR T treatment, clinicians cannot always guarantee ICU care and therefore have to delay treatment."

"The pandemic is challenging our employees, clinical partners, and patients with unforeseen shortcomings in personal health, limitations of the healthcare systems, and limitations for suppliers of R&D and manufacturing materials," agrees Jan Spanholtz, CSO at Glycostem. And Wenzhong Guo, CTO, Cell Therapy at Sorrento Therapeutics, adds, "Clinical trials for cancer and other diseases have been delayed by the COVID-19 pandemic."

More efficient scaling and production of cell and gene therapies were also key challenges for several speakers. "To me, scalability and manufacturability (meeting regulatory requirements) are the two closely related challenges the industry faces if cell and gene therapies are to fulfil their clinical potential," says Alessandra Cesano, CMO at ESSA Pharmaceuticals.

Finally, in light of the manufacturing and logistical challenges of autologous CAR T, Chris Heery, CMO at Precision BioSciences, pointed to the promise of allogeneic therapies. "If we can see comparable clinical effects with an off-the-shelf product, it would begin to address the cost and logistics challenges associated with autologous CAR T," he says.

CAR-TCR Summit Europe 2021 is a digital event for the European community of CAR and TCR drug developers: https://bit.ly/3r7SMuT

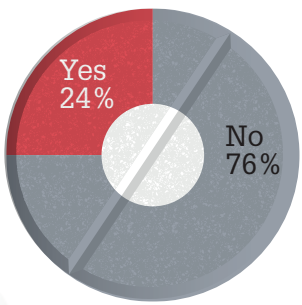
INFOGRAPHIC

Without Trust...

Survey paints a pessimistic view when it comes to what patients think about prescribed medicines

DrugDiscovered, (2020). Available at https://bit.ly/3n6pj2M

Do patients trust medicine advice from pharma companies?



Does pharma play a role in prescription decisions?

BUSINESS IN BRIEF

Sanofi lends a helping hand to COVID-19 vaccine manufacture, promising early-stage results in progeria – plus, new pandemic-related guidance from the FDA… What's new in business?

(DoD photo by Lisa Ferdinando)

- Sanofi will support the manufacture and supply of the Pfizer/BioNTech COVID-19 vaccine. Initially, Sanofi plans to produce over 125 million doses at its Frankfurt facilities from summer 2021. According to a statement, Sanofi is also committed to developing its own COVID-19 vaccine candidates; a recombinant protein-based vaccine is in development in collaboration with GSK, and an mRNA vaccine is being pursued with Translate Bio.
- Researchers injected a base editor (packaged into AAVs) into mouse models of progeria. The results? "Far better than we dared to hope," said Francis Collins, who was involved in the study. When the mice were examined six months later, between 20 percent and 60 percent of their bone, skeletal muscle, liver, heart, and aorta carried the DNA fix. And, most dramatically, the treated mice's lifespan increased from seven months to almost 1.5 years.
- New pandemic-related guidance for cell and gene therapy manufacturers has been issued by the FDA. Though the FDA is not aware of any CGT products that have been contaminated with SARS-CoV-2, there is the potential for SARS-CoV-2 expansion in autologous or allogeneic infected cells or tissues during cell culture. The FDA recommends that manufacturers consider whether, in the 28 days prior to HCT/P recovery, an allogeneic or autologous donor was in close contact with individuals diagnosed or suspected of having COVID-19, or had been diagnosed or had a positive test themselves.

Crisis-Ready: Building a Resilient Supply

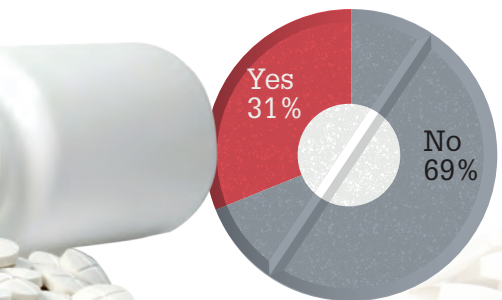
How can European pharma better prepare for future emergencies?

Drawing on lessons learned from the COVID-19 pandemic, the European Commission has developed a plan to secure affordable medicines for patients across the region. Pharmaceutical Strategy for Europe aims to create a regulatory approach that offers guidance on the management of future crises and supply chain resilience. The strategy also outlines the Commission's goals for creating a competitive industry with a "strong voice" on issues affecting the global pharmaceutical community.

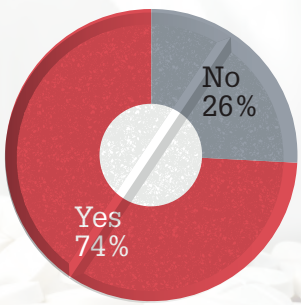
"Moving forward, there are too many public health, social and economic interests at stake here to get this wrong," said Medicines for Europe President Christoph Stoller in a statement. "We strongly believe that all concerned stakeholders need to work together […] if we are to effectively deliver on the strategy's ambition and ensure that patients receive the medicines they need when they need them, while keeping a strong, resilient and sustainable manufacturing base in Europe."

For more information about the plan, visit tmm.txp.to/european-commission

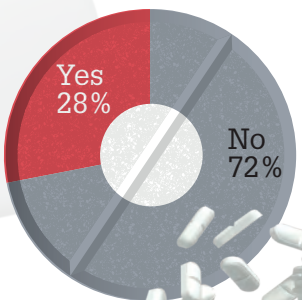
Do prescribed drugs work well?



Are there more benefits than drawbacks associated with the use of prescribed medicines?



Do patients believe their concerns are acknowledged?



Vaccine Wars

New EU "transparency" measures give member states the power to block vaccine exports if manufacturers can't meet contractual obligations

When the volume of vaccine exports "poses a threat to the execution of Union Advance Purchase Agreements concluded with vaccines manufacturers" (1), EU member states now have the power to block those exports – thanks to a new EU regulation aiming to provide "greater clarity" on vaccine production (2).

One major reason for the regulation? The EU's public spat with AstraZeneca, which informed the EU that it would be supplying considerably fewer doses of the vaccine than previously agreed (3).

AstraZeneca CEO Pascal Soriot blamed "yield issues" at one of its manufacturing sites in Europe. "The yield varies from one to three, by the factor of three," he said in an interview with la Republica (4). Soriot also cited a "best effort" clause in the contract. "Basically we said we're going to try our best, but we can't guarantee we're going to succeed."

The EU contended that AstraZeneca was contractually obliged to meet the scheduled doses, and to use AZ's UK manufacturing sites if necessary to do so – the UK government signed a separate deal with the company, three months prior to the EU agreement.

Both parties then agreed to publish the contract online, with certain parts redacted (5) (though some of the redacted information was accidentally made visible in the initial PDF uploaded by the EU). The contract does say that AZ must use "Best Reasonable Efforts" to manufacture the doses, but both parties disagreed on what that means.

The row culminated in the publication of the Export Authorisation Regulation. But controversially, the initial draft regulation included plans to invoke Article 16 of the Irish Protocol to prevent vaccines reaching the UK via Northern Ireland – which has a special status as part of the EU's customs territory and single market for goods to prevent border checks on the island of Ireland. The protocol is considered an emergency measure, only to be used in the case of serious "economic, societal or environmental difficulties."

The Commission later withdrew its intention to invoke Article 16, calling it a "mistake" (6), and published a revised regulation without reference to the article (1).

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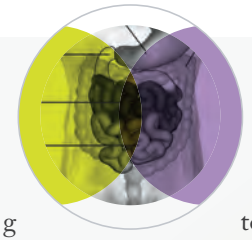
Crossing the Border

How to get macromolecules across the intestinal epithelial barrier



The BioMed X Institute located at the University of Heidelberg in Germany and Janssen Research and Development are commencing a new research project on novel transport mechanisms in the intestinal tract, which could result in the oral delivery of diverse therapeutic modalities – including biologics. In a statement, Christian Tidona, Founder and Managing Director of the BioMed X Institute, said, "There are several techniques available to shield these macromolecules from the harsh conditions of the gastrointestinal tract, but little progress has been made to translocate complex macromolecules across the intestinal epithelial barrier into systemic circulation. This project has the potential to provide us with a novel delivery platform that enables the development of a new generation of oral immunotherapies."

BioMed X has worked with Janssen on numerous other projects in the past and has an ongoing collaboration in immunology examining protective tissue factors in autoimmune diseases.

IMAGE OF THE MONTH

Credit: William Grover

Released On Time

Using a cheaply developed tool, researchers at the University of California, Riverside, are examining the single-granule dissolution profiles of a variety of medicines. They hope their work will help improve the development of time-release drugs.
https://go.nature.com/3gtCQ23

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Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"Manufacturing billions of doses for people across Europe and around the world is an unprecedented challenge involving multiple partners, working around the clock without ever compromising on the quality or safety of the vaccines. Fluctuations in the supply of doses, however frustrating, can be a feature of manufacturing complex biological products."

European Federation of Pharmaceutical Industries and Associations https://bit.ly/3thphsr

Paralyzed Mice Walk Again

Mice with severed spinal cords walk again after gene therapy

Paralyzed mice have walked again – a research first – following gene therapy treatment. A team from Ruhr University of Bochum, Germany, delivered an AAV expressing the designer cytokine, hIL-6 – previously used to stimulate nerve cell regeneration in the visual system – to the sensorimotor cortex of mice with complete cross-sectional injury. The mice were then able to produce hIL-6 themselves and deliver it to serotonergic brainstem neurons (1).

The result? "The previously paralyzed animals that received this treatment started walking after two to three weeks," said Dietmar Fischer, Chair of Cell Physiology at Ruhr and corresponding author, in a press release (2). "This came as a great surprise to us at the beginning, as it had never been shown to be possible before after full paraplegia."

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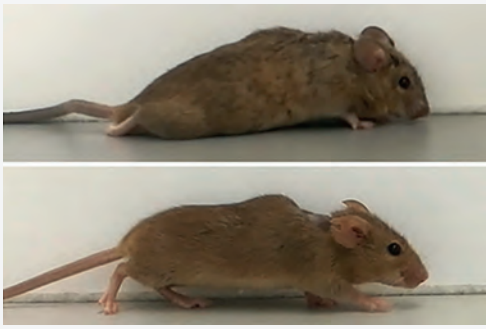

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In My View

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

Keeping Your Nose in Front

With the right partner to help you harness the many benefits, nasal delivery is not to be sniffed at

By Charles Evans, Vice President of Pharmaceutical Development, MedPharm

Pharmaceutical developers are waking up to the idea that drug delivery via the nose could offer advantages for their target product, patient population, and indication. Traditionally, many formulators tend to think of oral dosing first – their comfort zone – followed by an injectable, if the oral route is not suitable. Other routes of delivery, such as nasal sprays, were typically only considered when all else failed.

Thanks to an increased focus on patient needs over recent years, nasal delivery is now moving to the forefront of formulators' psyches – notably, at the very start of the development process. Development teams are establishing target product profiles early on and recognizing the benefits of establishing the needs of prescribers and patients from the outset.

The nasal cavity presents a large area of highly vascularized accessible mucosa. It offers a rapid way of getting drugs into the bloodstream and quickly circulated through the body as required, including the lungs. Nasal delivery may also allow central nervous system drugs to be delivered to the brain, which is close to the olfactory bulb in the nasal cavity. This direct route avoids first-pass metabolism and the tricky blood-brain barrier, while also being easy for the patient to administer themselves. The nose is also easily accessible when a patient is not conscious, which makes nasal delivery an ideal choice for revival from a diabetic coma or an opiate overdose.

More recently, in vitro models based on viable human nasal epithelia grown from tissue culture have become available – opening the door to more thorough investigation in the lab prior to the clinic. These models allow developers to test their products on viable human tissue; whereas historically they would have been reliant on either nasal tissue from human cadavers or animal models, which have limited applicability in part because naturally produced mucus and active transport mechanisms associated with living tissue (known to be important in drug performance) have been lost in tissues from these sources. These new models offer the advantage of having fully functioning cells that closely mimic the clinical situation.

Such models are ideal for screening the likely delivery efficacy of new formulations of existing drugs targeting new indications. In a COVID-19 dominated world, these models become even more important because they can test both the pharmacokinetics and efficacy of a drug to mitigate the transmission of viruses when the

"Delivery is now moving to the forefront of formulators' psyches – notably, at the very start of the development process."

cultured cells have been inoculated.

The new models can also be used to assess irritation. Nasal epithelia, like all mucosal membranes, are relatively sensitive, and formulators need to keep this in mind. The experienced formulator will focus on the specific excipients already approved for nasal delivery, if possible, to minimize regulatory hurdles. They will also be considering the delivery device alongside the formulation to ensure the best outcome for the patient.

Fundamentally, a good formulator will be focused on exactly where in the nose the formulation is to be delivered, while considering whether it is intended for local or systemic delivery. Depending on the properties of the API, this may point to a particular delivery device for which a specific type of formulation is developed – or vice versa.

Maintaining this specialist formulation expertise in-house is typically not cost-effective and many development companies turn to specialist contractors to support their nasal product development efforts. Outsourcing allows companies to benefit from the collective experience the contractor has gained from being involved in other similar developments. Ideally, the contractor will also be at the forefront of developing new methodologies – and will not be tied into a particular device that may not be suitable for the target site of delivery and/or the active(s) in question.

Fully considering nasal delivery as an option helps put the patient at the center of your development strategy. And it could help you keep your nose ahead of the competition.

Ready for Anything

If you could expand into a new therapeutic space, should you? And what's the right path forward, if you make the leap? Answers to follow.

By Blair Jackson, Executive Vice President and Chief Operating Officer, Alkermes

"All things are ready, if our mind be so." These powerful words, spoken by Henry V as he rallied his troops in William Shakespeare's drama, resonate today for biopharma companies considering new therapeutic areas – especially ones dominated by established, well-entrenched players. Entering a new therapeutic space – like going into battle – requires courage, commitment, competence, and (perhaps most of all) sound preparation.

Why expand into a new therapeutic area at all? This is the fundamental question. Thinking about the answer can reveal insights into how a company sees itself fulfilling its mission to help patients now and in the future. Most companies start with narrow expertise and aggressively pursue R&D and commercialization in that area until forced by market pressures to diversify. These pressures include genericization of key commercial assets, competition, or shifting treatment landscapes. A smaller subset of companies aren't forced to diversify, but instead leverage technical innovation (either organic or acquired) to advance their mission forward. Regardless of the catalyst, seasoned biopharma executives know that expansion beyond a core expertise can be fraught with many challenges, so a great deal of inward reflection and preparation is required.

Finding the right path forward is often not solely driven by the specific disease area, but by the attributes of the company itself. A critical review of research capabilities, development infrastructure, and commercial expertise can be used to determine if a company is compatible with the potential new direction. Leadership teams must make honest and critical assessments of the company's ability to compete in each of these domains and carefully complete a gap analysis to ensure any shortcomings are addressed. Only once these questions are satisfactorily answered can you begin to determine if therapeutic expansion is right for the business.

Not long ago, Alkermes found itself at these exact crossroads. Our entry into immuno-oncology was precipitated by innovation within our protein engineering group, as we considered applying our technology to new diseases. Seeking to augment our capabilities within biologics, we acquired a number of technologies from Acceleron Pharma that would allow us to manipulate protein structures to improve the clinical characteristics of a wide range of therapeutically relevant proteins. Through this work, we were able to design an investigational cytokine with the potential to harness the efficacy of the IL-2 pathway, while mitigating the tolerability issues that have limited IL-2 therapy in oncology. The molecule was a real breakthrough in protein engineering and had the potential to change the oncology space. Despite internal positivity, we still asked ourselves one more critical question. "Even if we could do it, should we do it?" Or, digging deeper, we had to ask ourselves whether the move was aligned with our mission: applying science to develop innovative medicines for serious, chronic diseases and raise the bar on how patients can survive – and thrive – with advanced treatments.

Expanding into a new therapeutic area is a weighty decision and a journey you can't make alone. You need the passion and expertise of employees, the support of the board and shareholders, and the partnership of clinical researchers outside of the company. As a company built on science, we felt we had all the right assets and the stakeholder support to move ahead. To complement our technology and guide our approach, we tapped into the experience of our researchers and scientists trained across multiple therapeutic areas, including immunology, molecular biology, and oncology – always advisable if you have this option.

The value and impact of any decision to expand will be revealed – in time. For us, success means bringing our oncology drug to market. Until then, it is important to stay agile, to adapt to new information, and to learn as we progress through development. We have come a long way in oncology so far, from initial discovery to ongoing clinical trials that have shown promising signs of safety and efficacy in certain solid tumors.

The R&D journey requires patience, ingenuity and determination. But if you start by asking the right questions and give yourself room and flexibility to explore new paths – or "follow your spirit" as King Henry puts it – as new answers emerge, you may eventually deliver innovation that significantly benefits patients in need.

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Big Pharma: Heal Thyself

Pharma hasn't always covered itself in glory – but as the world scrambles for viable COVID-19 interventions, it has a rare opportunity to rebrand

By Barry Silverstein, Executive Director and Co-Lead at InterbrandHealth

Pharmaceutical companies have a troubled reputation, with momentum building up to crisis levels in recent years. From the opioid scandal and excessive executive remuneration packages to criticism of drug prices and controversial direct to consumer (DTC) advertising practices, pharma brands have felt the heat from all sides. Though there are no doubts about the advances these companies make and their commitment to science and health, their reputation is one of profits first and people second. In other words, the good that pharma does is often lost in the quagmire of negative coverage.

Combating the coronavirus offers big pharma a chance to change perceptions – if companies have the will to do so. It is an opportunity to reframe the conversation, but it will require a shift from profit to people. They will need to be prepared to be more transparent in the way they operate and to speak as a corporate brand, not just a collection of individual products bombarding consumers with advertising and promotions for new, expensive drugs.

As we all face the most visible healthcare threat in recent memory, these businesses should showcase their extraordinary innovation and scientific expertise. The spotlight can be moved onto the breakthrough drugs they bring to market – how they extend the lives of people with cancer, the incredible achievement of making HIV a manageable condition, and the ongoing research into Alzheimer's.

As the race unfolds for a COVID-19 vaccine, pharmaceutical, biotech and life science companies are at the vanguard of helping the world come out of this healthcare emergency. These are the inventors and innovators who are most likely to provide the answer to our current crisis.

Pushing the boundaries of R&D in this context gives pharma companies the chance to rebuild their brand reputation – which also builds value. The S&P 500 pharmaceuticals, biotech and life sciences index has outperformed the broader S&P 500 index this year, while the Nasdaq biotech index has done the same.

Pharma companies have generally ignored their corporate brand – and hence brand reputation. The only pharmaceutical brand to make it into Interbrand's Best Global Brands ranking is Johnson & Johnson (and that's because of its consumer products, such as Johnson's Baby). To change their reputation, these firms need to lean into their corporate brand, expressing their mission and purpose, something they have generally shied away from. They must place more emphasis on people – inspiring employees, health care providers, and the public, in addition to their investors.

"Pharma companies have generally ignored their corporate brand – and, hence, brand reputation."

But companies must also tread carefully. Even where successes are achieved, it can be easy to mishandle the situation and risk doing damage to brand reputation. Transparency is vital but with it comes scrutiny. And younger consumers will evaluate good business practice in different ways to previous generations.

Healthcare was a central issue prior to COVID-19, and that has only been reinforced. But, at least in the US, the current healthcare system is simply not sustainable; it's too expensive, too many people lack insurance, rural hospitals are closing, Medicare is not being funded sufficiently, and we have falling life expectancy in segments of our population. In my view, Big Pharma should take the lead, rather than waiting for government mandates.

With several COVID-19 vaccines on the horizon – and some indeed approved – the industry is acting as a national (and international) service, demonstrating the positive value of innovative thinking. Whether pharmaceutical companies can maintain and build on this unique situation remains to be seen.

Companies must be brave, seize the opportunity, and strike a new tone. Big (brand) pharma has never been in better health; the time is now!

The Inhalation Advantage

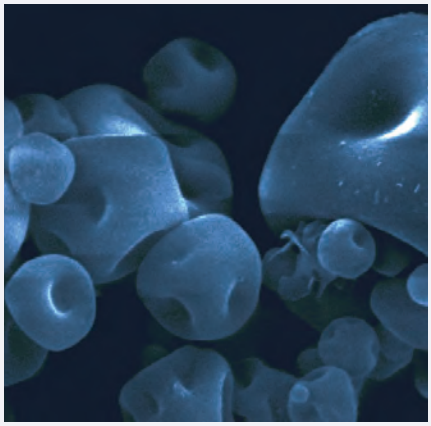
Faster and more affordable development of inhaled medicines

Vectura has more than 20 years' experience in helping customers bring inhaled medicines to the market, and integrates formulation, device and development capabilities to offer a broad range of services to accelerate inhaled products through the phases of drug development. Having expertise in product formulation and device development across a number of platforms offers customers both flexibility and continuity, forging true collaborative partnerships to combine the right drug with the right device.

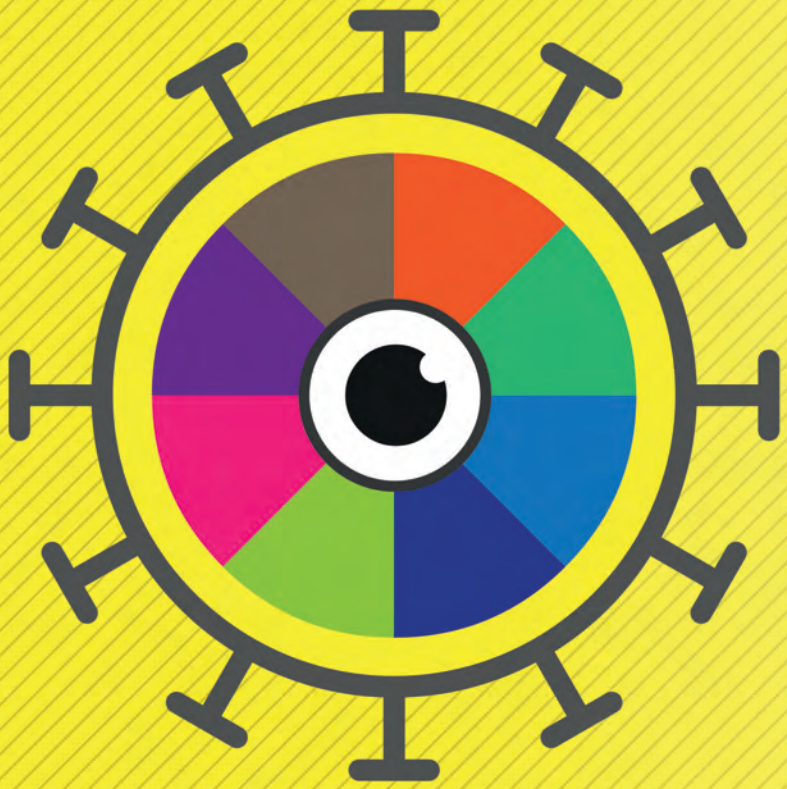
The trend within the industry to find new uses for old drugs has increased, and might take a drug already approved for one indication, and find utility in another; or create a new formulation to allow administration via a different route for the same indication. Alternatively, an existing drug may have its product profile improved or altered, while keeping the same administration route. Either way, as well as providing advantages for patients, it can offer new intellectual property coverage, driving additional revenue for innovators with lower risk and faster entry to market.

Inhaled delivery offers opportunities for improved dosing, simpler, less invasive administration, enhanced patient adherence, and product lifecycle management. By repurposing known drugs and leveraging pre-existing drug safety data, manufacturers benefit from shorter, less costly and less risky development programs, which has been particularly relevant for accelerating the progression of COVID-19 products.

In a recent webinar, Geraldine Venthoye, Chief Scientific Officer and Executive Vice President, Product Development at Vectura, discusses the value of inhaled drug delivery, and how repurposing or repositioning a drug can represent a safer, faster and more affordable way to develop new products than de novo drug discovery and development.



Dr. Venthoye also reviews the recent interest in inhaled COVID-19 products, choosing devices for repurposed products, device selection for repurposed biologics, and mitigating the environmental impact of devices. The webinar is available at https://bit.ly/3pdBQTD



PANDEMIC PERSPECTIVES

How to manage through a crisis. Exploring industry views and experiences with COVID-19.

By Stephanie Sutton and Maryam Mahdi

This time last year, COVID-19 was not a burning concern for most countries. In fact, in February 2020, the EMA released a statement: "According to the information provided by the national authorities, there is a strong overall level of preparedness with countries having response measures in place to provide treatment for the cases in the EU and to mitigate any further transmission within and into the EU."

In early March, however, the WHO characterized COVID-19 as a pandemic and warned countries to "detect, test, treat, isolate, trace, and mobilize their people in the response," but many remained either skeptical or overconfident. The UK, for example, was confident it could "turn the tide" within just 12 weeks...

Since March 2020, the virus has dominated conversations – and it will continue to do so for some time. To get a better grasp of reality nearly one year on, we gathered experts from across the industry to help measure the impact and explore the way ahead.

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A YEAR OF UNPRECEDENTED CHANGE

All eyes have been on the pharmaceutical industry throughout 2020 – assessing its capacity to provide an answer to a truly global challenge

HOW DID YOU INITIALLY RESPOND TO THE PANDEMIC?

Marijn Verhoef: Though COVID-19 has sent shockwaves through the industry, in a way, we were all anticipating it. At the Access to Medicine Foundation, we've been studying what we call Disease X – an unknown threat – for quite some time now. So, though we were asking ourselves what this unknown pathogenic challenge would be, the fact that it was a coronavirus wasn't a total surprise; coronaviruses had already been identified by WHO and others as a priority for industry to investigate, and the Access to Medicine Index assesses how companies were working on pandemic preparedness. Would they be able to manage supply chain threats? Would R&D continue as normal under the pressure of a pandemic?

There have certainly been challenges for us all to deal with, but the situation has proven how adaptable pharma is and, in recent months, we've seen increased collaboration between small and large companies to find solutions as quickly as possible.

Mark Quick: As Marijn says, we've certainly had to make rapid adjustments to deal with the changes. When the first wave of the pandemic hit, India and Northern Italy emerged as two of its epicenters – areas where Recipharm has significant operations. It was crucial for us to respond quickly. We implemented a business continuity plan to overcome the operational challenges and to mitigate the supply chain disruption caused by the global lockdown. Importantly, we also had to consider how we would protect the wellbeing of our colleagues operating production lines.

Boyer: In response to the growing spread of COVID-19 around the world, in March 2020 Colorcon implemented its existing formal, documented Business Continuity Management (BCM) system. This system is comprised of a long-established Business Continuity Plan (BCP) and a series of Disaster Recovery Guidelines that are an integral part of our global business strategy and day-to-day activities. We have seven film coating production plants at locations around the world – all of which can produce equivalent products. And that helped our response to the worsening situation as we were able to manage levels of raw material inventory, continue to manufacture, and mitigate supply disruption. To support the continuity of our operations around the world, like many companies, we implemented a remote work policy, embraced digital communication platforms, and are taking extra precautions in our production facilities to protect our employees and support manufacturing continuity.

Mortensen: As the other contributors have mentioned, Almac has taken steps to ensure continued operations Our global facilities have remained open and operational, without interruption, since the initial outbreak, and we have continued to ship and receive material globally. We've done this, in part, by maintaining a centrally managed, country-by-country approach, which ensures we follow best practices and government guidance in each of our global locations. By doing this, we can act as an advisor to clients on how to manage supply chain considerations to ensure that studies and projects are not disrupted. In many cases, this included a shift to a flexible supply strategy.

At the core of our response effort was our robust business continuity framework, which includes a provision for facilitating lines of decision-making through two tiers of command leadership, to ensure reliability and consistency across our organization. This tiered leadership system includes our main board of directors and executive directors, who continually assess the impact of the crisis on our employees and our assets; and other members of our senior team who execute new processes across facilities, and provide feedback from a regional perspective. Lastly, the implementation of communication platforms has ensured collaboration and teleconferencing capabilities across the globe. We've had to embrace digitization in other ways as well, such as rolling out a virtual auditing solution to confirm our ongoing site compliance with GMP.

Contributors:

KELLY BOYER, VICE PRESIDENT – FILM COATING AT COLORCON

MARIJN VERHOEF, ENGAGEMENT MANAGER AT THE ACCESS TO MEDICINE FOUNDATION

JONAS MORTENSEN, VP BUSINESS DEVELOPMENT, ALMAC PHARMA SERVICE

MARK QUICK, EXECUTIVE VICE PRESIDENT, CORPORATE DEVELOPMENT AT RECIPHARM

WHAT VULNERABILITIES HAS THE PANDEMIC HIGHLIGHTED?

Verhoef: I think it's fair to say that supply chains haven't always held during the pandemic. We'd already experienced drug shortages in 2018 and 2019, but COVID-19 has exacerbated the problem. Several governments have at times even mandated the domestic production of drugs, which has resulted in a concentration of manufacturing in specific geographies – and placed additional stresses on many companies.

But, in my opinion, rather than vulnerabilities, I think that new opportunities are opening up for the industry; we've all seen an unprecedented level of solidarity between industry players. By the same token, it is also becoming clear that the governments of some wealthier nations are blocking equitable access to emerging COVID-19 therapeutics through pre-orders. I think that pharma companies have a role to play in stopping this. They are the ones that control manufacturing and supply, so they should be able to ensure equitable distribution of COVID-19 related products as and when they receive approval.

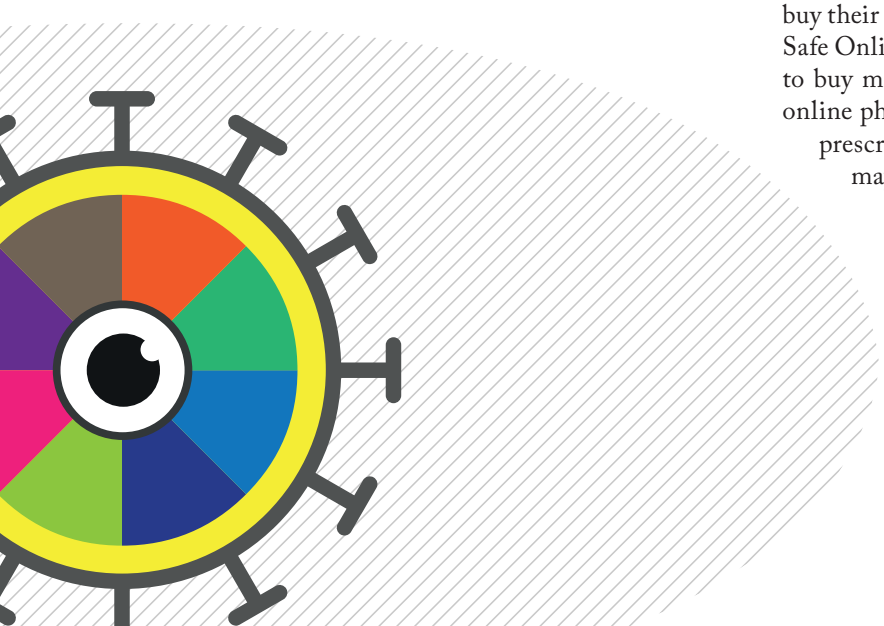
Quick: The pandemic has highlighted vulnerabilities in the industry's highly globalized supply chain. During the first wave of the outbreak, for example, the shortage of APIs caused by the closure of Chinese factories had to be managed and mitigated to maintain the international supply of vital medicines. As a result, many governments are now encouraging their local pharma sector to localize supply chains – or at least diversify them – to safeguard against disruption during future economic shutdowns. For example, the US, under President Trump, enacted an "America First" policy to on-shore API supplies, although there is uncertainty around the future of this approach as Biden takes over. The Indian government has also recently launched a scheme to incentivize the country's pharma industry to source APIs and other key ingredients from Indian suppliers. With manufacturers in India currently depending on China for 70 percent of their API supply, they were particularly impacted during the first lockdown.

As a result of government pressure, it is likely we will see manufacturers around the globe rethinking their supply chains to favor local providers. Ingredient suppliers and CDMOs with a local presence in each of their target markets will be well placed to support these companies.

Boyer: Another area of concern that should be discussed is the sale and distribution of fake and falsified medicines. We know it has been a problem for decades but is spiking now because of COVID-19. The WHO reports that over half of all drugs purchased from online pharmacies are suspected to be counterfeit. And with the number of illegal online pharmacies increasing dramatically since the start of the COVID-19 pandemic, there is a growing recognition that the serialization of medicines through packaging alone will not solve the problems. The Royal Pharmaceutical Society also warns that the UK, in particular, could see "an influx of counterfeit medicines" after the Falsified Medicines Directive ceases to apply at the end of the Brexit transition period.

The COVID-19 pandemic has led to a dramatic rise in online sales. It is estimated that 1 in 4 US consumers now buy their medicines online. But according to the Alliance for Safe Online Pharmacies, a high percentage of online searches to buy medicine return links for illegal pharmacies. These online pharmacies frequently operate without certification, prescribe drugs without adhering to legal guidelines, and may knowingly distribute counterfeit medicines.

Increasingly well-organized counterfeiters backed by sophisticated technologies are continuing to profit from drug counterfeiting at the expense of patients and legitimate companies. They see both Brexit and the pandemic as an opportunity to expand their operations. We'll all have to closely monitor the situation as we move into the new year.



WHAT POSITIVE ACTIONS HAVE BEEN DRIVEN BY THE PANDEMIC?

Mortensen: Well before the pandemic became a part of our lives, the clinical trial landscape was shifting – becoming increasingly faster, decentralized, and virtual. The specifics of the trials themselves (size, duration, and number of endpoints) are also changing. Protocols are becoming increasingly more intricate to design and implement given the need to target smaller, more niche populations. Last but certainly not least, there is a growing desire, now compounded by the pandemic, to shorten the timeline between final protocol to first patient visit. Therefore, it is clear that the pandemic has served as a catalyst to naturally implement new tools to support these models and accelerate the adoption of new approaches to increase the speed of drug development.

Boyer: Even before COVID-19 struck, the industry was already evolving. At Colorcon, we noticed an increasing number of companies were moving away from in-house tablet coating formulations, for example, to a leaner production model using ready-prepared formulations. Such trends continue to accelerate because of heightened concerns about the inherent risk in supply chains. Many companies have long recognized the benefits of newer production models but have feared disruption and so opted to keep existing systems in place. The pandemic has pushed companies to reassess their operations.

Quick: The desire to end COVID-19 disruption has highlighted the benefits of collaboration, with many companies working together and sharing knowledge. This willingness to collaborate to speed up the development process has filtered down to the commercialization phase as well. Drug developers are seeing the value of working with CDMOs to commercialize and deliver their products to market. CDMOs really do offer a host of benefits for both large- and small-scale developers – they already have the capacity, the in-house expertise, and technical infrastructure in place to manufacture new drugs and vaccines at a commercial scale. This minimizes expenditure on new drug development projects and significantly reduces time-to-market. And global CDMOs often have the local presence to support developers in streamlining and localizing their supply chains.

> *"The COVID-19 pandemic has led to a dramatic rise in online sales. It is estimated that 1 in 4 US consumers now buy their medicines online."*

Verhoef: Though the collaboration and investment in R&D that we've seen in recent months has been positive for the industry, we must ask ourselves what the long-term cost of it will be. We've directed both financial and human resources into COVID-19 R&D programs, but how will this affect development for other infectious disease indications? It is likely that staff working on treatments for other infectious diseases have switched focus to work on COVID-19 projects. What then will happen to the programs that they were previously working on? So, although the rapid response to the virus was and is necessary, we must think of the burden that will be placed on patients living with other infectious diseases and the future ramifications for pharma.

HOW IMPORTANT IS THE CONTINUED ROLE OF SMALL MOLECULES IN THE PHARMACEUTICAL INDUSTRY?

Quick: There has been a shift in the market in recent years toward innovative biologic and cell and gene therapy products, and many CDMOs are growing rapidly to service this new

"We need to get back on track, as it will indicate that companies aren't only thinking of medicines access as a form of philanthropy, but an essential part of their business models."

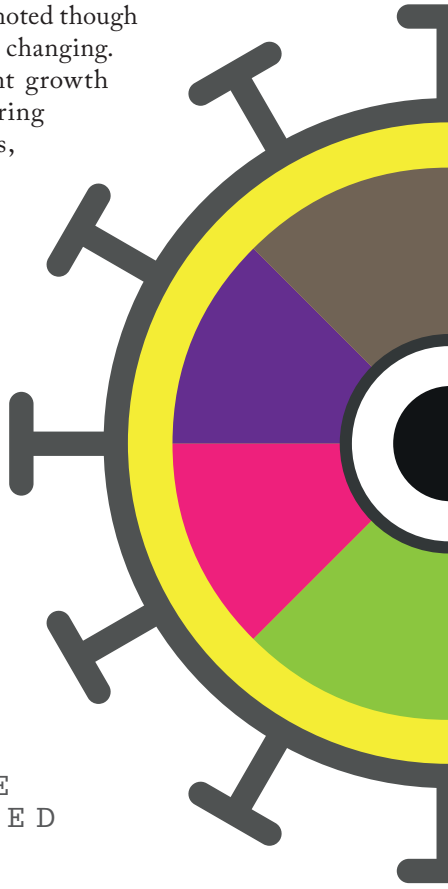
demand. Nevertheless, small molecules continue to play an important role in the sector and will account for the majority of prescribed drugs for the foreseeable future. As such, they will continue to be a major growth driver for the CDMO market for the next few years.

With regards to the development of new therapeutics, there remains strong interest in orphan drugs, specialized treatments, and innovative drug products based on existing small molecules to tackle rare chronic conditions, such as Parkinson's Disease. Small molecules are also being harnessed to develop new multiple-API products designed to boost the effectiveness of existing treatments through delayed or extended dosage. Such products are also ideal for enhancing patient compliance by reducing the number of doses users must take per day.

Verhoef: Small molecules have always been important to the pharma industry. Long before the introduction of biologics, they were relied upon to treat myriad diseases and continue to play a role in disease management today. Take dexamethasone, for example. The drug has now been repurposed as a COVID-19 therapeutic, but the drug has a broad spectrum of uses across a variety of disease areas.

In low- and middle-income countries, small molecules improve medicine access as they are usually cheaper and usually don't require refrigeration. But the role of advanced therapies and biologics is undeniable and governments worldwide should ensure that those in poorer nations can access them in a similar way to the 20 percent of the global population who live in high-income countries.

Mortensen: The continuing role of small molecules is also evident if we look at recent approvals of new molecular entities. Small molecules dominated new drug approvals by the FDA in 2019, accounting for 79 percent of all NME approvals. What we have noted though is that the type of drug product is changing. We are witnessing a significant growth in developing and manufacturing age-appropriate formulations, especially for pediatrics – mainly multi-particulate formulations, such as mini-tablets filled into stick packs. Potent drug products that require contained processing are also on the rise, together with decreasing batch sizes as medicines targeted towards smaller patient populations in line with the growing trend in orphan and ultra-orphan indications.



IN WHAT WAYS DO YOU THINK PHARMA CAN BE BETTER PREPARED FOR THE NEXT PANDEMIC?

Boyer: Simply put, we need to focus on supply chains – from raw materials to finished products. Managing raw materials is a critical part of the production process. So, implementing a process to measure how much each raw material contributes to products is key here. But the ability to map supply chains – knowing who makes a particular material, where they are located, how it is transported, and where it is housed – will be essential for dealing with any future crises.

Verhoef: Boyer is right. The crux of the issue is supply chain management – although it should also go without saying that pharma companies must invest in R&D targeting those pathogens that are known to have the potential to trigger a pandemic. Companies need to assess vulnerabilities in their supply network. Single sources of particular ingredients of APIs can hinder manufacturing, so companies need to establish global and regional hubs to assure them of security. If one provider of APIs is unable to supply companies with products, another should be able to fill the gap. This will also help to boost local capacity and capability. For example, a hub in any Sub-Saharan country will have the responsibilities of manufacturing and logistics – allowing it to supply the region. This will undoubtedly help if we are faced with another pandemic. Building these robust lines of supply will be our best defense.

Quick: Onshoring and localizing the supply of APIs is one step many pharmaceutical companies are taking to address this issue, encouraged by their governments. This positive measure will help manufacturers protect their supply of raw materials in the event of an economic shutdown in one part of the world during a future pandemic. Those who do not localize will look to diversify to ensure they are not reliant on one market for raw materials.

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WHAT DO YOU THINK THE INDUSTRY'S PRIORITIES NEED TO BE FOR 2021?

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Verhoef: A key focus for 2021 will be on how companies raise capital to improve access to medicines globally. The industry was making headway with this, but COVID-19 snowed on these developments. We need to get back on track as it will indicate that companies aren't only thinking of medicines access as a form of philanthropy but an essential part of their business models – this will help allow sustainable access to much-needed medicines in low- and middle-income countries.

COVID-19 has been at the forefront of the industry's collective mind this year and is guaranteed to impact the sector next year. Hopefully, we'll see a series of filings for registration and market authorizations for COVID-19 treatments and equitable access to them all. But, to reiterate a point I previously made, if government leaders fail to display solidarity, then the industry should step up to make a difference for patients across the globe. The pandemic will only be over when the majority of the world's population is immunized and has access to appropriate treatment. I hope we – as companies, organizations, and individuals – can remain engaged in taking appropriate steps to combat the disease until the WHO declares the pandemic over.

Boyer: Having robust business continuity plans in place to ensure continued supply is vital in ensuring the continued safe supply of medicines. But, as also mentioned earlier, we also need to pay attention to counterfeit and falsified drugs – and their prevalence will continue to increase. The growth in the number of illegal online pharmacies (over 600 new sites per month!) is further fuelling the counterfeit fire. Cost-effective and simple to implement technologies are needed more than ever to combat counterfeiting and provide greater security to the supply chain and greater safety for the patient.

Quick: For the next 12 months, it is imperative that the industry continues to use lessons learned from the pandemic (and its impact) to find new ways to ensure their operations and supply chains are more resilient in the future. As many COVID-19 vaccine candidates approach the final stages of development, it is likely we will see a considerable amount of manufacturing capacity devoted to the task of vaccinating the global population.

Though this is important, we also need to make sure we maintain our focus on existing drug development projects to help the global healthcare sector treat other serious conditions.

It is also important that we continue to prioritize the development of new drug products, dosage forms, and delivery systems to support patient-centric treatments. In doing so, we can help ease pressure on healthcare providers as they focus on dealing with the pandemic and its fallout.

LEADERSHIP IN TIMES OF CRISIS

At the CPhI Festival of Pharma held in 2020, The Medicine Maker held a roundtable discussion featuring members of our previous Power Lists to discuss the challenges of leadership during these trying times. Below is an excerpt from the discussion. You can watch the full video at: tmm.txp.to/covid19video

Stephanie Sutton: To start with, I'll ask our panelists to introduce themselves and provide an early glimpse of the pandemic impact.

Nigel Langley: I'm the global technologies director for the pharma solutions business of BASF. Like everybody, I've had to adapt to a new way of working – at home, and virtually. As I usually travel a lot, this has been quite challenging, and it was especially hard at the beginning. I miss visiting customers and I miss going to conferences. That said, I think I've coped quite well with the new digital working culture, although life has been quite one dimensional for my family and myself, especially in lockdown.

Bruce Levine: My background is as a cellular immunologist, and I am the founding director of the cell and gene manufacturing facility at the University of Pennsylvania. I'm currently serving as the president of the International Society for Cell and Gene Therapy (ISCT). The most immediate impact of COVID-19 has been on the opportunity to meet, interact, and network with colleagues. I also used to have quite a robust travel schedule, but now I have a layer of dust on my passport and have been connecting in virtual settings. We are able to view scientific and medical conference presentations (some of them are better at facilitating than others), but it's still the spontaneous in-person networking – being introduced to someone, being able to brainstorm with people – that has been impacted.

Cornell Stamoran: I am head of strategy for Catalent, and founder and co-chair of our Applied Drug Delivery Institute. I have also been working from home – and I've learned a couple of things. First and foremost, I need to be more intentional about reaching out to stay connected to people in my network, whom I would normally encounter at conferences and other places – as the other panelists have mentioned. Keeping those relationships active and vibrant takes extra work.

Miguel Forte: I'm the CEO of Bone Therapeutics, which is a cell therapy company developing mesenchymal stem cell approaches, primarily for orthopedics. COVID-19 is keeping us on our toes and making sure that we deliver the best of ourselves. It has been challenging from both a personal and professional point of view. To add a personal flavor, a couple of my children were PCR positive. On the professional side, we've been able to manage ongoing activities by working primarily from home but still maintaining production. We can exchange information still, but it's much more difficult to exchange emotions and to engage person-to-person.

Bruce mentioned before that, at a lot of the meetings – even this one, we can still exchange information, but it would be more lively and engaging if we were on a stage and directly interacting with the audience. We have to do what we currently have to do, but let's not forget how we did it before. Let's aim to be doing it again. In the meantime, we need to keep businesses running, keep the activity running, and focus on delivering value for patients.

Sutton: Miguel and Bruce, you both work in the regenerative medicine space. How has this sector fared during the pandemic? How have your institutes and the ISCT coped?

Levine: I can provide the perspective from an academic medical center. What's been affected most are the research laboratories. At the first peak, the university ordered a shutdown of all research laboratories. There was also a decrease in ambulatory visits and optional surgeries to make room for an expected surge of COVID-19 patients.

There was also an effect on enrolment of clinical trials. Patients either deferred or didn't want to come in. And principal investigators didn't want to continue enrolment if they weren't sure if patients would complete the screening, show up for the administration of the agent, or make follow up visits. But I have been told that commercial T cell therapies were fortunately unaffected.

With regards to the ISCT, we had to make a very rapid decision and pivot, because our meeting was scheduled to be in Paris at the end of May 2020. We identified a platform, and totally reconfigured our meeting from a four-day to a two-day virtual meeting. It was a learning experience! We received very positive feedback, but again some of the networking isn't what it would have been live in person in Paris.

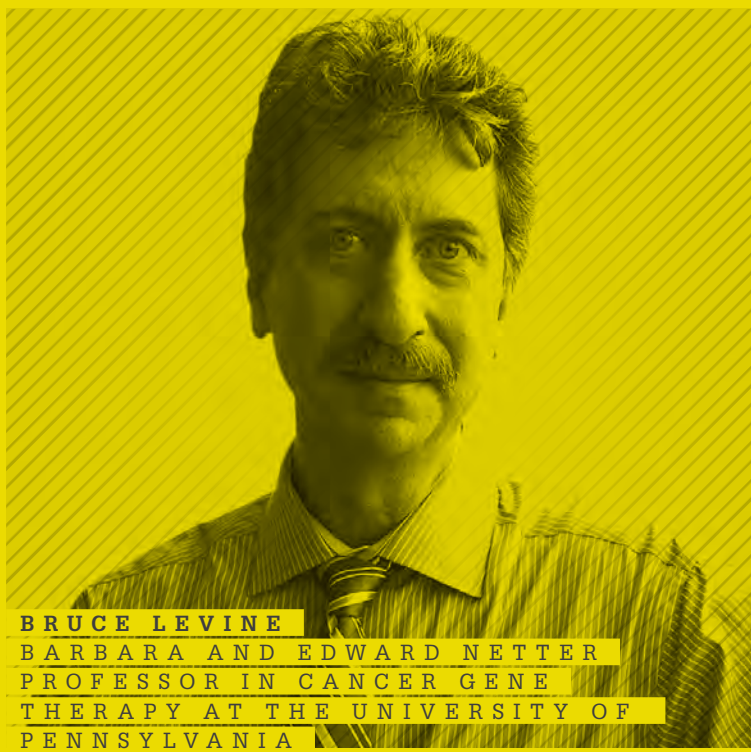
Forte: I chaired the ISCT commercialization committee up until our virtual annual meeting. It is an important forum where we

Meet the Experts

NIGEL LANGLEY
GLOBAL TECHNOLOGY DIRECTOR, BASF PHARMA SOLUTIONS

MIGUEL FORTE
CEO OF BONE THERAPEUTICS AND VISITING PROFESSOR AT THE LISBON UNIVERSITY IN PORTUGAL

CORNELL STAMORAN
VICE PRESIDENT, STRATEGY AND CORPORATE DEVELOPMENT, CATALENT PHARMA SOLUTIONS



BRUCE LEVINE
BARBARA AND EDWARD NETTER PROFESSOR IN CANCER GENE THERAPY AT THE UNIVERSITY OF PENNSYLVANIA

> *"Hospitals had been devoted entirely to managing COVID-19 and so we had to stop our company's studies."*

normally gather to exchange information. This time, we took the opportunity to exchange information about COVID-19, the challenges we were facing, and how to manage. Interestingly, we used to do the commercialization committee meetings on the phone. We now do them on video. In a way, the creeping of this technology is now becoming standard on all distance meetings – that is a plus.

What became really challenging were the activities dependent on interaction with others face to face; for instance, clinical trials. Hospitals had been devoted entirely to managing COVID-19 and so we had to stop our company's studies. There has also been an impact on the health system. Because patients were not going to hospital, there are published articles on increased heart conditions and reduction on identifying new oncology patients. We're seeing side effects on the overall population in terms of other diseases because of the pandemic.

We also had another challenge because we were producing live cells for our products. We closed our research and stopped the animal studies, but we couldn't stop production. We were able to do shifts by implementing social distancing and protective measures, but all of this required a lot of adaptation and communication in our business.

Sutton: Cornell and Nigel, how have your individual companies been affected by the pandemic?

Stamoran: Just to connect to the last question, part of our offerings and our manufacturing network includes gene therapy and manufacturing in viral vector production. So, on the regenerative medicine side, we have continued providing clinical supply – and continue to do so now. We also hosted a live FDA inspection in June 2020, which may have been one of their first field inspections of the timeframe.

First and foremost, keeping our employees safe was the main priority, but many of our facilities produce essential medicines. We continued to operate. We looked after the people essential to manufacturing or operations, but everybody else transitioned to working from home. We also set up a task force to figure out our operating policies and approaches. And that's been very successful and continues to operate, led by a senior executive. Focusing on employee safety and on maintaining product supply for patients has been our focus.

I am also involved with the Controlled Release Society. Like the ISCT, we also had to take a conference that was a live, global annual meeting and convert it to a virtual session, which was a very interesting learning experience.

Langley: The number one priority for BASF has also been the safety and wellbeing of all its employees, but also to keep production running. We didn't want to let down the industry in that respect, and I think that mission has really helped motivate the whole team. We also initiated a global COVID-19 task force. The purpose of the exercise was to assess the activity in the industry. Companies were repurposing drugs for COVID-19 therapy, developing antibody treatments, and, of course, developing new vaccines. We wanted to anticipate potential increases in demands for some of our ingredients, so that we could meet those demands. I think that task force was very successfully run. It was pretty frightening because at the beginning there were so many things that were being considered globally, and we were trying to tie that all together and understand it better. But it was a really good opportunity for us to focus on our customer needs in a much more concerted way.

Sutton: I'll also add that there were big challenges in keeping supply chains running and making sure patients were getting their medicines there were less flights and less opportunities to transport products around the globe…

Langley: That's right. The other thing to consider is the resulting shortages. It was mentioned that some clinical trials were either being delayed or stopped, and the concern we were seeing was whether suppliers could keep pace with the needs of the whole industry with the uptake of COVID-19 cases and potential therapies for the disease.

We have a very large employee base – about 120,000 people – and it was initially challenging to set up so many employees with a home base and internet connectivity – and then keep those people connected and motivated. We had to work harder to communicate with people, just to check to see whether they

were doing OK. One of the keys of leadership through a crisis or change is that you have to keep communicating and find more time for people. Connecting the teams with virtual happy hours and even virtual cooking sessions helped people socialize a little.

I'm also involved in the IPEC association and we've had virtual happy hours where we weren't talking about anything to do with the association – just trying to connect with people on a social level to keep the contact going. Things have improved since those early days, but we're not out of this yet.

Stamoran: From a supply chain standpoint, we reviewed our customers' product forecasts and needs early on. We reached out to their/our vendors for API or other key components to make sure we had adequate visibility for inventory for the production needed for an extended period, so we wouldn't disrupt product supply.

And at the same time, we were also doing significant expansions through our operational network, including some that are relevant to providing fill-finish capabilities for vaccines and other things. We've also been working on the construction and the equipment side to make sure these things happen on schedule or faster than originally planned to make sure we can provide availability for our customers.

Levine: On the supply chain side for the regenerative medicine sector, many companies depend on CDMOs for viral vector manufacturing and for manufacturing cell or gene therapies. I wonder and worry about the impact of vaccine manufacturing that may be going on at the CDMOs and how this will affect the timelines of companies in the regenerative medicine space.

Stamoran: In many respects, the cGMP capacity for gene therapy is based in dedicated suites – usually for the companies involved. Because of that, those dedicated suites would remain dedicated to those customers and their products, and any transfection for viral vector-based vaccines would likely happen in other capacity, unless it was one of the same companies that wanted a trade-off between a non-vaccine based viral vector product and a vaccine.

At least that's my answer based on what I've seen and what I'm familiar with. If we're talking about development capabilities or other things, there could be some constraints.

Forte: We saw quite a bit of demand for operators and space as vaccine activity ramped up. It did not necessarily impact us, but we clearly saw it around us. There are only so many hands available for certain jobs...

"We have also been thinking a lot more about employees' mental health."

We had some challenges managing our studies and the clinical trial supplies to those studies during the first peak of disruption, but as we went back reinitiating those studies and back to some activity, namely in terms of flight and flow, we were able to normalize. We actually lost some material in one of the sites because of this; clearly, there was an impact, but it was a manageable impact. But if we translate our experience to the rest of the industry, then there is clearly an accumulated impact.

Sutton: When it comes to leadership, what do you think have been the biggest challenges?

Levine: I'll start with a couple of personal challenges. In the summer, we had two severe storms, which knocked out the power to our house for two and half days each time. You can't very well do networking by video conference with no power! We solved that problem by installing a home generator. But in terms of ISCT, what I've tried to do is to have virtual networking in various regions.

ISCT is a global society active in North America, Europe, Australia and New Zealand, Asia, and South and Central America regions. I have requested to sit in on executive meetings with the leadership of each of those regions to stay in touch. We're going to be facilitating region-to-region interaction. In my communications to the society, I've also made a point of increasing my activity on social media. One of the bright spots of having these virtual interactions and virtual meetings, is the increase in democratization – and that's going to outlast this pandemic.

If we'd had an in-person meeting in Paris, there are people around the world that would not have been able to afford the travel and accommodations. Our 2020 virtual meeting was a truly global meeting where no one region had more than 50 percent attendance. I think we had much more attendance from China, India, and South and Central America than we would have for an in-person meeting.

That's an opportunity. The challenge is to maintain the same level of engagement in the future.

Langley: We've been using web tools to get a "pulse check" of people. It is quite challenging to make connections, but I think we need to use all of the tools that are available. There are many different ways to connect.

As Bruce says, one of the positive things to come from the tools and technology is that they will make us more inclusive and offer better representation for all regions. And I agree that will continue once we get back to the pre-COVID-19 normal. I think there probably will be a hybrid way of communicating in the future.

Stamoran: I would add from Catalent's perspective – and it's not just my own experience, but that of our leadership team – that internal communication has been important to keep our employees informed. We've gone to a model where certain senior leaders have weekly or bi-weekly virtual town halls. Second, I think it is becoming important to show the personal side of leaders. This can be harder to get through on some of these platforms, but it is also important. Simply reaching out to connect to direct reports, for example, or other people in the organization with more regularity than a normal busy schedule would usually permit has also been useful. In short, "over communication" I think has been very important for us.

Importantly, we have also been thinking a lot more about employees' mental health, including bringing in outside experts for some sessions – whether as part of our town halls or for other special sessions. It is important to think about how you manage mental health in situations like this.

Forte: I agree. The important thing is to maintain communication; everybody found themselves at home with challenges, including managing personal issues, such as children and family, and being disconnected with colleagues.

We implemented several changes. For example, the leadership team met every day during the lockdown and we would review the situation and have a casual chat – to build team spirit and keep the flow of information going. We had virtual town halls, too. But the impromptu meetings were missing – when you bump into someone to pick up your coffee and you talk about a project.

And we've also continued to have discussions with potential partners. In short, we're making the business run, but we're not able to replicate full interaction – and I think that may impact subtle areas, like building confidence. We have to work harder and we have to think twice about our connections. If you overcome the challenges, you can achieve – at the very least – a significant proportion of your business needs while at home.

In short, it is possible to be successful at a distance!

Capturing Value in Changing Times

The increasing complexity of biologics raises significant manufacturing challenges – not least regarding cost control and downstream purification. Thermo Fisher Scientific's answer? To boost capture efficiency with a scalable, broadly applicable platform technology called CaptureSelect™.

Laurens Sierkstra (Business Segment Leader, CaptureSelect Affinity Products) has been involved in CaptureSelect technology from the beginning and has almost 25 years' experience with the technology.

Pim Hermans (Manager, CaptureSelect Ligand Discovery) also worked on CaptureSelect technology during its genesis and today continues to liaise closely with clients to develop the ideal affinity resins for their needs.

Innovative biotherapeutics promise to more fully meet patient needs, but only if manufactured at appropriate cost and quality. Unfortunately, standard purification processes tend to be incompatible with advanced biologics. This mismatch adds time and expense to biotherapeutics development, as manufacturers often must develop a new process using inefficient capture systems. Fortunately, there is a better way. Imagine adopting an affinity resin system that could be customized for nearly any biologic – and rapidly scaled up to cGMP manufacture. We asked the Thermo Fisher Scientific's experts to tell us more about CaptureSelect affinity resins.

What changes have you seen in biologics manufacturing?

Laurens Sierkstra: Back in 2003, everybody focused on standard monoclonal antibodies purified with Protein A. In fact, the original business plan for the CaptureSelect technology began its life as a direct competitor for Protein A. But we immediately found that our customers wanted to process molecules for which Protein A was unsuitable, so we developed purification products that customers needed – resins for recombinant proteins, non-standard antibodies, gene therapy vectors, and other innovative biologics.

Pim Hermans: Discovering that customers were moving to biologics incompatible with Protein A was a real eye-opener for us – and this shift in the biologics landscape continues today. Fifteen years ago, customers might have wanted to purify Factor VIII; now they want to purify exosomes, viral vectors, or hard-to-process antibody fragments, while avoiding co-purification of light chains. Clinical pipelines reflect this evolution. Back then, over 90 percent of biologics entering the clinic were monoclonals; today, 25–30 percent comprise entities such as viral vectors, cell therapies, bispecific proteins, antibody fragments, and Fc fusion proteins.

Have other aspects – for example, timelines – also become more challenging?

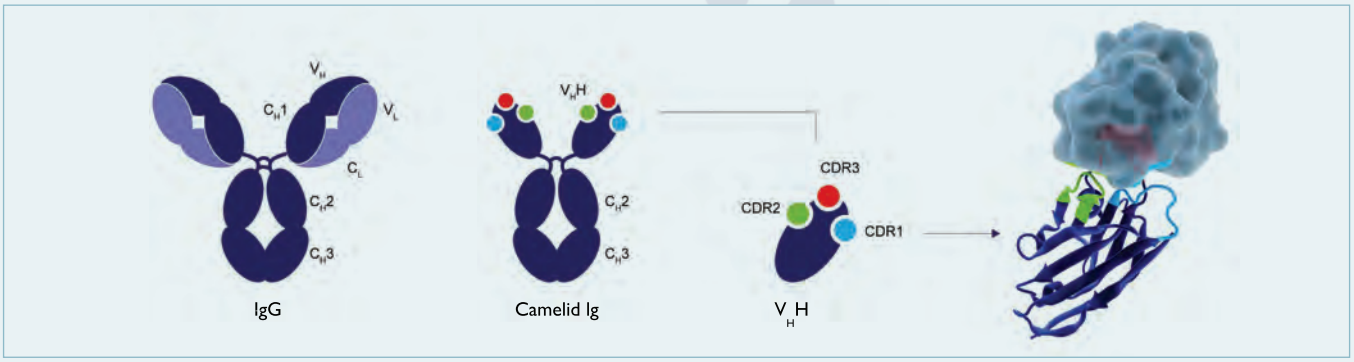
LS: Well, manufacturers have always wanted to get to the clinic as fast as possible! Fortunately, the CaptureSelect platform has time advantages as it can purify virtually any biologic without needing to develop a whole process from scratch. Just as manufacturers use Protein A and polishing to purify standard monoclonal antibodies, CaptureSelect is a standardized platform for purifying biologics that Protein A cannot accommodate. Thus, CaptureSelect accelerates processes by reducing downstream complexity.

PH: Notably, the technology isn't just for non-antibody products – it also meets antibody purification needs that Protein A cannot address. For example, we can direct ligand specificity to precise FAb or Fc domains, thus enriching for advantageous properties.

What makes CaptureSelect unique?

LS: Firstly, the technology works through antibody-based selectivity, so we can develop an affinity resin for virtually any biologic – indeed, we have never failed to make a purification system for a proteinaceous molecule. Others have tried to make antibody-based affinity resins, but conventional antibodies are somewhat unstable, expensive to produce, and difficult to upscale. CaptureSelect, however, uses single domains from antibody heavy chains: these are robust and compatible with large-scale manufacture. And that's why they are ideal for affinity resins intended for biotherapeutics manufacture.

Secondly, CaptureSelect is highly efficient. Remember, biologics must be manufactured at an acceptable cost-of-goods, and this requires high yield. Reaching the clinic quickly with an inefficient process only results in a cost-of-goods disadvantage compared with a manufacturer who has a more efficient



CaptureSelect technology is based on the variable domain of Camelid heavy-chain only antibodies (single domain or V_HH fragment). In contrast to conventional IgG molecules, camelid antibodies are devoid of light chains but they maintain the same level of specificity. V_HH fragments are exceptionally small antigen binding fragments (~15kD) which allows binding to alternative epitopes, leading to a unique affinity profile. Compared to standard antibodies, these fragments are very robust and can withstand the harsh conditions used during chromatography.

process. Our capture step provides increased yields, partly because of its intrinsic efficiency and partly because we can design our resins to preferentially select active (rather than inactive) forms of the biologic. Thus, CaptureSelect provides manufacturers not only with high yield but also with a high proportion of functionality.

Thirdly, CaptureSelect reduces the number of purification steps, which saves time and cost. And finally, fewer columns, in turn, reduces the clean-room footprint, and increases efficiency of clean-room utilization. Together, these four attributes give manufacturers a valuable cost-of-goods advantage.

How do you help manufacturers who are struggling with biologics purification?

LS: Our *modus operandi* is highly collaborative and customized. Put simply, we begin by understanding the client's problem, and then we develop a program to solve that specific issue. Often – due to CaptureSelect's high selectivity – we can suggest solutions that manufacturers have not even considered.

PH: Usually, manufacturers assess available purification products and then design a process that fits those products. But we do it the other way around; we work with the client to identify the ideal process, and then we make a resin that fits the ideal. Conventional purification technologies can't provide customized resins that perfectly match the needs of a given client.

How else do you differ from other providers of purification technology?

LS: Firstly, we are a one-stop shop: we can take clients all the way from initial concept to a fully developed affinity resin compatible with GMP manufacture. We have the ability to both produce a ligand of interest and make a scalable, GMP-compliant affinity resin. And that requires excellent infrastructure and expertise. We were fortunate in that we had the right assets from the very beginning. Many companies with good ligand identification technologies have failed because they could not turn ligands into products that can be manufactured at appropriate quality criteria and scale – finding something that binds a particular molecule is the easy part! But with CaptureSelect, we can guarantee development of a GMP-compliant affinity resin within about ten months, scalable from ~1 mL to ~200 liters as necessary. In brief, manufacturers need certainty regarding scale, price and timescale, and we provide all three.

If we only offered ligand discovery technology, and not the ability to make scalable, GMP-compliant affinity resins, we would have to license the affinity ligands to clients. Instead, our model is to make and sell affinity resins for clinical trials and cGMP manufacturing.

How are you positioned to meet future challenges?

LS: Biologics will continue to become more complex; advanced Fc fusions, fusion proteins, new gene therapy vectors (such as exosomes or red blood cells), or allogeneic cell therapies are key trends. But we too will evolve; we are always adapting the CaptureSelect technology to address more complex products by working closely with customers.

PH: We ensure that we keep track of market developments. Years ago, we realized that adeno-associated virus vectors would become important, and developed products for that niche. Today, we are doing likewise for exosome technology. The goal is always to give customers excellent downstream processing tools – while staying ahead of the technology curve.

Better Methods for Better Vaccines

When it comes to virus and viral protein analysis, settling for "gold-standard methods" isn't good enough. To navigate the roadblocks ahead of successful vaccine development, we must dig deep into the analytical armamentarium.

By Ewoud van Tricht, Senior Scientist, Analytical Development, Janssen Vaccines and Prevention, Leiden, the Netherlands

Since Jenner first inoculated a young volunteer with his magic cure for smallpox in 1797, the power of vaccination in preventing infection and eradicating infectious diseases has surely been realized. This year, the spotlight has once again turned towards vaccines, as both scientists and the general public cling to somewhat remote hopes of a return to "normal." Before now, the fastest we have ever managed to produce a vaccine in response to an outbreak was for Ebola – and that took five years to achieve full licensure. The rulebook may have been ripped up, but it is perhaps now more vital than ever that the entire vaccine development process is as efficient, precise, and cost-effective as possible. Developing the right analytical methods using the best tools for the job has an absolutely key role to play.

An insight into adenovirus vector development

Ordinarily, our work at Janssen Vaccines and Prevention – a pharmaceutical company of Johnson and Johnson – is focused on the research and development of vaccine products against infectious diseases like Ebola, HIV, and RSV. So it should come as no surprise that our attention has turned to COVID-19 this past year. Typically, we look at developing modified adenoviruses for intracellular delivery of DNA. Our Advac® technology allows the production of adenovirus vectors in which the viral DNA can be modified to encode an immunogen of interest. In the case of our Ebola vaccine, this is a particular viral glycoprotein – upon vaccination, a protective host immune response against the virus is achieved.

The same Advac® technology has been used across our COVID-19, Zika, RSV, and HIV vaccine candidates. Overall, more than 100,000 people have been immunized with vaccines based on Advac® technology, which demonstrates the safety of our platform. Such technology platforms make it possible to quickly develop new candidate vaccines and then produce the optimal ones on a larger scale. Our Zika, RSV, and HIV vaccines are currently in phase 2 or phase 3 clinical trials. On July 22, the first healthy volunteer was injected with our COVID-19 candidate vaccine; interim results from the phase 1/2a clinical study showed that the safety profile and immunogenicity after a single vaccination were supportive of further development. In September, the first patient was dosed in a phase 3 clinical trial to evaluate safety and efficacy of the vaccine in up to 60,000

"The fastest we have ever managed to produce a vaccine in response to an outbreak was for Ebola – and that took five years to achieve full licensure."

adults worldwide. In addition to this single-dose regimen ENSEMBLE study, as of November, Janssen initiated a two-dose regimen ENSEMBLE 2 trial which will study the safety and efficacy of the vaccine in a further 30,000 participants . Though we are accelerating vaccine development at the moment, safety and efficacy are never compromised.

My work within the analytical assays (AA) group has been to improve the methods used for analysis of viruses and viral proteins throughout the entire vaccine production process. Our aim was to extend the analytical toolbox for the characterization of vaccine products, helping to overcome the challenges associated with traditional methods. Not only have we developed three new analytical techniques for vaccine development in recent years, we have also implemented a systematic analytical quality by design (AQbD) approach to ensure the right method is developed for the right purpose.

The true value of analysis

The focus of our AA group is on developing, validating, and transferring methods for different groups within the organization – namely, Process Development, Formulation Development, Product Characterization and the Production Plant. Each department can request method development, validation, and transfer through an analytical target profile (ATP). The purpose of the ATP is to give clear direction to the AA group –

Meet Ewoud

An analytical chemist with over 14 years' experience in the pharmaceutical industry, Ewoud started working for Solvay Pharmaceuticals in 2006 after finishing his MBO (middle-level applied education – the equivalent of junior college education in the US), but quickly realized he needed at least a Bachelor's to pursue his dream of becoming an analytical method developer. He decided to take on part-time study alongside his fulltime job, and between 2006 and 2020 he has completed a Bachelor's, Master's, and PhD in analytical chemistry while working for both Abbott Healthcare (2006-2010) and Janssen Vaccines and Prevention (2011-2020).

During this time, he's held many different positions across a broad range of departments. He started working at Janssen Vaccines and Prevention (previously Crucell) as a senior technician in Quality Control back in 2011. Now, he is a senior scientist in the AA department. AA is a group of 25 people within the wider Analytical Development department responsible for the development, validation, and transfer of analytical methods for the analysis of vaccines products. The focus of this group is on developing analytical methods with separation technologies (capillary electrophoresis, LC, MS) and physical characterization technologies (field flow fractionation, analytical ultracentrifugation). Not only do they analyze the main component of vaccine products – typically a virus or a protein – but also the additives and impurities respectively created during the production process or added to the final formulation.

For the last few years Ewoud has been focusing on statistical analysis, dossier writing, and analytical quality by design (AQbD).

it should capture the purpose of the test method, the method requirements, and the reportable results. Importantly, it is defined upfront and agreed between the method developer and the person who requested it.

Clearly, the requirements of any analytical method depend on what it will be used for. For example, quality control methods must be validated, straightforward, robust and reliable. On the other hand, the typical requirements for a process optimization method are a rapid time to result (so as not to delay the production process) and large sample throughput.

We develop analytical methods for a diverse set of purposes:

- Release of material for clinical use – to assure safety and quality of the product
- Stability studies – to assure quality of the product throughout its lifecycle
- Product knowledge – for in-depth characterization
- Process optimization – for example, yield or formulation

After a method has been developed, we then look at its transfer and validation. Analytical methods routinely used for release of clinical material or stability

studies will be transferred to the quality control laboratory, which operates under good manufacturing practices (GMP) regulations with validated analytical methods. The methods routinely used for process optimization are transferred to the Biophysics and Process Analytics group, which analyzes up to 30,000 samples per year and is specialized in supporting process and formulation development.

Complex and new analytical methods – or methods that are only used for a single study – are not transferred. In these cases, analysis is performed within our own AA group by those who developed the methods.

"Viruses are best adapted to surviving and efficiently replicating in the ideal host environment."

A path fraught with difficulty

The nature of viruses throws up a number of hurdles that must be navigated by analytical method development teams. First of all, the instability of viruses outside the host environment makes it particularly difficult to select the right technology for the quantification of viruses or viral proteins. Viruses are best adapted to surviving and efficiently replicating in the ideal host environment. Outside the host, however, viruses are more easily affected by pH, salt, and temperature changes, which can cause degradation or aggregation. Many technologies require a complex sample treatment to infect cells, to achieve antibody-antigen complexes, to reduce viruses into proteins, or to provide cleanup of the complex sample matrix of viral products (like a vaccine). In addition, many analytical methods require separation conditions – such as organic solvents, surfactants, ion pairing agents or silica-based stationary phases – which may be unfavorable for viruses.

Secondly, the adsorption of viruses and viral proteins can pose a serious challenge; viruses and proteins tend to adsorb to sample vials and instrument parts, such as the injector, valves, tubing, columns, and capillaries.

Finally, the matrix of the crude viral product is typically highly complex and could contain host cell DNA, proteins, cell debris, salts, and surfactants in different ratios and amounts. There is a distinct challenge in separating the virus from these matrix components and preventing their interference with the analytical measurements.

All of these challenges must be carefully considered in analytical method development to ensure successful analysis of viruses and viral proteins.

A three-pronged attack

To overcome the issues typically observed with traditional methods, such as low throughput, limited sensitivity, and matrix incompatibility, our AA team developed three new analytical methods – all previously published – for the analysis of viruses and viral proteins throughout the vaccine production process.

The first is a capillary gel electrophoresis (CGE) method for the quantification of influenza virus proteins and virosomes (virus-like particles) (1). In comparison to single radial immunodiffusion (SRID), RP-HPLC, and SDS-PAGE, the CGE method confers some key advantages. Using the CGE method, we found it was possible to determine three other major proteins in addition to the main influenza protein: HA fragment 2, matrix protein, and nuclear protein. Although CGE could reproducibly separate all four major proteins, quantification was not possible because of the lack of (commercial) reference standards. However, the fingerprint of the CGE electropherogram of the four proteins was specific and could be used to identify the virus strain. The precision and accuracy of CGE was similar to SRID, but the total analysis time for the CGE method was much shorter, allowing analysis of 100 samples in four days instead of ten days for SRID.

The second method we developed uses RP-UHPLC-UV for quantitative adenovirus protein profiling (2). Using our method, all adenovirus proteins could be baseline separated within 17 minutes on a C4 column (300 Å, 1.7 µm, 2.1 x 150 mm) with a water-acetonitrile gradient containing 0.175 percent w/v TFA as the ion-pairing agent. The adenovirus test samples were directly injected into the UHPLC system without the need for sample pre-treatment and the viruses dissociated into the viral proteins upon contact with the acetonitrile/water mobile phase. Our RP-UHPLC-UV method was successfully validated for two purposes: confirmation of the identity of the test sample and detection of protein modifications or degradation products of the adenovirus vector. The method can detect changes in the adenovirus protein composition as a result of thermal or oxidative stress, as well as impurities, such as protein degradants, leachables, and host cell proteins. For RP-UHPLC-UV, the sample throughput was increased by a factor of 6 by reducing the run time from 130 min to 17 min. With the improved run time, up to 50 samples could be run in a single sequence without impacting sample stability.

Thirdly, we also developed a patented (3) capillary zone electrophoresis (CZE) method for precise and accurate analysis of adenovirus samples containing variable

amounts of cell debris, cell lysate, host cell proteins, host cell DNA, salts, detergents, and additives (4,5). The CZE method offers an alternative that circumvents issues with current methods – qPCR and anion exchange (AE)-HPLC. Intact adenoviruses from upstream (USP) and downstream processing DSP can be directly analyzed by CZE and only samples with high amounts of host cell DNA require a simple benzonase sample pre-treatment. The CZE method has been validated for the quantification of adenovirus throughout the production process. A great advantage of CZE is its compatibility with USP and DSP samples – and their variable matrices. In contrast, AE-HPLC is only suitable for purified adenovirus samples. And with a run time of only 3 min, CZE allows the analysis of 30 samples within 4 hours compared with 3 days by qPCR! Precision and accuracy is also significantly improved compared with AE-HPLC and qPCR. In particular, the improved precision of the CZE method makes it possible to improve the formulation or production process, as smaller process improvements can be detected with adequate statistical confidence.

How we got there: analytical quality by design

As part of a continuous improvement project alongside this work, we mapped the process of method development in detail based on input from scientists (6,7). We learned that the complexity of the process and a lack of standardization can result in long lead times for method development and lack of robustness in resulting methods. In short, redevelopment and troubleshooting were too common.

Additionally, for many of the methods the purpose was not clearly defined upfront and that led to improper use or implementation. Analytical method development was typically technology/method-driven rather than product/analyte-driven; methods were often selected because the technique was commonly used, in-house experience was available, or the technique was "at hand." An assessment to verify whether the selected method is indeed the best choice for the specific product and analyte was mostly lacking. Finally – and especially for complex vaccine products – the matrix and the analyte did not typically match up with the analytical method conditions used.

Put another way, concessions were being made in favor of the analytical technique, but were not optimal for the tested product. The final developed method only produced the "best result" that could be obtained within the restrictions of the analytical method rather than the best result from a given sample. As a result, complex and extensive sample treatments were introduced, and a compromise of suboptimal conditions were being selected.

Based on this information, we decided to implement an analytical quality by design (AQbD) approach when it came to the method development outlined earlier. AQbD consists of six defined steps:

- Definition of the analytical target profile (ATP) describing the objective of the test and the requirements
- Technology selection
- Definition of the critical method parameters by a criticality (risk) assessment
- Method development by design of experiments (DOE)
- Method validation and control strategy
- Method maintenance or method life cycle management

The first challenge we encountered was the lack of guidelines describing the application of AQbD in practice. Typically, only the vision, rationale and a high-level approach to AQbD are described in the literature, meaning tailor-made tools had to be created and developed for most of the AQbD steps. We have now successfully developed and implemented tools for each of the AQbD steps, and we have created training material and courses for scientists in analytical development.

The AQbD process overcomes the issues associated with a lack of standardization. AQbD offers a structured, risk-based approach for method development. The knowledge and decisions made are captured and can be shared and reused. As a result, training of new operators is more focused and there are fewer invalid analyses when the method is applied to real samples.

After all steps of AQbD were applied, and a comparison of six analytical methodologies was carried out, CZE was selected as the method of choice for adenovirus analysis.

Change is never easy, but it is possible: a CZE success story

Despite the clear advantages, it took years for our CZE method to be implemented within the organization. In particular, we had to overcome prejudice with regards to the robustness of capillary electrophoresis instruments and a general belief that CE could never be run in a QC environment. We sent our colleagues to theoretical CE training to get the background knowledge they needed and our team gave over 50 presentations about the possibilities and versatility of CE. At last, we convinced them (with the data to back it up) that CZE could indeed compete with the current technologies.

Two years after finishing the method development, CZE was to be qualified in a QCD laboratory for their in-process control test of virus particle concentration during the production process. The virus concentration could be reported within 2 hours – it had taken 1 to 3 days with the previous techniques. An extensive system suitability test and trending of critical data from the analytical method assured them that, after 525 analytical runs (over two years),

the precision and bias of the method still adhered to the original requirements from the analytical target profile. Continuous improvement of the CZE test method after implementation and training of the operators proved key to successful daily operation. In 99.4 percent of cases, the sample data could be generated on the same day adhering to ATP requirements. For other techniques, the data was typically reported on the same day in 75 to 95 percent of cases.

Since then, we have bought eight CE instruments, trained over 20 operators, implemented CZE at six locations, run more than 15,000 samples and we now routinely use three CZE applications.

What does all this mean for COVID-19?

Further to these benefits, the new analytical technologies we developed have also allowed for quick adaptation and implementation with our new COVID-19 vaccine program. I am the responsible scientist for the Ebola vaccine project, but this year I have also been brought in as the subject matter expert for the CZE method that is used for in-process control testing of our COVID-19 vaccine. I am also the responsible scientist for the method used for aggregation determination for characterization of the vaccine product, and have supported the COVID-19 dossier by reviewing the sections describing our analytical release and stability methods.

Our group had two main analytical activities when COVID-19 was announced as our new candidate-vaccine. The main advantage of many of the analytical methods developed in our team is that they can be used for the accurate and precise determination of any type of adenovirus-associated vaccine, such as COVID-19 or Ebola. Our job was to make sure that all these analytical methods were ready to use before COVID-19 production started – thankfully, our platform methods significantly reduce the amount of development and validation work that is needed for a new project. Once all analytical methods used for the characterization of the vaccine were shown to be suitable for our COVID-19 program, they were successfully used to characterize the vaccine batches currently in clinic.

I am extremely grateful and proud that our AQbD approach has finally offered a standardized approach for method development, validation, and implementation for virus analysis. It's great to know that our organization is now ready for upcoming guidelines (ICH Q14 and USP <1220>) that will recommend using the AQbD approach. Being able to align different development groups and scientists has fast-tracked our vaccine development program – and we've also ensured method development knowledge is captured, reusable, and shareable. Our approach to analysis has not only saved us time and money, it has also provided more information than traditional methods. It has allowed for more efficient production processes, higher quality vaccines, a better understanding of these vaccines, and ultimately made them more affordable.

Please see references online at: http://tas.txp.to/BetterMethodsBetterVaccines.
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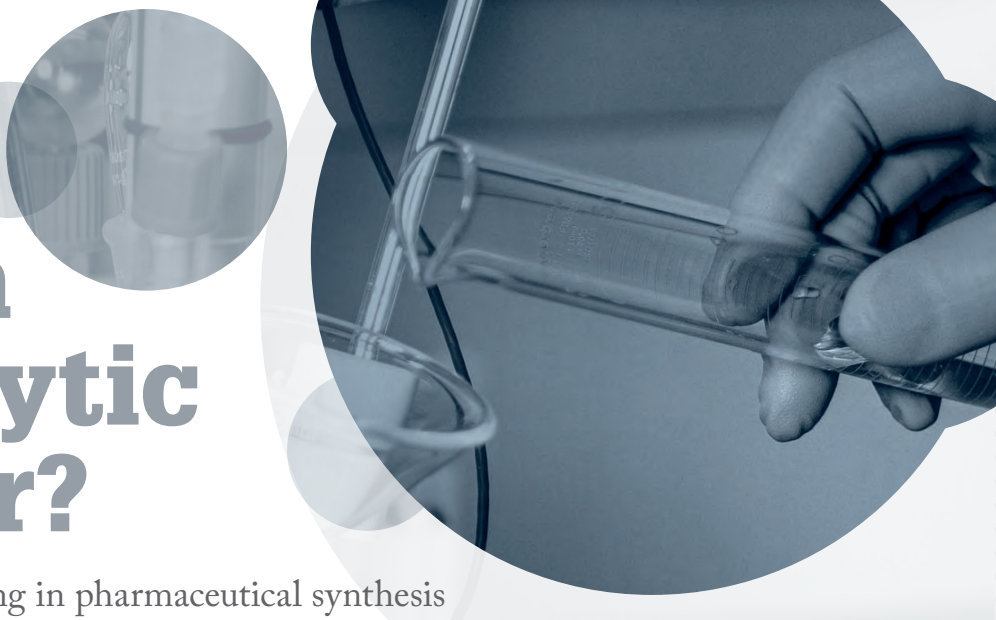

Are You a Bio-Catalytic Converter?

Speed and efficiency are everything in pharmaceutical synthesis – and that's why biocatalysis is an increasingly attractive option

By Alice Dunbabin

The industry continues to face unrelenting demand for faster and more efficient chemical processes. In response, chemists continue to seek new solutions to expand the toolkit. One increasingly important approach in the chemist's toolkit is biocatalysis. Already a well-established methodology, the profile of biocatalysis was further raised in 2018 when Frances H. Arnold won the Nobel Prize in Chemistry for her group's work in the area of directed evolution. In short, they developed novel bioengineering methods that harnessed the principles of evolution to access new biocatalysts in the laboratory. Breakthroughs in this area and others have enabled chemocatalysts to be replaced by biocatalysts in many industrial processes – and they have also opened up new avenues for small molecule transformations in the pharmaceutical industry.

Bio versus chemo

Compared with chemocatalysts, biocatalysts offer many advantages. Many catalytic processes use expensive transition metals to mediate transformations; these are unnecessary with cheaper biocatalysts, which also remove the need for high temperatures and pressures. Chemocatalysts are also often moisture and air sensitive, requiring strictly anhydrous conditions. Biocatalysis, on the other hand, is usually conducted in aqueous media. Put simply, the cost of drug development can be reduced.

Biocatalysts also offer exquisite selectivity. With chemocatalysis, transition metals often require ligands to create a 3D structure that influences the selectivity, which further drives up costs. Biocatalysts have chemo-, regio- and stereo-selectivity built in; they only bind specific substrates in certain conformations to the active site. Also, thanks to their high selectivity, biocatalysts often bypass the need for addition and removal of protecting groups.

Ensuring the safety of reactions is of paramount importance to chemists. In addition to cost savings above, the use of ambient temperatures and pressures, aqueous media (rather than flammable solvents) and avoidance of metals with limited availability, makes biocatalysis a much safer option than chemo-catalyzed routes. In addition, biocatalysts provide an environmentally friendly and more sustainable route for small molecule transformations.

Cheaper? Check. Safer? Check.

Biocatalysts are also non-toxic and biodegradable – and they can be reused multiple times when immobilized on a support. Alongside waste reduction, fewer toxic solvents are required. Lower environmental footprint? Check.

Given the advantages, why are some chemists reluctant to add biocatalysis to their toolkit? The ubiquity and reliability of transition metals and other chemocatalysis approaches certainly give them a head start. But biocatalysis does have one distinct disadvantage: enzyme screening and engineering are not quick processes – although advances in screening technology are being made (see box: Engineering Advances). One example is the use of simple-to-use colorimetric screening assays that reduce the work required to find successful hits by simply changing color when the desired reaction has occurred. In silico modeling of enzyme active sites has also aided enzyme engineering and mutation. By computationally visualizing the interactions between the substrate and the enzyme active site, changes can be made to avoid unfavorable interactions and increase the likelihood of a successful transformation.

Many enzymes require a cofactor to function, which can also pose challenges. Transaminases, for example, require an enzymatic amount of pyridoxal phosphate to covalently bind the substrate, which is straightforward to implement in a process. But there are times where the addition of cofactors can add extra complications to reactions; keto reductases, for example, need NADPH – a cofactor used in anabolic reactions – to function. As this cofactor can

Enzyme Engineering

For drug developers to benefit from biocatalysis, a screening process is needed to find the most suitable enzyme for a reaction. Screening can be done in-house using commercially available kits or outsourced to a specialist company.

Once an enzyme of interest is found, it may need to be engineered to make it fit for purpose. For example, the chosen enzyme may need to be altered to increase its tolerance to heat or organic solvents. Many factors, including temperature, pH, and substrate concentrations, can affect enzymes and their active sites – and all factors must be considered during the engineering phase. As an enzyme's shape is directly related to its function, with the active site complementary to the shape of its specific substrate, the structure can also be modified so that different substrates fit the active site. Advances in this field have allowed many unnatural substrates to be converted, further increasing the applicability of biocatalysts.

The Evergrowing Enzyme Inventory

Some enzyme classes have been extensively studied and are widely available, whereas others are relatively new to the field. Enzymes are named based on the reaction they catalyze and most enzymes can perform their reaction in the forward or reverse direction. For example, lipases catalyze the stereoselective formation or hydrolysis of esters, and are commonly used in the kinetic resolution of racemic alcohols, amines and acids. Other examples include transaminases, which catalyze the formation of chiral amines, and ketoreductases, which perform the stereoselective reduction of ketones and the oxidation of alcohols. The list of enzyme-catalyzed reactions continues to extend as more novel enzymes are discovered, with enzymes such as ene reductases, imine reductases, and nitrilases all now being available. Some enzymes even perform named reactions, such as Baeyer-Villager monooxygenases and Pictet-Spenglerases.

To further extend the scope of biocatalysis, scientists are using metagenomics. By analyzing environmental samples, scientists have been able to discover new and exciting enzymes from all over the world; for example, in deep oceans, arctic ice, and even in the sands of Peru.

be very expensive, it is usually necessary to recycle these cofactors by adding in another enzyme and cosubstrate to the reaction. Fortunately, as the recyclable cofactors are well known, the reactions can be easily adapted to incorporate them.

There can also be challenges relating to the use of biocatalysis during the process development stage; for example, insolubility of the reaction materials in water. Enzymes typically tolerate 10-20 percent of an organic cosolvent, but if this does not provide enough solubility, it is possible to engineer enzymes with higher tolerance for organic solvents.

Finally, at the end of a reaction, emulsions and foaming can be problematic. After all, enzymes are proteins, so they can naturally denature and unfold, resulting in aggregates. Various solutions have been developed to overcome this issue, including the addition of cosolvents and anti-foaming agents.

Taking into account these limitations, choosing a biocatalyst for a process should still be relatively straightforward. After identifying which class of enzyme is able to perform your transformation, a screening kit of that class can be purchased – or the enzyme screening can be outsourced. Once a hit is identified, optimization can be carried out by looking at parameters (such as temperature, pH, and substrate concentration), before moving on to process development and addressing any issues with cofactor recycling or isolation of the product from the aqueous media. During this process, the need for enzyme engineering could also arise to combat problems with enzyme stability, heat or solvent tolerance.

Further afield

Biocatalysis is an evolving success story in the industry. In my view, one of the most important accomplishments using biological catalysts was the development of the anti-diabetic drug, sitagliptin (1). Its manufacture originally used a rhodium-catalyzed process, which required hydrogen pressure during the reaction. This catalyst was then replaced with a transaminase biocatalyst, which provided higher stereoselectivity than the chemical process, along with excellent yields. As well as better productivity, waste was reduced, and the cost decreased as the rare metal was no longer required.

Another recent success was the application of a ketoreductase in the synthesis of the asthma drug montelukast (2). A suitable ketoreductase was obtained through a directed evolution approach, and the reaction was higher yielding with an improved enantiomeric excess.

There are still improvements in the field of biocatalysis that can be made, particularly improving the engineering of enzymes and exploring enzyme cascades. Nature could also teach us more; thousands of enzymes are found in nature, with more being uncovered every day, and we can still learn from the many existing enzyme cascades and pathways to design more elegant processes. And, if cost and efficiency aren't your main drivers, by embracing biocatalysts, we can also shift toward a greener and more sustainable future in drug development.

Alice Dunbabin is Senior Scientist at CatSci Ltd

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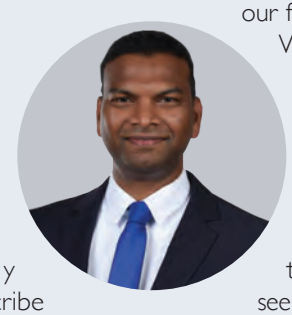
Putting Patients First

Injections are increasingly administered by patients at home, so convenience and useability are essential. Patient perspectives can make a huge difference when designing drug delivery devices that are truly fit for real-world use. And that's why Terumo Pharmaceutical Solutions works so closely with its customers on product design that addresses the resulting patient needs. Here, Anil Busimi, Marketing Director, explains how the company supports its customers – and how a new website will further enrich the customer journey.



What's the Terumo Pharmaceutical Solutions mission and backstory?

In short, we are dedicated to delivering outstanding solutions to the pharma industry and ultimately patients. We like to describe ourselves as proactive innovators – and we feel it's important to create solutions in the context of the larger issues facing medicine – from reducing patient burden to improving safety in support of medical efficiency and improved care.

Like many others, I love working in the pharmaceutical industry because it offers a great opportunity to make a positive difference to people's lives. Our customers in pharma and biotech are working hard to find effective medicines against many diseases to improve quality of life for patients – and we are part of that story. Companies like Terumo play a crucial role in investing all possible resources to strive for drug delivery devices – especially injection devices and accessories – being safe, convenient, and of greater comfort.

As for the backstory, we are part of the Terumo Group – a global healthcare technology leader with almost 100 years of experience and the mission of "Contributing to Society through Healthcare." The company was established in 1921 in Tokyo, and now employs over 25,000 associates across key international markets, delivering a full portfolio of medical and parenteral delivery solutions to more than 160 countries.

What are your views on patient centricity?

In simple words: "The patient is our end user." Everything we do should always take into account the patient and we must always ask if we are improving products for end users. We supply our products to pharma companies, so we rely on our customers to incorporate patient perspectives right from our first interactions on a project. Where possible, we also engage closely with patient groups to fully understand real-world challenges with drug and injection devices. Just recently, our team conducted a research project amongst the hemophilia community to see how safety winged infusion sets are used. Our aim was to gather insights into the daily activities of patients to see how we could improve on the process of administering medication. These important insights will fuel our future innovations and ensure the voice of the patient is embedded in the projects we pursue. It is amazing how even a minor detail in a device design can have such a huge impact.

How do you work with customers to design user-friendly devices?

We pride ourselves on being patient centric in our thinking and customer centric in our actions – meaning that we support our customers in the design and development of patient-centric devices. Generally speaking, our pharma customers have three key drivers: i) ensuring time to market for new drugs, ii) lowering the risk for both during the development and post commercial launch, and iii) lowering total cost of ownership. We must address each of these drivers to ensure a smooth customer journey.

Tackling Today's Challenges

Drug developers face a number of demands and challenges; choosing the right partner and the right drug delivery technologies has never been more important

Challenge 1 – a significant pipeline of injectables and biologic drugs

There are more than 3000 injectable drugs in the pipeline – many of which are sensitive biologic drugs with potential stability challenges. Thus, primary packaging solutions must reduce drug-container interactions throughout the shelf life. In addition, many biologic drugs in the pipeline are targeted towards smaller patient populations, which requires the manufacture of smaller batches even in pre-filled syringes – without compromising on quality. Flex filling lines in combination with ready-to-fill components like PLAJEX is the answer to address this trend.

Our PLAJEX™ ready-to-fill polymer syringes are designed to meet the needs of a wide variety of drug types, including highly sensitive biologic drugs. PLAJEX provides lower interaction with proteins, lower sub-visible particles, and excellent strength and clarity. In addition, the syringes


significantly reduce the drug container interactions, with its silicone oil-free, tungsten-free, and adhesive-free features, as well as an autoclaving process to reduce potential leachables or free radicals.

PLAJEX also applies Terumo's proprietary i-coating™ to the surface of the stopper and it is chemically bonded to the substrate, resulting in a silicone oil-free container for drug products that require lower interactive surfaces.

Challenge 2 – achieving safe, convenient, and painless drug delivery

Prefilled syringes kickstarted a trend that moved injectable drug delivery from hospital to home environments. Today's pharma companies want to make the self-administration of injectables as safe, convenient, and painless as possible. Combining pre-filled syringes with autoinjectors is a popular approach. And it is also possible to combine drug delivery devices with electronics to collect data at the time of administration. For example, we work with external partners to ensure compatibility of PLAJEX with autoinjectors and safety devices so that our customers have an integrated solution.

Considerable efforts have been made to minimize pain when injecting medication. Success has been achieved by reducing the diameter of the needle, but this may raise injectability challenges, especially for viscous formulations. Resistance to flow can be reduced by using a conically-shaped needle with small diameter at the tip and a larger diameter at the bottom. Our Tapered Needle of 34G combines these approaches by achieving similar emptying forces as 30G normal wall needles, even for viscous drug products.

Challenge 3 – increasingly stringent regulatory requirements

Regulators demand that drug manufacturers pay close attention to the safety and efficacy of their delivery devices, and also ask for robust documentation to ensure that no risks stem from the drug delivery device design or manufacturing process. In the EU, the change from Medical Devices Directive (MDD) to Medical Devices Regulation (MDR) may affect how pharma companies think about their devices for example equip them with needle intended to prevent accidental needle stick injuries. Terumo has developed the K-Pack Surshield™ – a hypodermic needle with an integrated sharps protection feature for (pre)-filled syringes.

Challenge 4 – digitalization

The increasing use of digital technologies in the pharma industry – from drug discovery to post-market surveillance – brings positive change. Digital tools incorporated into devices can be used to collect patient data to improve adherence and treatment outcomes. And the move to Industry 4.0 is also encouraging companies to think more about data and process capability. One example is track and trace of medical devices to fully protect patients. In this regard, Terumo offers the K-Pack® II needle, which features color-coded, tamper-evident labels and a 2D-code. It can also be used to implement full 360°camera inspection for optimal packaging processes to facilitate device identification and inventory control. Supporting the customer journey from drug discovery to lifecycle management is crucial. To complement our existing touch points, we plan to introduce additional digital touch points to make the customer journey even more seamless and to help them get the right information when they need it.

Challenge 5 – sustainability and a reduced carbon footprint

Reducing environmental impact is a social responsibility. Terumo has established and applied its proprietary Human×Eco Development Guidelines to product development.

With this approach, we ensure our products have a low carbon footprint and we continue to drive innovations to improve sustainability.

In tune with the industry

At Terumo, we are passionate about solving customers' and end users' problems in the areas of primary packaging, drug delivery devices, and fill and finish. To do this successfully, it is important that we keep in touch with industry trends and challenges and ensure that our products are well-positioned to offer effective solutions.

Why is the 2021 launch of your new website such an important moment – and how will it benefit customers?

Websites are the first place most people go to when they are searching for information. Our new website is designed to give visitors easy access to comprehensive information on all our products and services. Another key advantage for customers is that they can stay in touch with us from across the world! In the current climate, a digital presence is crucial and websites should be simple and easy to navigate.

Modern customers have high expectations at every touchpoint. And we'll continue exploring opportunities to further personalize and enhance our customers' journeys.

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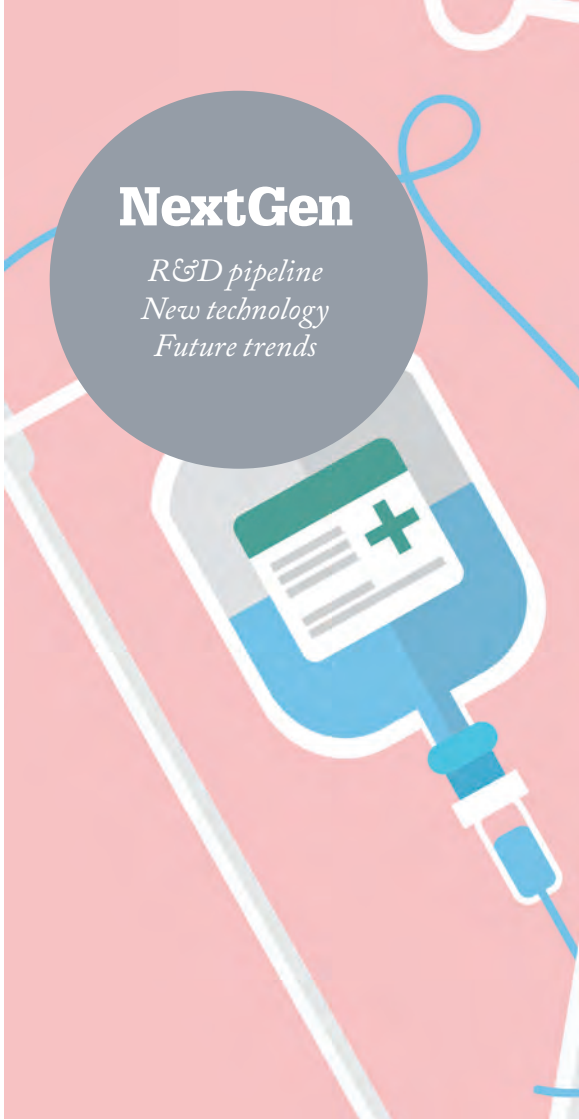

How to Standardize Advanced Therapy Manufacture

Cell and gene therapy manufacturing technologies and methods are advancing rapidly, but can regulators keep up? Given the uniqueness of each product, what will it take to make high standards and best practices a reality across the board?

By James Strachan

Pharmaceutical regulation has evolved from a group of independent and divergent regulators to an increasingly harmonized system, underpinned by international standards-setting bodies (1). The benefits for companies are obvious: no longer having to produce multiple different dossiers for each regulatory environment means faster approvals, allowing for greater patent life and, therefore, greater return on investment.

For both small and large molecules, the trend towards global regulatory harmonization has been taking place for decades. But, in recent years, cell and gene therapies have emerged as a new therapeutic class, with the potential to revolutionize medicine – and give regulators serious headaches. Because of their often complex and unique manufacturing processes, it can be difficult for regulators to agree on clear guidelines – especially given the frantic pace of development.

Here, Michael Lehmicke, Alliance for Regenerative Medicine, and Angela Myers, Merck, scan the global cell and gene therapy regulatory landscape – focusing on the differences between the EU and the US, discussing where the industry is right now, and exploring what needs to change.

What are the central challenges when manufacturing a cell or gene therapy?

Michael Lehmicke: Both cell and gene therapies are facing challenges of scale. Cell therapy manufacturing is still largely a manual process, with complex supply-chain logistics. Some of the analytical procedures are complex and manually intensive too. In the case of gene therapy manufacturing, legacy processes are often not readily scalable, and yields can be quite low. There is a focus now on building capacity (which has continued despite the COVID-19 pandemic), but we also need manufacturing technologies and methods that can be optimized for greater scale (suspension culture systems, alternative producer cell lines, fully automated analytics, and so on).

Angela Myers: Michael is right; the cell and gene therapy industry has only just started on its industrialization journey and, consequently, there are many opportunities to improve the efficiency and robustness of processes. As a CDMO, we often need more time to drive a deeper understanding of critical quality attributes and the factors that impact control of a process. These challenges are compounded by accelerated development timelines that reduce the ability to improve the process at late approval stages. Addressing these issues

early on is critical to enabling the industry to reach its transformative potential for patients.

Are many companies struggling with CMC issues in clinical trials?

Lehmicke: I think that companies struggle when they move too quickly to begin a phase I/II trial trial – especially when they've not adequately considered if their process will be able to support a larger phase III trial or commercialization. When a process change is required to increase production volume, it raises questions of comparability. In some cases, the requirement to generate additional clinical data results in delays.

There are also significant gaps in regulatory guidance as to what is required at the BLA stage. This means that early and frequent communication with, for example, the FDA about the agency's expectations around CMC is critical. Communication can be challenging, however, because the FDA's Center for Biologics Evaluation and Research (and its counterpart at the EMA) faces severe resource constraints.

Myers: Indeed, there are many challenges associated with taking an originally academic process with minimum optimization all the way through clinical development into commercialization. While this might allow a company to go fast, changes to the process will likely be needed to ensure scalability, cost effectiveness, and regulatory compliance, which will lengthen time to market or incur higher development cost.

In addition to establishing frequent and early communication with the regulatory agencies, I would also recommend companies to proactively discuss CMC

Introductions

"My name is Angela Myers and I lead a new business initiative in gene editing and cell and gene therapy (CGT) manufacturing at Merck. In this role, I am responsible for R&D, commercial, marketing, strategy functions for the viral vector CDMO business, and the CGT manufacturing technologies such as cell lines and acoustic cell therapy manufacturing."

"Hello, I'm Michael Lehmicke, the Director of Science and Industry Affairs at the Alliance for Regenerative Medicine. ARM is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines – cell, gene, and tissue-based therapies. My role at ARM is to work with our members to identify best practices for establishing robust manufacturing processes. We also work collaboratively to identify CMC guidance gaps. We have a good working relationship with the FDA and EMA and engage with both regulators regularly to address these gaps."

Regulatory Disharmony

A 2019 Alliance for Regenerative Medicine report (2) found key differences between US and EU regulatory requirements for cell and gene therapies. Here, we highlight some of the "high-impact" differences.

Donor eligibility:

- US donor screening for Variant Creutzfeldt-Jakob Disease (vCJD) risk excludes most Europeans from HCT/P donation
- Disease-specific donor testing requirements are not harmonized
- In the US, you must use donor tests that are approved, cleared, or licensed by the FDA
- The FDA requires donor screening for Zika Virus
- In the US, testing laboratories must be CLIA certified
- In the EU, all records pertaining to traceability must be retained for 30 years
- The EU has repeat donor sampling and serology requirements for living donors

cGMP regulations:

- Timing and extent of GMP implementation
- In the EU, a potency assay with acceptance criteria is required for Ph1/FIH trials
- In the EU, a Qualified Person must ensure GMP compliance and authorize FP release
- US Cleanroom Air Classification Standards differ from European Guidelines

Long-term follow up requirements:

- There are regional differences in vector-specific LTFU study duration recommendations
- US LTFU studies are focused on safety and presence of the vector; EU LTFU studies are focused on safety and efficacy

requirements with their manufacturing partners or expert advisors, and openly discuss what it takes to establish a process that is reliable, reproduceable, and ultimately able to be validated.

How could greater regulatory standardization help?

Myers: Greater standardization across regulatory authorities could reduce the burden on therapeutic companies and CDMOs to ensure compliance at every phase of the development and commercialization process.

In addition, there are still topics that have not been clarified in any regulatory guidance that are unique to cell and gene therapy. For example, with commercialization still relatively new, there is a lack of standardization in areas such as planning for and implementing commercial manufacturing capacity, and handling process changes. Commercial capacity is still somewhat of a bottleneck, and there are many unknowns at this time with respect to specific qualification and validation requirements based on how similar the new space and throughput will be to the existing manufacturing space. If there are process changes, what is specifically required to show comparability is still a work in progress for regulators. Another important topic that needs further standardization and clarification is the definition and requirements of viral vectors being a "raw material" or a "starting material" for an ex-vivo therapy instead of a Drug Product.

Lehmicke: ARM commissioned a report by IQVIA in 2019 to identify disparities between European and US regulations in the cell and gene therapy space. The report identified differences in donor eligibility requirements and testing (donor cells), differences in requirements related to potency assays, and differing approaches to comparability (see sidebar: Regulatory Disharmony). Greater standardization would broaden the donor base, eliminate duplicative testing, and, in general, make it less onerous for therapeutic developers to seek approvals in multiple regions.

Where is the industry at in terms of standardization today?

Myers: In 2020, we saw new guidance documents specific to cell and gene therapy from the FDA, as well as formalization of the EU's Annex 1 for advanced therapies and medicinal products (ATMPs). Note

that the vernacular is different (CGTs, ATMPs, and so on), and certain terms lack definition. This presents a challenge for companies who are expected to consider aspects of life cycle changes without specific definitions released. It is still a work-in-progress. Therefore, it is important to keep abreast of regulators' current thinking and consider how it may impact a process, facility expansion, or filing. I can appreciate how challenging standardization is given the diversity in the cell and gene therapy space. General guidance is available, but specific guidance per therapy types is still needed. Validation of analytical methods is another challenge – it is sometimes not clear how much and where validation is needed for early stages. Experiences with PMDA and other geographies show that the definitions and approaches are still in their infancy and that we are learning from each other.

Lehmicke: The USP has released multiple standards for cell and gene therapies, notably USP <1043> Ancillary Materials, USP <1046> Cell and Tissue Based Products, and USP <1047> Gene Therapy Products. The Standards Coordinating Body is involved in 14 standards projects at varying stages of completion. There is a lot of good work going on, but the industry has a way to go.

What will it take to make better standards and best practices a reality?

Lehmicke: The development of standards and best practices can be challenging in a rapidly evolving field. No one wants to develop a standard or best practice that becomes obsolete by the time it is released, and some elements of manufacturing cell and gene therapies do not lend themselves readily to standardization. The key is to find the right areas to focus on, and I think that the Standards Coordinating Body is doing a good job of this.

An example of best practices is the Alliance for Regenerative Medicine's A-Gene project, which is nearing completion. A-Gene is a case study describing the application of Quality by Design (QbD) principles to AAV vector manufacturing. The purpose is not to teach someone how to make AAV per se, but rather to establish a framework for robust process development. Alliance members, including subject-matter experts from more than 25 gene therapy companies, have invested a lot of work into A-Gene over the past few years. We look forward to making this important resource available to the cell and gene community soon.

Myers: There are several industry working groups that are facilitating discussions between companies. As a direct result, there are white papers and additional considerations that are being highlighted with respect to the unique challenges of cell and gene therapy development and commercialization. In the areas where it is unclear how an authority will approach a particular challenge, there is robust discussion. Ultimately, each company has to have targeted dialog with regulators (Type C meetings with the FDA, for example) so that they can get feedback on their specific approach prior to their regulatory filing. This activity increases knowledge in both the industry and within regulatory bodies, which translates to better standards and established best practices. Working with industry associations allows companies to somewhat self-govern in the absence of specific regulatory guidance for specific modalities.

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Luis Alvarez, then an Army lieutenant colonel, with his neuro-engineering research group at West Point in 2017.

Painting the Future of Drug Delivery

US Army combat veteran Luis Alvarez has developed a new drug delivery technology that can convert any recombinant protein into a material-binding variant. Here, we find out how the tech can help coat implants and enable long-term local delivery.

From war to drug delivery. Tell us more…

I always loved science and I knew from an early age that I wanted to go into something related to biotech. But when I was younger, I also wanted to serve – and figured that was best while I was still young! My original plan was to serve for around five years and then go off to grad school to begin my second career.

After high school, I went straight into the military academy, where I majored in chemistry and life sciences. Normally, when you graduate from the military academy at West Point, you enter military service, but I was able to obtain the Hertz Foundation Fellowship, which allowed me to spend two years at graduate school. I then went back into regular military service, serving in infantry and cavalry units. While deployed in Baghdad, Iraq, I saw many serious injuries – injuries that would influence my research later down the line. After deployment, I used the remaining years of support from the Hertz Foundation Fellowship to do a PhD at MIT – so I was on active duty the whole time I was studying.

I was fortunate enough to have the flexibility within the military to pursue assignments that were technical in nature; I was able to serve in the Research and Development Command for the US Army, which allowed me to continue with military service while

"Viruses are best adapted to surviving and efficiently replicating in the ideal host environment."

completing three technically connected programs within the biopharma space.

A military career and a scientific career are not a very common combination – and actually I don't recommend it because of the difficulties of navigating the requirements for each – but it worked out for me.

Luis Alvarez describes the precision targeting of proteins for tissue regeneration to Bill Gates at the 2009 Hertz Foundation Symposium.

How did your experiences in Iraq influence your research?

I noticed that people would suffer serious injuries, mainly to limbs, which doctors would be able to save. Then, many months later, they'd have to be amputated because the limb had deeper tissues (bone, vessels or nerves) that hadn't healed properly. It seemed strange to me that we hadn't figured out how to target certain tissues for regenerative repair. So my aim was to develop a technology for the targeted delivery of biologics to enable tissue repair – bone regeneration in particular. And that was the basis of my research in Linda Griffith's lab at MIT and Richard Lee at Harvard. Linda is a pioneer in tissue engineering, and I was able to learn about the techniques for modifying implants and influencing how the body regenerates. I retired from the military in 2017 to commercialize the technology with Theradaptive.

Could you tell us more about Theradaptive's platform technology?

For tissue to regenerate, biological cues must be presented at the right time and place. Though we know what many of the cues are, there has been no way to deliver them to the right tissues and keep them there long enough to have a regenerative effect. In our work we developed a means of modifying proteins via a simple one-step process that doesn't require chemical modification so that they stick – like paint – to surfaces, such as medical devices. By coating medical devices with bioactive beacons for healing, the body is triggered to surround the implant with regenerating tissue. We made a variant of a protein called bone morphogenetic protein 2. Our variant is called AMP2, and it binds to both permanent and resorbable implants and causes the body to produce bone wherever it is placed in the body. In all studies we have conducted to date we have beaten the standard of care in bone repair and spinal fusion using AMP2 – and we've had several meetings with the FDA. We're hoping to begin the human phase of development within the next year and a half.

Combining Active Duty and Scientific Research

Luis began his military service in 1997. He served in numerous intelligence assignments, including with the 2nd Infantry Division (Korea) and 1st Cavalry Division (deployed to Baghdad, Iraq, 2004-2005). His other experience includes:

- Headquarters Detachment Commander
- Natick Soldier Systems Center
- Military Deputy Director of the Natick Research, Development, and Engineering Center

His military awards include the Bronze Star Medal, Legion of Merit, Defense Meritorious Service Medal, Global War on Terrorism Expeditionary Medal, the Global War on Terror Service Medal, Korean Defense Service Medal, and the Combat Action Badge.

Luis also earned a bachelor's degree in Chemistry and Life Science from the United States Military Academy in West Point, New York, in 1997 – and was commissioned as a military intelligence officer. He was selected as a Hertz Foundation Fellow and continued his education at the Massachusetts Institute of Technology (MIT) where he earned a master's degree in Chemical Engineering in 1999. In 2006, Luis returned to MIT to earn a doctor of philosophy degree in Biological Engineering (2009).

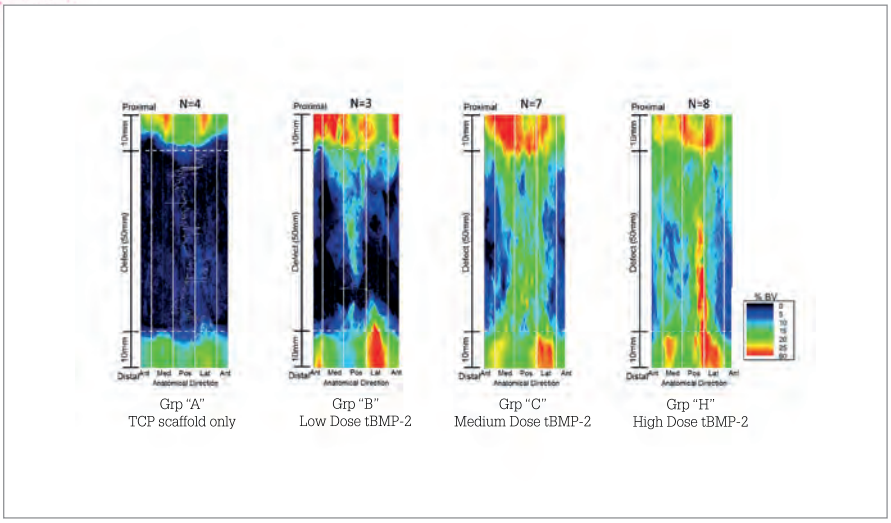

Figure 1. The highest dose of tBMP-2 demonstrates the greatest new bone volume (1).

What other applications could benefit from your coating technology?

We also have promising results in cartilage repair, with another implant binding protein. The idea is that we might be able to take a "legacy" implant and regenerate the tissue it is working to support. The original idea for the technology was related to traumatic injuries sustained by soldiers, but we now see a great deal of benefit in orthopedic conditions. The projected orthopedic repair market in the US exceeds $15 billion annually, which highlights the need for targeted tissue repair in the general population. But we also believe the technology could improve cell therapy by giving cells long-lasting, local, and highly-concentrated biological stimuli. We're still a relatively small company, hence our initial focus on trauma and the spine (funded primarily by the Department of Defense and the State of Maryland). We just closed a Series A investment round, which will allow us to expand into additional areas.

Do you think a career in the military prepared you well for the business world?

Yes, I think so. In business, you have to deal with difficult situations (and people!), for which the military certainly prepares you. I've gained a certain amount of resilience to overcome things that at first may seem difficult – or even impossible. For example, if the company is running low on funding or you are facing daunting challenges, persistence and resilience are great assets. The military also teaches you leadership skills – the ability to assemble a team and give them a mission to go after. But I would say that, whatever your background, starting a company is difficult and time consuming, with many unexpected twists and turns. On the other hand, it's a lot of fun too.

What advice would you give to someone in the military, perhaps with an interest in science, who is thinking about changing careers?

I would say that moving into drug development or biotech can feel intimidating – but it's a lot like jumping into cold water: it's always scarier before you've done it.

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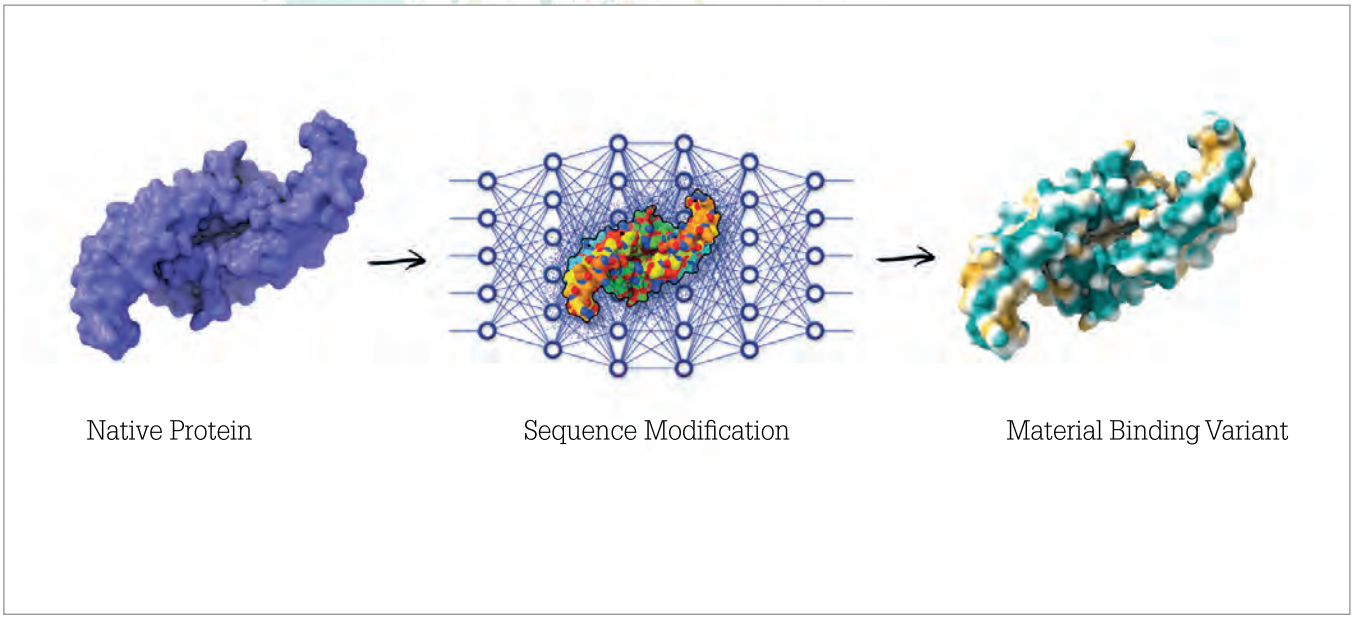


Figure 2. Proteins are converted into a material-binding variant via sequence modification.

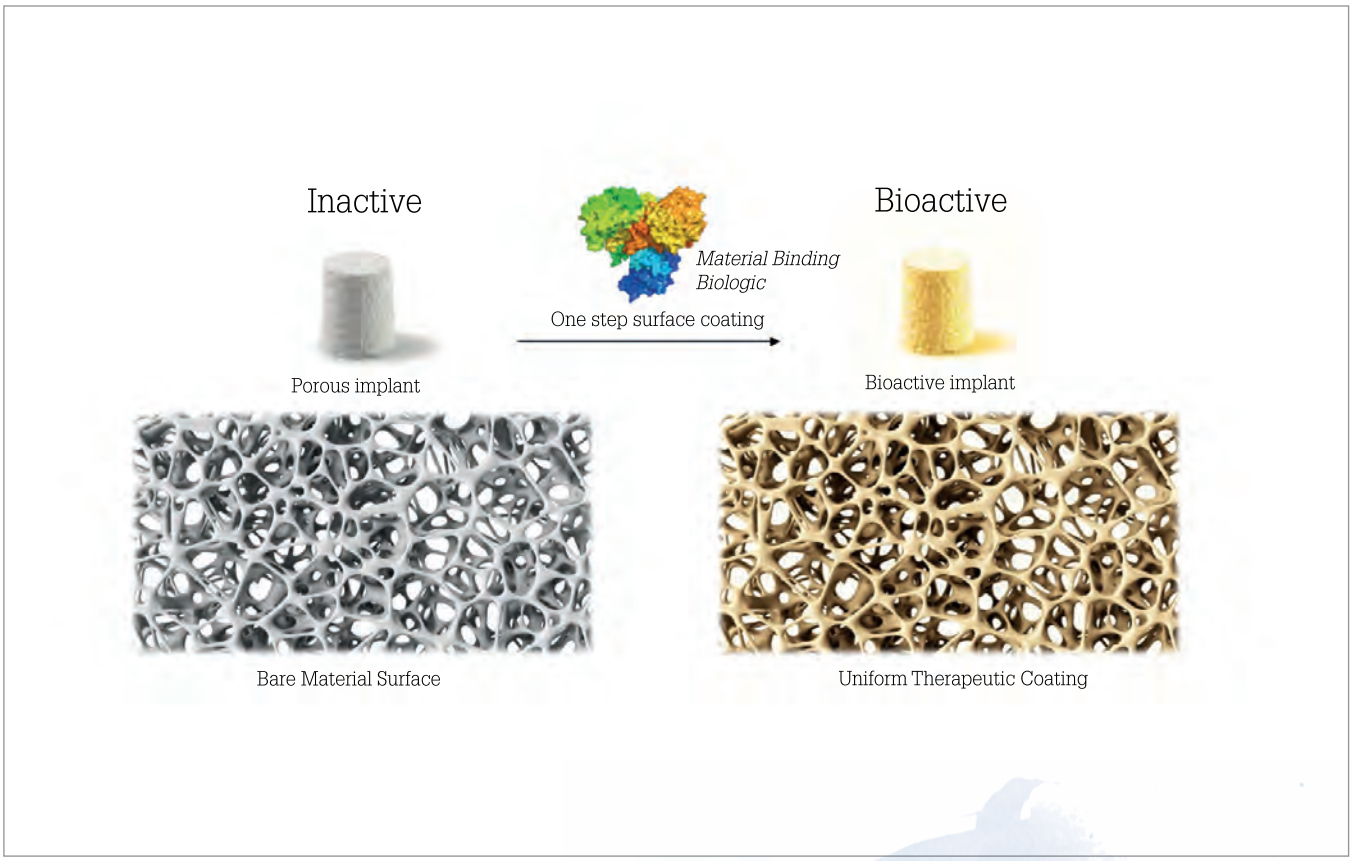


Figure 3. Materials are coated in one step with with bioactive proteins.

Of Plumbing and Poetry

Sitting Down With… Sandy Macrae, Chief Executive Officer, Sangamo Therapeutics, USA

You started out in medicine, but what happened next?

I studied medicine and pharmacology at the University of Glasgow. During my time there, I did an internship at a pharma company, which completely changed my perspective of the industry. I was impressed by the professionalism and the way science was focused toward a clear goal. I then studied for a PhD at the University of Cambridge and a postdoc at Duke University Medical Center, and was offered a grant from the Wellcome Trust to set up my lab and my first PhD student. But I realized that I would never be able to compete as a full-time physician only working in the lab a couple of times a week. So I looked to industry and took a job at SmithKline Beecham (which of course became GSK). This move provided me with incredibly powerful training in how to carry out quality scientific and clinical research. I spent the next 19 years in industry, before being offered the chance to head up Sangamo in 2016.

Do you think your background in medicine and academia prepared you well for the job of leading a cell and gene therapy company?

It is rather unusual for a physician/scientist to lead a cell and gene therapy company, but I think it does help to coordinate the technology and development arms – especially important for advanced medicine. No matter the excitement around your technology, you must understand how to recruit patients with the specific disease you're trying to treat, inclusion/exclusion criteria, and ultimately how to meet your endpoints and validate your technology. But nobody knows it all. Leaders with my background will lean on a good chief business officer, with a real understanding of how to make our therapies available to patients – how to price them and how they'll fit into the various healthcare systems. Similarly, someone from a business background would require a strong head of R&D or chief medical officer. A good balance of skills and perspectives is a must.

Are there any leadership qualities you've found to be especially important?

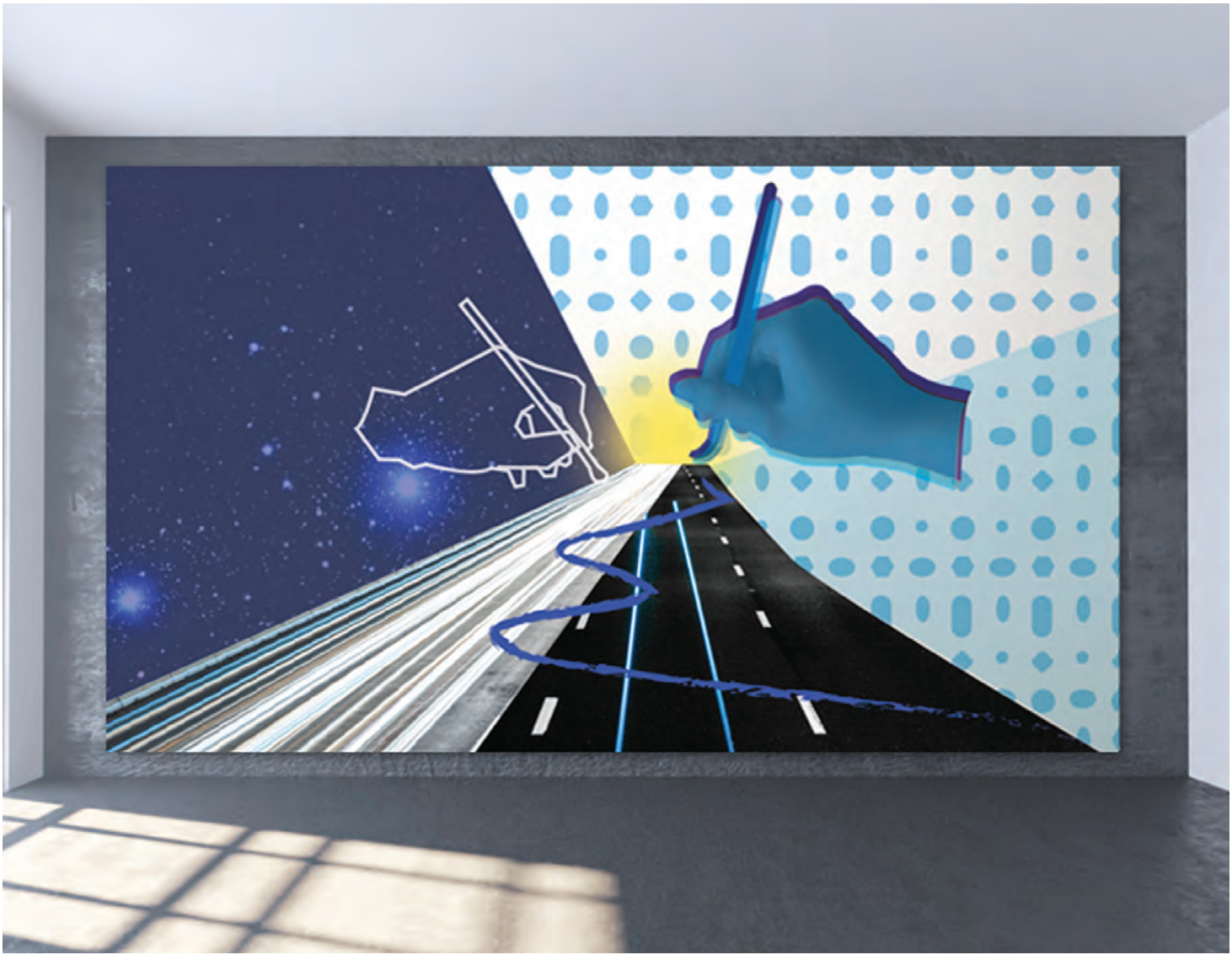
My wife – a psychiatrist and a chief medical officer – gave me a book by James G. March, called On Leadership, in which he describes leadership as a combination of plumbing and poetry. A leader must inspire – think Henry V at Agincourt – and give people a real sense of purpose. Fortunately for us, most people in the pharmaceutical industry are inherently purpose-driven. To keep employees motivated and engaged, we need to join the dots between what they're doing and the patient. We spend a lot of time bringing patients into the organization – last week we had a couple of children with autism and before that we had men with BLS (an inherited immunodeficiency); meeting patients really helps people make those connections.

That's the poetry side, but the plumbing is a little more prosaic. Imagine you're staying at a hotel and the plumbing works – you don't go down and thank the staff. But if you flush the toilet and it doesn't work, there's a good chance you'll complain or never go back. My job is to ensure there are few obstructions – that the organization is balanced, that people are working well together and have good facilities, IT systems and benefits. In other words, I'm there to make sure the plumbing works. Leaders must listen for gurglings in the pipes and see that they are sorted before they burst!

"The dream: for those with inherited diseases to have the choice to get it remedied by a single DNA-editing treatment."

What is your ultimate vision for the cell and gene therapy field?

The dream: for those with inherited diseases to have the choice to get it remedied by a single DNA-editing treatment. But there's also the prospect of being able to identify genetic factors in more common diseases and modify them so that we reduce the probability that you'll develop it in your lifetime – that's the next stage. With cell therapies, we may be able to do a whole series of things to a cell so that, when you give it to a patient, it would control autoimmune diseases or cancer in a way that would usually require multiple (potentially toxic) medicines. And that's why it's good to see our knowledge of cancer regulation and immunology advancing in tandem with our ability to modify cells. Eventually, I envisage a world with three treatment pillars: vaccines used to prevent disease, short-term treatments to alleviate things like pain and hypertension, and changes to fundamental DNA to reduce your risk of disease – or even cure it. I don't know how far away we are, but the field is moving so quickly that, if delivery is sorted, the tools are ready to be used.



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