SEPTEMBER 2020 # 68

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When Fast Science Spells Bad Science

Drug development needs to move more rapidly, but not at the expense of safety

Russia's rapid approval of a COVID-19 vaccine has been greeted with global scepticism. Using an adenovirus vector, "Sputnik V" delivers the gene for the SARS-CoV-2 spike protein – a promising approach being pursued by other teams working on COVID-19 vaccines. Mass vaccination is reportedly due to start in Russia over the coming weeks. There's just one problem: Sputnik V has not been through phase III trials.

COVID-19 is spurring research communities and the pharma industry to move faster than ever before, but how fast is too fast? Most COVID-19 trials registered on ClinicalTrials.gov are single center and expected to generate only low-level evidence – and researchers have called for tighter reviews to ensure studies are well designed (1). An opinion piece published in the BMJ explained how high-speed development could do more harm than good (2). "This focus on rapid vaccine development, fueled by unprecedented political, financial, and populist pressures, risks missing the target of global access to effective vaccines that can curb the pandemic, while irreparably damaging the public confidence of people desperate to return to their lives," wrote Els Torreele, a former director of the MSF Access Campaign.

The FDA has also recently been accused of potentially moving too fast when it comes COVID-19 treatments. In August, the agency issued emergency use authorization (EUA) for convalescent plasma to help hospitalized COVID-19 patients (3). However, there seems to be a lack of randomized controlled trials and published data (4). The Trump administration was fast to take credit for the EUA, also prompting concerns that the authorization was politically motivated. "The FDA's emergency authorization for convalescent plasma is a milestone achievement in President Trump's efforts to save lives from COVID-19," said Alex Azar, Health and Human Services Secretary, in a statement (3). "The Trump Administration recognized the potential of convalescent plasma early on."

FDA Commissioner, Stephen Hahn, has since apologized (via news outlets) for not adequately explaining the data on convalescent plasma.

Clearly, speed is of the essence; global deaths caused by COVID-19 are approaching one million – and economies worldwide are in tatters. Nevertheless, the scientific community must not lose its head. Good science must continue only as fast as it can – and that means without compromising quality or safety.

Stephanie Sutton
Editor

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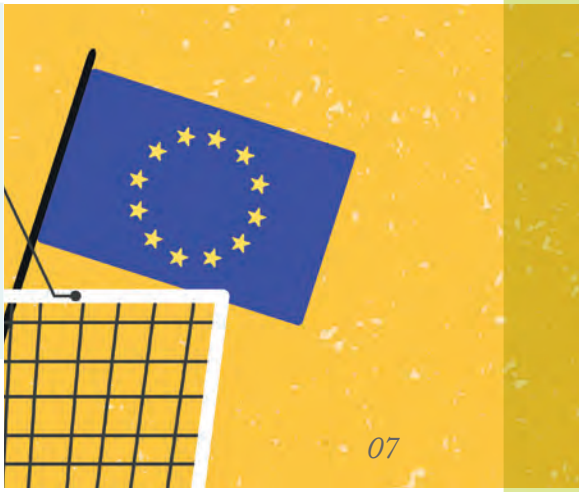
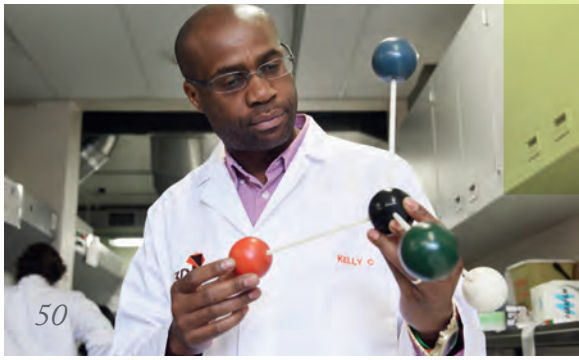


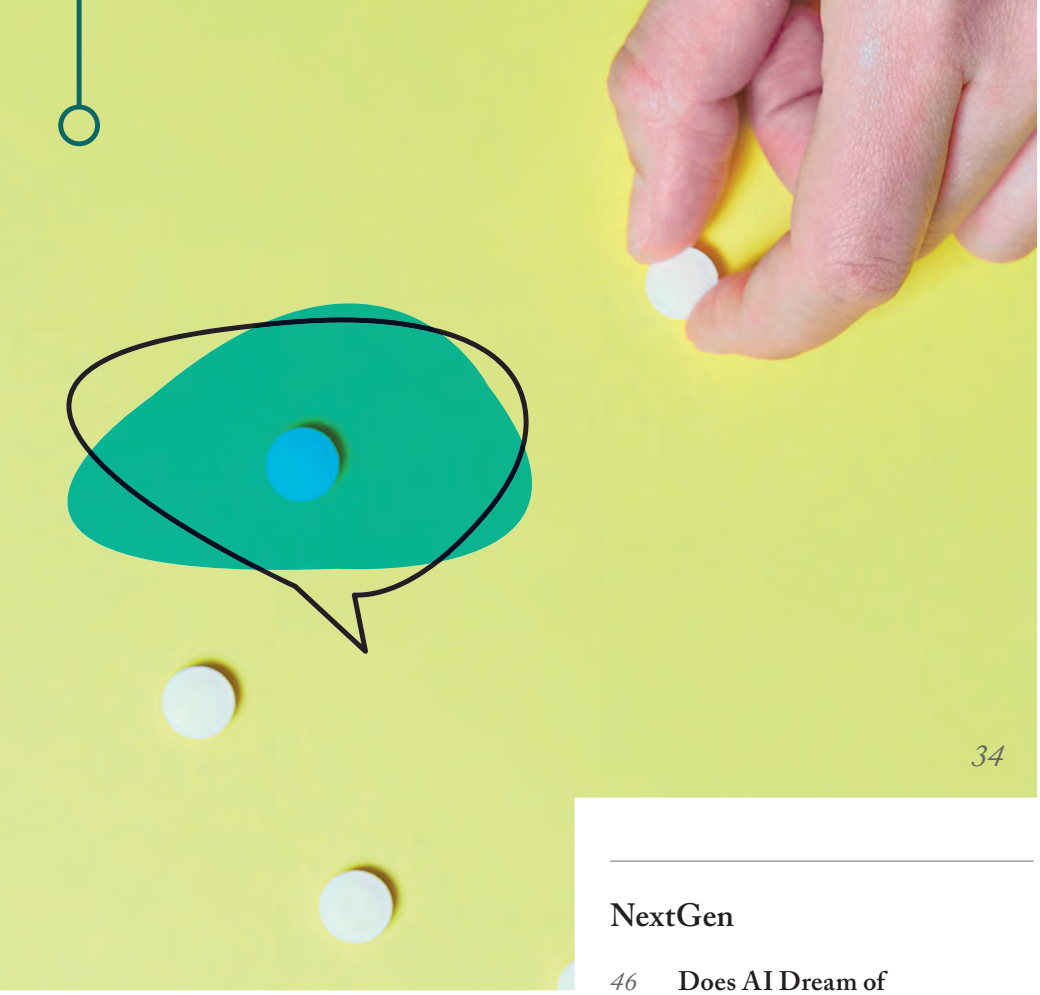


Upfront

In My View

On The Cover

The unlimited potential of human innovation. Marie Curie image courtesy of Wellcome Images.



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Upfront

Research
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Innovation

A Matter of Trial Trust

Do economic incentives damage the integrity of clinical trials?

The high stakes and uncertainty involved in trials has led to numerous concerns about how economic incentives may generate conflicts of interests for investigators. But the need for a vaccine to treat SARS-CoV-2 means the integrity of trials is arguably more important than ever before.

Contrary to previous concerns about the potential for trial results to be manipulated, a study published in PNAS shows that integrity remains high (1). The paper focused on the differences between phase II and III trials registered on ClinicalTrials.gov to establish whether the threshold value of statistical significance established in smaller trials was confirmed in larger cohorts. "Previous studies that analyzed results published in academic journals showed that results tend to bunch right above the threshold for significance. This led some to question whether investigators were selective in reporting their results," says study co-author Marco Ottaviani, Professor of Economics at the University of Bocconi, Italy. "But our study found nothing to suggest that results are changed to clear the hurdle."

Ottaviani's analysis also revealed subtle patterns across trials. Small companies, when compared with big pharma, were less likely to terminate a project with phase II results under the threshold and were also more likely to report a higher share of significant results in phase III. "Smaller companies are often built around one or two projects – the failure of which could result in their commercial death. Managers of smaller companies, who often hold substantial financial shares of the company themselves are, therefore, more reluctant to give up, even if their phase II results are poor," says Ottaviani. But with little definitive evidence to support this explanation, the researchers are digging deeper to understand the influence of economic incentives on investigators' decisions to accurately disclose study results.

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INFOGRAPHIC

An R&D Overhaul

A survey examines how pharma's digital transformation will affect R&D

70%
of respondents have restructured their organizations because of digital transformation plans

More than **65%** of pharma companies plan to spend between 20 and 50% of their digital transformation budgets on data management

Top four technologies for enhancing R&D

- Advanced analytics and AI
- Biomarkers
- Clinical registries
- Electronic health records

Brexit on the horizon, a Nestle acquisition, and everyone loves pharma…? What's new in business?

- The UK government has asked pharma companies to maintain six weeks' worth of supplies on UK soil when the Brexit transition period comes to an end on January 21 2021. They also warned freight operators delivering medical supplies from Europe to avoid the Channel Ports as "a matter of priority." In response, the ABPI reiterated their call for a Mutual Recognition Agreement covering drug safety testing and inspections.
- Nestle is set to acquire Aimmune Therapeutics for $2.6 billion. Aimmune developed Palforzia, the first and only FDA-approved treatment for peanut allergy, which works by exposing children to small but increasing amounts of peanut. The news came a few weeks after DBV Technologies' skin patch for peanut allergy – a potential Palforzia competitor – was rejected by the FDA 21 months after the company first filed for approval.
- Researchers from The Harris Poll found that 40 percent of the American public believe that pharma's reputation has improved since the beginning of the COVID-19 outbreak, with 81 percent recalling seeing or hearing something about the industry during that time. The industry is at its highest ever point in terms of its reputation and relevance, according to Rob Jekielek, managing director at Harris. The company has been polling pharma for almost two decades.

CRISPRing Up Brown Fat

The first steps toward an autologous cell therapy for obesity

In the hope of treating obesity or type 2 diabetes, researchers from the Joslin Diabetes Center, USA, have used CRISPR to boost expression of the UCP1 gene in progenitor white fat cells to create brown-fat-like cells (1). Brown fat cells are said to be beneficial because they burn energy instead of storing energy, as white fat cells do.

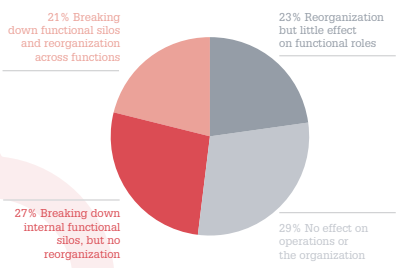
The researchers transplanted their "HUMBLE" progenitor cells into mice on a high fat diet and found that the mice had greater sensitivity to insulin and a greater ability to clear glucose from the blood than the control group. The HUMBLE mice also put on less weight.

Though human trials are still some way off, the team has envisaged an autologous cell therapy protocol whereby a patient's white fat cells are removed, the progenitor cells isolated and modified to boost expression of UCP1, and the resulting HUMBLE cells returned to the patient.

Reference

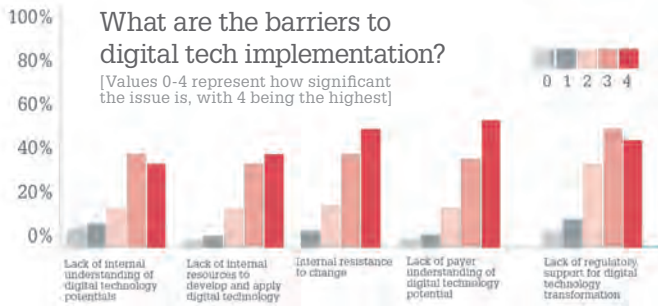
1. *CH Wang et al., "CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice," Sci Trans Med, 12, 558 (2020). Available at: https://bit.ly/32NqJX1.*

How have digital technologies affected company operations?



What are the barriers to digital tech implementation?

[Values 0-4 represent how significant the issue is, with 4 being the highest]



Sources: ICON, "Digital Disruption in Biopharma: How digital transformation can reverse declining ROI in R&D", (2020). Available at https://bit.ly/2Y2DzhD

Nominate Now

Nominations are open for The Medicine Maker 2021 Power List

The year 2020 unexpectedly became one of the most challenging for the pharmaceutical industry, as COVID-19 bared its fangs. Scientists race to find effective treatments and vaccines, while businesses grapple to find new normality in the disruption to standard working practices.

In these difficult – and sometimes dark times – it is more important than ever to recognize and reward success; to remind ourselves of the good in the world. And that's why The Medicine Maker's annual Power List will be back in 2021. The aim? To celebrate influential medicine makers. We want to shine a spotlight on those individuals who are contributing to the development and manufacture of new drugs, including biopharmaceuticals, small molecules and advanced therapies – whether for COVID-19 or other therapeutic areas.

For inspiration, check out the 2020 Power List available at https://themedicinemaker.com/power-list/2020.

It's an open nomination process – and you're free to nominate as many individuals as you like. But please note that nominations will close on January 25,2021. Nominate at tmm.txp.to/pl2021-noms

What is the format of the List?
The Power List is divided into three categories: Small Molecules, Biopharmaceuticals, and Advanced Medicine.

The final List will include 20 names per category.

Who's eligible?
Anyone involved in the development or manufacture of new medicinal products. Previous lists have featured individuals from academia, research institutes, big pharma, SMEs, start ups, societies, not-for-profit institutes, consultancies, and more. We invite nominations from all corners of the industry.

Is there a limit to how many people I can nominate?
You can nominate as many individuals as you like.

Can I nominate myself?
Yes, if you must.

How are nominations judged?
Nominations are passed to a judging panel. Judges will consider each individual's achievements and profile in the industry.

When will the List be revealed?
The 2021 List will be published in the April 2021 edition of The Medicine Maker.

Questions?
stephanie.sutton@texerepublishing.com

Save Our Shots!

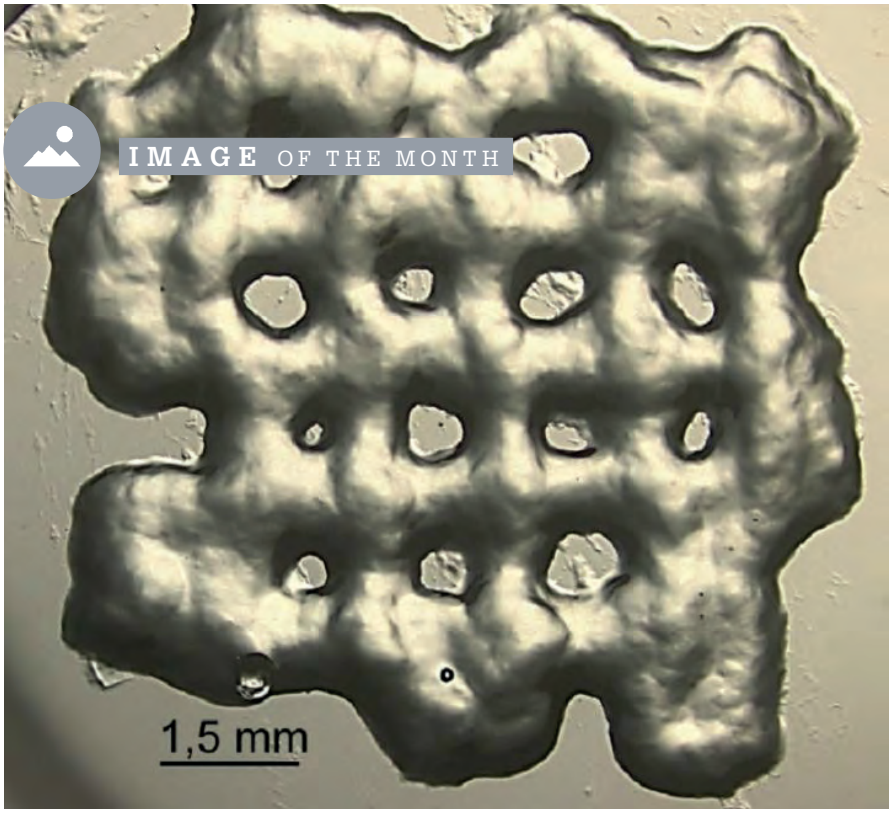
Immunization rates drop amidst the pandemic

GlaxoSmithKline has launched a vaccine awareness campaign in the USA. The "Brought to You By Vaccines" campaign aims to educate adults over the age of 50 about the value of vaccines. According to GSK, the COVID-19 outbreak has led to a drop in routine healthcare visits and a decline in immunization in adults; ordering rates across adult vaccines in healthcare practices have dropped by over 60 percent since the start of the pandemic.

Ahead of the campaign, GSK commissioned The Harris Poll to conduct a survey. In a statement, GSK explained that COVID-19 has made older adults more aware of the importance of vaccinations, but that this awareness has not converted into intent to seek vaccination (1): "Seventy-two percent of older adults say that COVID-19 has made them realize how important vaccines are for everyone, but less than half (47 percent) report they are more likely to get at least one of the recommended vaccines for adults over the age of 50 as a result of the pandemic."

Reference

1. *GSK, "Low adult immunization rates decline further due to pandemic," (2020). Available at https://bit.ly/2G2YSKN.*



Waffly Versatile

Spanish National Research Council scientists have designed a 3D-printed hydrogel that cultures T cells and T-lymphocytes (for use in adoptive cell therapy) by mimicking the structure and chemistry of the lymph nodes.
Credit: ICMAB-CSIC; IBEC. *Find out more at: https://bit.ly/2EG1X3e*

Would you like your photo featured in Image of the Month?
Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"When we launch the first COVID vaccines, the public needs to know that they have been rigorously evaluated for safety and efficacy and that they can trust those vaccines… If people lose trust in [COVID] vaccines, then that jeopardizes trust in all vaccines, which we've worked so hard to build over time."

Rajeev Venkayya, President of Takeda's Global Vaccine Business: https://bit.ly/32OGGfx

End of an Era

The UK's medicines regulator releases new guidance for Brexit

As the Brexit transition period comes to a close, the MHRA has issued guidance for pharma companies (1). The documents cover clinical trials, licensing, IT systems, and pharmacovigilance, and are intended to help support businesses from January 1, 2021 – the point at which the MHRA will become the UK's sole medicines regulator. The guidance also outlines specific protocols for Northern Ireland, which shares a border with Europe.

"If we are to ensure uninterrupted supply for the NHS from January, the MHRA must continue to work closely with them on details related to individual medicines as well as on issues related to the Northern Ireland Protocol," said Richard Torbett, Chief Executive of the Association of the British Pharmaceutical Industry, in a statement responding to the news (2). "However, we have always said that the best way to avoid disruption in the long term is for both sides to consider the impact on patients in the UK and the EU and agree a deal."

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The COVID-19 Curator

Your roundup of the key scientific studies and industry announcements emerging from the pandemic

Our weekly newsletter collates the science behind the outbreak and delivers it straight to your inbox. Sign up: www.texerenewsletters.com/covid19newsletter

Here, we share just some of the research and company announcements made during August.

Industry news

AstraZeneca has dosed participants in a phase I trial of AZD7442 – a combination of two monoclonal antibodies derived from convalescent patients with SARS-CoV-2. AstraZeneca licensed the mAbs from Vanderbilt University Medical Center and has since optimized them with a half-life extension and reduced Fc receptor binding. The trial will evaluate safety, tolerability and pharmacokinetics.

CARE consortium. The CARE (Corona Accelerated R&D in Europe) initiative has launched, supported by Europe's Innovative Medicines Initiative, to accelerate the discovery and development of medicines to treat SARS-CoV-2. Almost 40 partners are involved in the initiative, including Boehringer Ingelheim, Novartis, Pfizer, Merck KGaA, and Bayer. The consortium will focus on drug repositioning, small molecule drug discovery, and virus neutralizing antibody discovery.

Novavax has announced several collaborations during August focusing on its COVID-19 vaccine candidate NVX-CoV2373, including deals with Serum Institute of India, Takeda, Sk bioscience, and the UK government. The company has also commenced a phase IIb clinical trial of NVX-CoV2373 in South Africa – which is experiencing a winter surge of COVID-19 cases – and the phase II portion of an ongoing trial involving volunteers in the US and Australia.

COVAX. More than 172 economies have expressed interest in the COVAX initiative, co-led by CEPI, GAVI, and the WHO. The goal of the initiative is to provide equitable access to COVID-19 vaccines once they are available. COVAX's portfolio currently comprises nine vaccine candidates, and a further nine are under discussion.

Early research

Nasal vaccine. Scientists at Washington University School of Medicine in St Louis have developed a nasal vaccine, which has been tested in mice. With one dose, the vaccine was able to create a strong immune response throughout the body – but particularly so in the nose and respiratory tract. The vaccine uses an adenovirus to deliver the SARS-CoV-2 spike protein.
AO Hassan et al., "A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2," Cell, Pre-Proof (2020).

Ace in the hole. Collaborating with the US Army Medical Research Institute of Infectious Diseases, a team at the University of Illinois has engineered a novel receptor protein that resembles ACE2 – the receptor that SARS-CoV-2 uses to invade cells – so that it may act as a "decoy."
KK Chan et al., "Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2," Science (2020).

Drink your tea. Could a traditional Chinese antiviral stop SARS-CoV-2 in its tracks? Research shows that MIR2911, a microRNA found in honeysuckle decoction, can inhibit replication of the virus and hasten recovery.
L-K Zhou et al., "Absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and accelerates the negative conversion of infected patients," Cell Discovery, 6 (2020).

Other avenues

Agile analytics. An international research group has created a centralized repository for electronic medical records. The system has already yielded some early insights into COVID-19, but researchers hope its utility will increase with more data.
GA Brat et al., "International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium," npj Digital Medicine, 3 (2020).

Sustain your studies! After a coronavirus outbreak, research volumes skyrocket – but they drop precipitously after containment. This lack of sustained research prevents us from understanding and responding rapidly to new outbreaks such as COVID-19.
D Kagan, J Moran-Gilad, M Fire, "Scientometric trends for coronaviruses and other emerging viral infections," GigaScience, 9 (2020).

Sharing is caring. Different countries present different COVID-19 public health data – and in a wide range of different formats – limiting its use across distant sites. Researchers

recommend identifying key data and standardizing a format for international sharing.
J LoTempio et al., "We Can Do Better: Lessons Learned on Data Sharing in COVID-19 Pandemic Can Inform Future Outbreak Preparedness and Response," Science & Diplomacy (2020).

Missing link. Researchers have analyzed the link between COVID-19 cases in countries with and without mandated BCG vaccination, concluding that BCG may offer some protection.
MK Berg et al., "Mandated Bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19," Science Advances, 6 (2020).

Understanding COVID-19

This, not that. A human protein-protein interaction network may explain why COVID-19 selectively damages some organs, but not others.
E Estrada, "Fractional diffusion on the human proteome as an alternative to the multi-organ damage of SARS-CoV-2," Chaos, 30 (2020).

Structural problems. Postmortem analyses of severely affected COVID-19 patients reveal a lack of germinal centers in lymph nodes and spleens – perhaps explaining the inability to produce lasting antibody immunity.
N Kaneko, "Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19," Cell (2020).

Asymptomatic danger. A study has found similar viral loads in infected symptomatic and asymptomatic patients, indicating that isolation may be necessary regardless of symptoms.
S Lee et al., "Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea," JAMA Intern Med., (2020).

Not out of the woods. Researchers have presented a new mean estimate for the SARS-CoV-2 incubation period: 7.76 days, which is longer than previously thought.
J Qin et al., "Estimation of incubation period distribution of COVID-19 using disease onset forward time: A novel cross-sectional and forward follow-up study," Science Advances, 6 (2020).

In My View

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

Let's Focus on Filtration

No patient has contracted a viral infection from a recombinant product – but, with fewer options downstream, gene therapy manufacturers will need to focus on upstream filtration to achieve the same success

By Morven McAlister, Senior Director of Regulatory and Validation Consultancy, and Aernout Martens, Global Product Manager Virus Filtration, both at Pall Biotech

Gene therapies are an exciting new class of treatment that alters the genetic composition of cells to correct disease-causing mutations – offering patients new therapies for previously untreatable genetic diseases. In 2017, the FDA approved its first gene therapy; at the time of writing, there are 17 approved cell and gene therapies, with many more on the way (1).

Although the pace of discovery is promising, it is only half the battle. Without robust manufacturing processes, these therapies will remain out of reach for the vast majority of patients. Viral vectors, used to transport therapeutic genetic material into cells, must be effectively processed and purified for clinical use. Manufacturing viral vectors for rare diseases already poses challenges, even if the number of patients requiring treatment – and therefore the volume of viral vectors – is low. Therapies for more common diseases such as Alzheimer's, which impacts at least 50 million people worldwide, would be even more challenging to manufacture (2).

Fortunately, the industrialization of gene therapy manufacture has improved in recent years, with large-scale production becoming a reality. But, we must approach gene therapy manufacture with the same commitment to safety as that of other biopharma products. In the case of monoclonal antibodies (mAbs) and recombinant proteins, virus safety countermeasures have been so robust that there has not been a single case of someone contracting a viral infection from a contaminated recombinant product. The question is whether this level of safety can also be assured for gene therapies – and what lessons the advanced medicine field can learn from mAbs.

For recombinant and mAb manufacturing, the most common approach is to select and test incoming raw materials. Components such as cell culture media are treated to mitigate the risk of adventitious agents using techniques such as gamma irradiation or high temperature before transfer to the bioreactor. In the downstream process, virus safety is achieved by validating several viral reduction and inactivation steps, both dedicated like virus filtration and low pH inactivation, as well as non-dedicated, like chromatography steps that primarily serve for purification purposes. The downstream viral safety measures have proven ample to keep patients safe, while the upstream measures have mainly contributed to safeguarding continuity of production by reducing bioreactor infection frequency with its potentially devastating operational and financial consequences. Lately, virus filtration in the upstream is also considered as an additional measure to further reduce the risk of downtime, especially in single use facilities without access to high temperature equipment and in flexible multiproduct factories, that can't afford missing deadlines and milestones due to a potential bioreactor infection.

When manufacturing cell and gene therapies, there are fewer options to prevent virus infection or inactivate viruses downstream because such measures could damage or remove the product itself. This is especially true for therapies that use lentivirus (LV) vectors, which are more fragile than adeno-associated virus (AAV). AAV can be treated "harshly" (with a detergent, pH treatment, and a coarse >20 nm virus filter to remove larger viruses) and still maintain a good yield. LV is larger and these treatments would irreparably remove or damage the viral vector itself. But there is still the need to remove a wide range of adventitious agents that could potentially ingress adherent and suspension-based viral vector cell culture. Therefore, manufacturers should look at ensuring a maximum log reduction value (LRV) safety barrier for upstream processing.

Are viral filters the answer? Some manufacturers don't currently use them in the upstream process. This is partly because robust downstream virus clearance historically provided ample patient safety for mAbs and recombinants, and upstream virus filters were in many cases not deemed financially viable to cover the risk of bioreactor infection. In gene therapy, these downstream "safety nets" are only partially in place, so there is a real risk that a bioreactor infection upstream could directly impact patients.

With safety and quality increasingly prioritized in gene therapy manufacturing and fewer options downstream, we believe more companies will look to virus filtration of cell culture media. Viral filters can robustly remove viruses from biotech and plasma processes using a polymeric membrane barrier to retain virus particles based on size. Similarly, AAV can be separated from larger adventitious agents in the downstream with a course >20 nm virus filter. The integral performance criterion is the LRV and throughput over time. These specifications can be altered and influenced by various interrelating aspects such as viral load, protein concentration, presence of foulants, pressure, operating flux, ionic strength, and process interruptions. Choosing and validating a virus filter appropriate for the expected range of conditions is therefore imperative.

We're seeing an increasing number of manufacturers turning to these products as the maturing field addresses the risks associated with gene therapy manufacturing. When the first gene therapies came onto the market, patients were willing to accept associated risks if they had a chance of curing their once incurable and often fatal genetic condition. Now, as the industry invests in appropriate adventitious agent control with a high focus on safety, patients will not have to take this risk.

As industrial-scale gene therapies are being developed, it's up to us as an industry to make sure we produce them in the safest way possible, to help as many patients as we can.

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Quality Control: The Power of Precision

A growing number of analytical tools can – and should – be used to assess drug quality and purity. But one technique that is seeing increasing popularity, in part due to its precision and reproducibility, is capillary electrophoresis.

By Mark Lies, Global Business Manager – Capillary Electrophoresis at SCIEX, California, USA

Common methods for the analysis of medicinal products include ligand binding assays (LBAs) and chromatographic methods, such as liquid chromatography (LC) or gas chromatography (GC), which are typically used in combination with mass spectrometry (MS). However, over the past decade, another separation technique – capillary electrophoresis (CE) – is being increasingly used to check and confirm the purity, heterogeneity, and glycan association of biologic drugs (1).

One good example is the application of capillary zone electrophoresis (CZE) for the analysis of synthetic human erythropoietin (EPO), which is used for the treatment of anemia associated with certain clinical conditions, including kidney disease and inflammatory bowel disease. EPO treatments must contain a specific mix of protein isoforms to be fully effective, and so accurate and precise quality control assays are required to check EPO isoform heterogeneity.

Why choose CE? Because it is a simple, quick, and effective technique, with exceptional resolving power and a high degree of precision.

We understand precision as the reproducibility of a method's quantitative and qualitative accuracy relative to data obtained using the same type of instrument and protocol. Industry guidance from the FDA on the validation of analytical methods used for the development and manufacture of biopharmaceuticals specifies that they must be precise, accurate, and of sufficient dynamic range (2). As biologics become increasingly complex, the industry needs – and regulators demand – increasingly precise analytical methods. Precision speaks not only to the analytical validity of a measurement method but, ultimately, to its utility.

In pursuit of CE precision, "home-brew" methods and reagents are progressively being replaced by specialized and standardized reagents and kits optimized for specific CE methods, such as capillary isoelectric focusing (CIEF) and CE-sodium dodecyl sulfate (CE-SDS). The aim is typically to develop a complete workflow solution that is precise but also simple and flexible enough for QC purposes.

Ensuring the precision of commercially available assays is critical for QC during clinical development and commercial manufacture. When addressing robustness, engagement between assay manufacturers and users is key. Critical assay specifications, including precision, of CE analyses can be assessed to meet everyone's requirements. To that end, cross-company collaborations conducted with (bio)pharmaceutical companies and regulatory authorities have demonstrated the precision of CIEF technology for the analysis of monoclonal antibodies, capillary zone electrophoresis for charge heterogeneity testing of monoclonal antibodies, CE – laser induced fluorescence (CE-LIF) for mapping multi-site N-glycans, and CE-SDS for the analysis of biomolecules (3, 4, 5, 6).

The purity of gene therapy products is also being increasingly monitored using CE and MS technologies. CE-MS data are also used to confirm and corroborate the data obtained using LBAs and other methods. In my view, we will continue to see the rise of CE as an orthogonal tool to address the increasing complexity of QC for new modalities in biologics. After all, precision drives quality.

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Getting to Grips with Bagging

Bags that cannot be processed properly can cause operational issues. It's time for a more standardized approach.

By Tilman Roedle, Lead Expert Drug Delivery Systems at Vetter Pharma-Fertigung GmbH & Co KG

When the pre-sterilized syringe format was introduced in 1980, it was intended for laboratory purposes and small-scale filling. Tubs were manually unbagged and opened to fill the syringes. Today, it's a very different story, with regulations stipulating specific processes and quality for aseptic filling. Because of their ease of use, pre-sterilized primary containers are the standard for biopharma companies filling injectables, creating demand for high-speed filling machines. Some of these machines have outputs over 50,000 units per hour and six double-bagged tubs per minute. With such large handling volumes, the unbagging process is usually fully automated. Double-bagged tubs can be beneficial due to aseptic quality requirements and the new Annex 1 guidance of the EU GMP Guide incoming!

Understanding the actual bagging and unbagging process is important. It starts with the inner bag, which must be folded after being sealed during the production process so that it can fit into the outer bag. When the automated unbagging process begins, the outer bag is cut and the tub with the remaining inner bag is pushed through an opening ("mousehole") into the class C area. During this process, the inner bag should unfold, making it possible to be properly cut when the tub enters the class A area.

It sounds straightforward, doesn't it? But there is a common problem: incompatibility between the alignment of manual and automated processes. The manual element is the folding of the inner bag – which each supplier does their own way, often with suboptimal instructions. The automated process is the cutting of the bags at the filling manufacturer, which requires accurate and reproducible characteristics to operate at high performance.

Any therapist will tell you, "Don't force together pieces that don't fit. It rarely works out." An inner bag that cannot be properly cut will stop the machine. Manual intervention at this stage is not possible due to the tub's sterility requirements when entering the Class A area. Consequently, the tub must be removed and discarded – and around 160 syringes will be lost. Additionally, machine downtime from occurrence to restart is around 40 seconds. During this time, another four tubs could have been processed. Value (in terms of both discarded syringes and production time) is lost because of inefficient machine use. We estimate that 10 percent of non-processable tubs occur because of improperly folded bags – extending production time by approximately 50 percent.

"Any therapist will tell you, 'Don't force together pieces that don't fit. It rarely works out.' An inner bag that cannot be properly cut will stop the machine."

In my view, it is time for a standardized approach! ISO 11040-7, "Packaging systems for sterilized sub-assembled syringes ready for filling," introduced in 2015, agreed on measures for tubs, nests, and bags – but it does not go far enough. Today, there is a varied market portfolio of different suppliers and formats. To maximize automated handling of double-bagged tubs, characteristics like a folding scheme, the definition of the tub position in the bag, and smaller bag dimension tolerances must be considered for the next revision of the ISO. These changes will help us achieve more efficient processing of bagged tubs.

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The Pandemic Diaries

We ask medicine makers around the world to tell us how their professional and personal lives have changed over the course of the COVID-19 crisis

By David Underwood, founding CEO and Chairman at Quanticate

As a statistician, I closely watched the data that was being collected as the pandemic broke. For those in my age range (60-70), the statistics were not for the faint hearted. It quickly became clear that COVID-19 would be the biggest challenge the world has faced in decades. It has affected every aspect of daily life.

From a business perspective, the integrity and feasibility of ongoing clinical trials have been threatened by the outbreak. At Quanticate, we switched our entire workforce to remote working – and the industry as a whole is now showing huge interest in remote source data verification (rSDV) due to lockdown, travel restrictions, and social distancing.

But trial sponsors have no such flexibility and have been greatly hampered. The impact ranged from a marked slow-down in recruitment rates due to enforced social distancing policies to a complete halt in drug development programs, as pharmaceutical companies rationalized their investments or pivoted focus to join the race for a vaccine. In this environment, it is unfeasible and often impossible to keep a trial running "as usual" for a variety of reasons.

I'm lucky to work with an excellent team that quickly realized these challenges and focused on supporting our clients through the pandemic with the provision of "rescue support" for clinical trials. There are several statistical methodologies that can be applied to provide protection against issues, such as missing data, reduced patient visits and reductions in patient recruitment, that have the potential to impede the scientific integrity of a trial.

The pandemic's impact over the coming years will be widespread and although the severity is still unknown, it is possible to examine core components of studies with centralized statistical monitoring on an individual basis, and identify the most affected areas. By putting mitigating strategies in place, it may be possible to salvage some of – if not all – a study's potential.

On a personal level, as the outbreak began, I invited my mother who lived alone to live with me. If you had told me 30 years ago that I would be living with my elderly mother, abiding to a lockdown, and washing all deliveries to avoid a deadly virus, all while running a 250-employee strong global organization, I would never have believed it. But every cloud has a silver lining and I am grateful to be spending this time with my mother and family.

By Zahid Tharia, consultant at the Pistoia Alliance

The COVID-19 pandemic has meant that many conferences have been transformed into digitally accessible events – and this has affected the Pistoia Alliance too. A few months ago, we replaced a physical event with a series of virtual events that explored the implementation and adoption of digital technologies in pharma. Speakers from across the industry addressed themes including emerging science and technology, the lab of the future, and the impact of AI and its underlying disciplines on real world-data. The success of these events motivated us to

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"Our goal is to help biopharma developers across the world optimize their drug development journey – from early phase to commercialization," says Abizer Harianawala, Site Leader for the Boston Center. "And where better to locate our new Center than in a leading hub of biopharma innovation? From here, we can support the global biopharma community via a dedicated team of experts in materials science, chemistry, mechanical engineering, pharmaceutical sciences and drug delivery systems."

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"Stevanato Group has always helped clients consider the full life cycle of their product so that they can make the right choice about the primary container and closure system in the very early stages of the project, streamlining the overall development process," says Drake. "And our new Center further improves on this winning formula."

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replace our annual conference, with a digital one this October.

Fortunately, we have a lot of experience in this area and have actually been operating as a virtual organization for a long time! We've always been focused on ways to collaborate that aren't hampered by geography. So, we've had the tools and platforms in place to host virtual events like this for a while.

Over the last few months, remote working has been implemented relatively smoothly across the industry. Even before the pandemic, we'd already seen many companies embracing digital and virtual technologies within the laboratory setting through our Lab of the Future (LotF) initiatives, and this has now picked up further pace. In areas like clinical trials, virtual and digital technology is proving invaluable as companies explore ways of keeping patients enrolled in trials despite social distancing barriers. Now, the challenge is to ensure new digital projects are interoperable, and that we do not end up with a surfeit of digital tools in a year's time that only benefit a limited number of companies and patients. If we work together, we can ensure that innovations borne of COVID-19 have long-lasting positive effects.

We recently launched a new series of programs to help organizations collaborate on advancing the role of digital technology in life sciences R&D and healthcare – the first initiative will aim to define standards for collecting patient-centric data using digital tools. This theme was on our agenda long before COVID-19, but the pace at which digital solutions are adopted can only be accelerated. Social distancing will continue for some time, meaning organizations and researchers will need digital tools to change how, for instance, clinical trials are run, and how people can continue to work within clinical settings and laboratories. This acceleration of digitalization against the backdrop of COVID-19 makes it even more crucial that the industry works together, shares its knowledge, and adopts industry-wide standards so that data can be shared and therapies identified much faster.

Looking forward, we can but wait and see what the future holds for physical events – and we look forward to being able to come together again to share expertise and network face to face. Our priority for now remains supporting collaboration. And it's great to see our members doing so much to identify treatments and therapies for COVID-19 and to see examples of collaborative projects.

By Kenneth Lee, Commercial Head and Director of Business Development at GenScript ProBio

Almost everyone in the world has been affected by COVID-19 and it's clear that we must prepare for the long haul. This issue is not going to disappear in a few months. Fortunately, there are many outstanding drug development technologies available and I have seen many good therapeutic candidates. At my company, we see many projects related to COVID-19, including oral medicines, vaccines, antibodies, and antibody drug conjugates. Many scientists are putting a lot of effort into devising new ways to deal with the virus – and it's my sincere hope that the industry has the development and manufacturing flexibility to bring treatments and vaccines to communities as soon as possible.

It can take anywhere from five to 15 years to develop and fully commercialize a biologic product – but we cannot wait that long for a drug to tackle COVID-19. Fortunately, regulatory authorities are working favourably with drug manufacturers to move projects along as quickly as possible – and, in some cases, there is room to bypass certain aspects of development and move faster (while of course still adhering to safety requirements). I'm seeing some projects benefiting from huge reductions in manufacturing turnaround times after discussions with regulatory agencies.

I encourage companies who are interested in this space to be creative, to work with their manufacturing partners to develop effective solutions, and to work with regulators to see how timelines can be shortened. Together, we can discover the best way of maximizing the chances of approval.

By Mike Jagielski, CEO at KCR, UK

The first half of 2020 brought unexpected and unprecedented challenges – both personally and professionally. As a CRO organization, we felt the impact of COVID-19 immediately so our response had to be quick. We developed the KCR

Task Force for COVID-19 to gather regional regulatory information for daily evaluation and to gauge the probability of impact on all our portfolio projects. This information kept our project teams fully informed and ensured the most optimal health and safety of all patients, employees, and healthcare professionals involved in our projects. Our leadership team also worked to understand how decentralized processes and technologies could be leveraged to alleviate risks.

Like many other R&D industry organizations, we experienced substantial site-level impacts on trial operations as the pandemic spread. Using methodologies such as remote monitoring allowed our organization to make it through Q2 – and brings me to one key point: these times, though difficult for many reasons, perfectly displayed our full potential as human beings and as research professionals.

Our teams not only proved that we are supportive and committed, but also capable of developing skills in remote management, communication, and time management with unprecedented speed and efficiency. This crisis brought us closer together and revealed that progress does not always necessarily need to be planned or methodically tested to be achieved when times are tough (though undoubtedly, a planned and methodical research process is essential to developing innovative and safe medicines – and processes in this regard must stay the same). Simply, sometimes extraordinary circumstances force deviations from the norm for the rapid advancement of new solutions.

For instance, when the COVID-19 pandemic began to intensify in late February, I had already recorded a podcast episode on the long-standing need for sustainability in the research industry. The episode discussed how more energy-conscious solutions could keep the clinical industry from adding to the climate crisis. When the pandemic began to intensify, it exaggerated the need for advanced trial technology and integration. Thus, when the podcast was released in May, the speed and uncertainty of the pandemic had already launched many of the topics discussed into reality. While remote monitoring, reduced business travel, and telehealth operations seemed like difficult tasks to implement industry-wide in January, the pandemic presented a dire situation and industry professionals across the globe implemented "green" solutions to ensure the survival of clinical studies.

During this time, country borders, cultural differences, and competitive business were not important, but the health and safety of patients, employees, and healthcare professionals were. The industry has certainly banded together to support one another all while achieving extraordinary progress.

By Ger Brophy, Executive Vice President – Biopharma Production at Avantor

A global pandemic is unique in its ability to affect every aspect of life, and right now, everyone is experiencing significant challenges in managing the disruption.

For me, COVID-19 has emphasized why business continuity planning is so crucial. Business continuity means considering, among other things, partnerships with global life sciences companies that provide chemicals and single-use products, and the breadth of their supply chains. Acute problems for chemicals and single-use providers in a specific region could affect the entire world's production of a critical ingredient.

Quality, logistics, and supply chain have always been fundamental to our biopharmaceutical production business – even before the pandemic – but the pandemic has tested some of what we knew to be true but didn't think about every day.

Our supply chain and our global distribution network have allowed us to maintain our ability to operate and move critical materials around the globe, while taking proactive safety measures to ensure business continuity. For example, having plants in different jurisdictions, potentially with different restrictions, has always been part of our business plan. Especially during this time, being global has given us the flexibility to maintain our operations continuously. Our distribution infrastructure has also allowed us to navigate our network and work around obstacles.

We have always known that our relationship with our partners is not simply transactional. A situation like this demonstrates how strong partnerships between manufacturers and suppliers not only help to increase process efficiency but also to minimize potential missteps in the development and scale-up of therapies.

Additionally, these relationships enable better monitoring and measuring of a raw material supplier's quality management system to ensure consistency over time. Manufacturers may notice some vulnerabilities there – and address them. Breakdowns in QMS can be catastrophic, so the importance of collaborations, routine audits and quality agreements cannot be understated.

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"CURING CANCER? THAT'S CUTE"

FROM THE FRINGE OF THE FRINGE TO THE BRINK OF A REVOLUTION IN MEDICINE; THIS IS THE CELL AND GENE THERAPY STORY AS TOLD BY THE SOCIETY THAT WAS THERE AT THE VERY BEGINNING – THE ISCT

BY JAMES STRACHAN

In the early 2000s, Catherine Bollard took the stage at an international scientific meeting to tell delegates about her work using T cells to treat cancer – an approach that would eventually be described by an FDA Commissioner as "revolutionary." But she wasn't presenting to a packed auditorium. She was in a small room away from the bigger sessions and recalls, "Pretty much everyone there was a friend."

Cell and gene therapies may be an integral part of today's treatment triumvirate: small molecules, large molecules, and advanced medicines. But it wasn't long ago that today's star researchers were seen as outsiders by the mainstream. "There wasn't a lot of enthusiasm for cell therapy," says Bollard, Professor of Pediatrics and Immunology at The George Washington University and Children's National Hospital and Past-President of the International Society for Cell and Gene Therapy (ISCT). "Colleagues were either impressed that we were working on something so 'out there' or, more often than not, skeptical or dismissive. The idea of using the body's immune system to kill cancer was like voodoo to many oncologists."

Clockwise: ISCT 2011 Rotterdam Co-Chairs (L to R): Massimo Dominici, Ineke Slaper-Cortenbach, Fred Falkenburg. ISCT members enjoying the poster hall. 90's era ISCT exhibit hall *Credit: ISCT Photo Archives*

"The scientific community would say, 'Well, isn't that cute, but will it ever work?'" says Bruce Levine, Barbara and Edward Netter Professor in Cancer Gene Therapy at the University of Pennsylvania and ISCT President. "That skepticism was always in the back of your mind."

In the early days of cell therapy, researchers came together – escaping the back rooms of bigger conferences – to share their radical ideas at ISCT meetings. Back then, ISCT was known as ISHAGE ("ice age"): the International Society for Hematotherapy and Graft Engineering. "There were researchers looking at stem cell transplants, graft engineering, T cell depletion, and things like that," says Levine, who joined in 1999, just after he and Carl June re-established their cell manufacturing facility at the University of Pennsylvania. "We saw the society as an important resource because there was no roadmap for cell therapy – you had to chart your own path."

"They were quite small, boutique meetings back then," says Bollard. "And they were more focused on stem cell processing, so we in cancer immunotherapy were actually on the fringes – the fringe of the fringe!"

"They were small in comparison with today's meetings," adds Levine. "But they were and remain a great source of support, education, and monitoring. Perhaps most importantly, in those early days, they were eye-opening for attendees. They realized they weren't alone in their institutions – there were people on all six continents working alongside them in the field."

Miguel Forte, Chief Executive Officer at Bone Therapeutics and ISCT Immediate Past Chief Commercialization Officer, remembers being "flabbergasted" at the cultural difference between the ISCT meetings and the big oncology and rheumatology meetings. "When I first attended 10 years ago, it felt like a handful of people with different starting technologies ranging from reconstructing a lung to using mesenchymal stem cells (MSCs) to treat autoimmune diseases," he says. "As Bruce said, it was seen as a 'cute' thing – like we were just playing with technology. But look where we are only a decade later…"

GOOD SCIENCE, GOOD MENTORS – AND PASSION

At its core, the cell and gene therapy story is about innovation. For any innovation to succeed, you need something simple, yet crucial – belief. So what was it that made the early pioneers in advanced medicine believe that they, despite skepticism from colleagues, would bring about a revolution in medicine?

For Bollard, it came down to three things: mentorship, confidence, and passion. "This year's ISCT annual meeting is a special one because I had the chance to present the Lifetime Achievement Award to my mentor and former boss, Malcolm K. Brenner," she says. "If it weren't for Malcolm being President of ISCT, I probably wouldn't have joined ISCT in the early 2000s. His support was invaluable early in my career – and now I'm presenting his award as past-president. It feels like I've come full circle."

Science was also of paramount importance. Bollard says that she was convinced of the merit of focusing on the immune system – and "wasn't willing to take no for an answer." The experience of watching a friend suffering from Hodgkin's lymphoma go through

multiple, ultimately unsuccessful, rounds of chemotherapy and radiotherapy solidified her belief that there had to be another way – and fueled her passion for finding it.

"The treatment was initially successful and she went into durable remission. She then got married, immigrated to America, and was getting on with her life before being struck with acute leukemia. She died within six months of her diagnosis," says Bollard. "That leukemia was the direct result of the previous bouts of chemo and radiation she had received, and I just thought, 'There has to be a way to kill cancer without killing healthy cells.' Even then, researchers knew that the immune system was our best natural defense against cancer." With that, Bollard's path was set. "When you've got strong beliefs in the science, fantastic mentors, passion, and drive, you're going to be resilient and find new angles when you face challenges – even when people tell you that what you're doing is crazy."

Levine says one of the most impactful books he read early in his career was Commotion in the Blood (1997), which laid out the roller coaster history of the first 100 years of immunotherapy. "Throughout the book you can relive the disappointments of early investigators and the skepticism and scorn of the wider scientific community," he says. "I read this just after Carl June had asked me to start a cell manufacturing laboratory to support an adoptive immunotherapy trial, and we were collaborating with Cell Genesys on the very first Chimeric Antigen Receptor clinical trials. Now Carl is the ultimate optimist and mentor. But, if the rest of science is putting you down, who is right? Well, into my career comes ISHAGE/ISCT, and I thought that if Carl's crazy and I am crazy, we might as well be crazy together trying to get this technology to work."

For Levine, it was meeting patients that most kept him motivated in the face of skepticism. "I will never forget going in to meet a patient on one of our myeloma trials to thank her for enrolling," he says. "She kindly looked at me and said, 'Why would I not volunteer?' These patients placed their faith and hope in us and that was a great responsibility to them and to their families. Mix in the great team when we moved to the University of Pennsylvania and the support from colleagues and friends in ISCT and you have all the motivation needed."

COMPLETING THE REVOLUTION

As the years went by, cell therapy's clinical results spoke for themselves. Early skepticism regarding therapeutic efficacy gave way to concerns about logistics and commercialization. All the while, the number of people entering the field increased substantially across various disciplines. "Traditionally, only bone marrow transplant doctors administered cell therapies," says Bollard. "Now, the field is open to oncologists, cardiologists, orthopedists, and many more disciplines – and this is reflected

in the growth of ISCT membership and its annual meeting."

Fast-forward through years of scientific advancements, hurdles, and setbacks to 2017, when Novartis pulled off the impossible: the first CAR T cell therapy approval – a huge moment for the field. But, according to Forte, economics was key: "Here, we had Novartis come in and say, 'We're going to do this at a large scale and spend a lot of money taking the products through clinical trials – and be successful with the approval.' It proved to other big pharma and biotech companies that the business model was viable. It was game-changing."

So far, where CAR T has been adopted, healthcare systems have coped well with the logistical challenges. Payers, too, have been generally willing to consider new pricing and reimbursement models to support curative (though often expensive) treatments. But, as the afterglow of the first approvals begins to wear off, the cell and gene therapy field is coming to terms with the fact that it hasn't revolutionized medicine – yet. For that to happen, it will have to crack solid tumors – and to deliver at scale it will likely go down the allogeneic (off-the-shelf) route.

"We're beginning to see success with allogeneic "off the shelf" approaches, which is great, but the next step for the field is for cell and gene therapy approvals to become more "mainstream"– that will really put advanced cell therapies on par with the more traditional approaches," says Bollard. "But the real blue-sky potential is finding a cell therapy to routinely cure solid tumors. An approved therapy there could be groundbreaking for the field and, more importantly, for patients. We could potentially treat millions of people worldwide."

"I'm excited about combination approaches to enhance the efficacy of CARs and the progress that is being made in solid tumors," says Levine. "As the field evolves, we're going to see an increase in the integration of diagnostics and biomarkers in determining which cell and gene therapy to give to a patient. We've already done some work on predicting responses in CAR T patients."

Although looking forward to allogeneic cell therapy's evolution in the coming years, Forte mainly wants to see the field optimize existing approaches. "Now that we know the cell works – and that it can be made into a commercial product – we need to optimize everything," he says. "That means modulating cell function to make treatments more effective or off-the-shelf, improving how we source cells – induced pluripotent stem cells (iPSCs) will become increasingly important here – and how we deliver them."

HOLDING IT ALL TOGETHER

Forte says the growth of the society has mirrored the growth of the industry. "For example, ISCT's commercialization committee was established to keep track of the challenges facing developers trying to turn these therapies into commercial realities," he says. "There are many such challenges – but they're good problems to have." And over the years, the organization has further broadened its scope to include committees on legal and regulatory affairs and quality/operations, as well as other stakeholder committees, such as the Presidential Task Force (PTF) on the Use of Unproven and/or Unethical Cell & Gene Therapies, and Early Stage Professionals Committee.

> "THE REAL BLUE-SKY POTENTIAL IS FINDING A CELL THERAPY TO ROUTINELY CURE SOLID TUMORS."

In recent months, the field has joined countless others in facing the difficulties raised by the COVID-19 pandemic. In many countries, hospitals simply weren't permitted by governments to conduct non-COVID-19 related trials. Elsewhere, patients have been more reluctant to travel to hospitals because of the risk of infection, which has affected trial recruitment. "Bone Therapeutics had two studies approved at the beginning of the pandemic; we had to halt recruitment and wait for the situation to improve," says Forte. "We saw that things were improving in Hong Kong, which is where we recruited our first patients, but we have now (at the time of writing in July) started to recruit patients in Europe too."

Investor attitudes have also shifted as the scale of the pandemic unfolded. "Investment by no means dried up, but the discussions did change with the onset of the pandemic," Forte says.

Unscrupulous "clinics" preying on pandemic fear also popped up. And so, ISCT members have intensified their efforts against unproven cell and gene therapies for COVID-19 and led calls for proper clinical procedures for legitimate COVID-19 therapies (both of which you can read more about in The Cell Therapy Guardians on page 30). The pandemic also affected ISCT's annual meeting, which was due to take place at the end of May in Paris. ISCT decided to go virtual; our "How to Deliver a Virtual Conference in Under Two Months"

sidebar reveals how they did it – and how it went.

But, at the time of writing, economies are beginning to open back up, paving the way for advanced medicine development to resume. So, as the field continues to evolve, what will ISCT look like in the next 10 to 20 years?

Forte believes ISCT may have to play a greater role in the ethical debates that will take place as the field reaches its full potential. "The sky's the limit when it comes to what you can do with cells in terms of reconstructing, modulating, and improving function," he says. "The benefits for patients will be tremendous, but we're not too far away from being able to go beyond restoring health to designing specific traits." Cell and gene therapies could be used to change how we look, how we think, and even how long we live – raising a wide range of ethical questions. "We might be entering the realms of science fiction here, but CAR T cell therapy sounded like science fiction just 10 years ago," says Forte. "ISCT is well placed to be part of these discussions and to take a position on them – we have to make sure there's an ethical dimension to everything we do."

Another interesting development is the rise of China as a hotspot of advanced therapy development. "China's importance to the global cell and gene therapy industry is set to increase and that has important implications – especially as their regulations continue to evolve – for companies in Europe and the US," says Levine. "Many discussions are taking place between Western and Chinese companies about potential partnerships. But challenges such as IP protection, movement of goods and people, and cultural differences must be overcome. ISCT is a global organization with recognition in China, but I think there is scope to increase our presence there and to engage Chinese players further to help facilitate collaboration."

For Levine, as President of ISCT, the big challenge is having a global perspective and vision while also respecting local needs. "We need a global exchange of ideas and information, but cell therapy must also respect patients and physicians at the local level," he says. "We recognize that not every country has the infrastructure or the expertise to review and regulate the conduct of translational and clinical research in cell and gene therapies. This is exactly where ISCT can serve as a resource and forum to connect researchers, clinicians, and regulators."

For Bollard, it is amusing to discuss how we can bring together the global cell and gene therapy industry, given how different things were only a decade ago. "You could have never predicted back then, ostracized as we were, that we would be embraced by the scientific community and industry and talking about how to get proven technologies to millions of patients," she says. "The whole thing just takes you by surprise. But the craziest part? The field is still in its infancy and we can still take it so much further."

HOW TO DELIVER A VIRTUAL CONFERENCE IN UNDER TWO MONTHS

By Queenie Jang

As soon as we heard the news of a viral outbreak, we began monitoring the situation very carefully as it spread first through China, then Europe, to Italy, Spain and France – where we were planning to host the ISCT 2020 Annual Meeting . As a global organization, we knew that many of our delegates would be flying in from the USA and elsewhere. We didn't know what government bans on group gatherings and international travel restrictions would be in place. Should we cancel the meeting? Could we postpone it, and if so, to when? What about a virtual meeting? These were the options everyone on the executive management committee (the three presidents, the global treasurer, the global secretary, and myself as CEO and chair) had to weigh up in our weekly discussions about the situation.

Other societies postponed their meetings and, for some, it seemed a no-brainer that we should do the same. But we didn't know what restrictions would be in place, how long the "peak" would last, or whether there would be a second wave. Would we end up in the same situation a few months later? We also had to keep in mind our members. The ISCT annual meeting is a business meeting, an educational forum, and one of the most important events of the year for our industry. In the end, after a lot of soul-searching, we decided in mid-March that the only viable option was a virtual meeting.

Making the decision was the easy part. Once we had chosen our path, we had just seven weeks and, like so many others, very little experience in delivering virtual meetings. Fortunately, we recognized early that this might happen (having world-leading immunologists in your team certainly helps during a pandemic!), so we had researched virtual platforms as early as January. This meant that we were able to sign a contract with our chosen virtual meeting platform provider 48 hours after we decided to go virtual.

One thing we didn't want was just a series of webinar streams. A lot of our members were working extremely hard during the pandemic – many on the frontlines – and most were dealing with screen fatigue. We wanted to offer people a bit of a break and a chance to learn and to engage with peers. But we also wanted to capture some of the magic of the physical meeting and provide something that felt like ISCT. I've always believed that, when someone attends an ISCT meeting,

it should be about the experience – people should know it's an ISCT meeting. And that's what we tried to recreate in a virtual setting.

When you enter the platform, you're greeted with a screen that looks something like the actual entrance of the convention center – with ISCT branding everywhere and even avatars of our meeting co-chairs, president, and president-elect greeting you. But the really interesting element is the "exhibition hall." We spent a lot of time working with our exhibitors to make each "stand" unique – they had their own customized branding and arrangement of chairs, posters, and so on. More importantly, attendees could chat via text (which could also be translated live into over 40 different languages) with exhibitors. We gamified the whole LIVE event so attendees could win prizes for interacting. We also had posters in the "poster hall," which were scored as they would be at the physical meeting – and you could chat with poster presenters. Networking sessions were planned during the meeting, but messages could also be exchanged for 12 months after the event. The same was true of sessions, many of which were panel discussions delivered live and available also as on demand pre-recorded sessions. We tried to use the same terminology and event structure we have always used. We did everything we could to make it quintessentially an ISCT meeting.

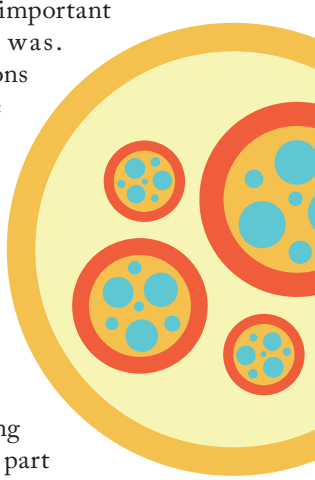
Putting this together in under two months was, to put it mildly, a real challenge! Even during the event, things were somewhat frantic behind the scenes. We'd spent hours brainstorming how things might go wrong – what to do if a speaker disconnected or people couldn't gain access or register properly – but we still learned things after every live session. Going live across the globe was also tricky. We had people working 12-hour shifts so we could help with technical issues anywhere in the world. We also had to consider whether our bandwidth requirements were appropriate for attendees from across the world. Overall though, we were really happy with how the event went – in spite of the butterflies in our stomachs beforehand. For the two day LIVE: delegates spent an average of 19 hours on the virtual meeting platform during these two LIVE dates; over 32,000 views of the sessions and over 17,000 poster hall visits. Attendee numbers for the two LIVE dates are 2024.

That said, we could never totally recreate everything that happens at a live event – the chance meeting, the introduction from a colleague, going out for a meal or a drink. Plus, with people working from home, colleagues may act as though they aren't "really" at a conference – they'll still respond to emails and messages they might postpone during a physical event. There's something about traveling to a location away from the office – including the home office – that makes it a unique experience.

> "ONCE WE HAD CHOSEN OUR PATH, WE HAD JUST SEVEN WEEKS AND, LIKE SO MANY OTHERS, VERY LITTLE EXPERIENCE IN DELIVERING VIRTUAL MEETINGS."

The big question is: what are our plans for next year? We know that a lot of our membership really liked the virtual offering; indeed, for a number of attendees – especially those early in their career, or those in the developing world – this was the first time they could attend an ISCT meeting. So the future plan is to aim for the best of both worlds – a hybrid model. Going forward, we'll hold the physical meeting as we normally would, but keep a virtual component for those who can't attend in person. There's a lot to iron out in terms of how to make that happen, but we're confident it can be done. The good news is that we've got a little more time to prepare!

We had to put in a herculean effort to pull it off this year, but we knew how important the meeting was. The conversations that take place during panel discussions – between industry leaders, academics, and regulators – are the oil that greases the wheels of industry. The same can be said of the business meetings that take place. How many innovations in our industry began, or were sped up, by conversations had at a conference? Conferences like ours help our industry develop and deliver life-saving treatments. And we're pleased to be a part of that.



THE CELL THERAPY GUARDIANS

We speak with Laertis Ikonomou, Chair of the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies, and Associate Professor of Oral Biology at the University at Buffalo, SUNY, and Dan Weiss, ISCT Chief Scientific Officer and Professor of Medicine at the University of Vermont, about the ISCT's work to combat unproven cell therapies and its drive to ensure that studies into legitimate COVID-19 cell therapies rigorously demonstrate safety and efficacy.

How widespread is the problem of unproven therapies?

Laertis Ikonomou: The problem of unproven cell therapies is a global one. A decade ago, this phenomenon was known as "stem cell medical tourism" in which patients in the USA and Europe would travel abroad to access unproven "stem cell" treatments. Now, there's no need. Most Americans can find an unproven "stem cell" clinic within driving distance – and the same is true of Canada, Australia, New Zealand, Europe, and parts of Asia. Why? These clinics have undoubtedly benefited from the hype surrounding legitimate cell therapies.

What procedures do the clinics offer and what are the consequences?

Ikonomou: Interventions include autologous bone marrow extracts and, until recently, stromal vascular fraction from adipose tissue. These have been reduced in the USA after injunctions against companies. Increasingly, companies are offering perinatal tissue-derived products and exosomes.

Patients have suffered serious injuries and even death because of these procedures. The time spent accessing an unproven therapy is time that could be spent receiving a proven therapy. Financial damage is important, too, as none of these unproven approaches are covered by insurance. Some clinics encourage people to take on debts or crowdfund to pay for expensive treatments, which can affect their ability to afford proven therapies and cause psychological harm.

What is the main aim of the Task Force?

Ikonomou: The main aim of the Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies is to monitor the situation, educate all parties involved, and protect patients worldwide. Initially, we published an extensive guide – a series of articles in Cytotherapy – in which we defined "unproven therapy" and examined several aspects of the phenomenon. How are they offered? What are the regulatory implications? How does this impact legitimate cell and gene therapy development? We also actively monitor where these clinics emerge and what kinds of procedures they offer, and we send out regular press releases and issue statements jointly with other societies.

Dan Weiss: The ISCT is a nonprofit organization, which means we cannot lobby politicians to effect change. But what we can do is raise awareness and, most importantly, educate people – especially patients and their families – so they can make informed choices about their healthcare.

What about clinics offering unproven treatments for COVID-19?

Ikonomou: A number of clinics have claimed to treat COVID-19 using unproven cell and gene therapies – particularly in the USA. Usually, they will simply add COVID-19 to the list of conditions their "therapies" claim to treat, obviously without proof of efficacy. The ISCT has issued statements to strongly condemn such practices. We recently released a statement with the International Society for Extracellular Vesicles to point out that exosomes are not a proven modality for COVID-19.

Weiss: In the USA, the FDA has taken a proactive stance against companies offering unproven COVID-19 treatments. They've sent out several letters a week essentially telling these clinics to stop advertising this garbage! I'm paraphrasing of course, but they clearly recognize that this is a growing problem.

What about legitimate therapies for COVID-19? ISCT has recently argued for the importance of proper clinical trials. Why was it important to get this message out?

Weiss: Finding an effective treatment for COVID-19 could not be more pressing. But we need to rigorously demonstrate, first and foremost, that these therapies are safe and that they provide benefits beyond what is already available. We can't have companies saying, "We've got some cells and we're going to inject them into patients and hope they do something." Existing protocols for establishing safety and efficacy must be followed, even in exceptional circumstances, such as the COVID-19 pandemic.

There are also specific reasons we need to be especially careful with cellular therapies for COVID-19. We know that, when we inject cells into the bloodstream, they can sit in the lungs for a couple of days before being cleared out. This hasn't been a problem with other therapies, but we know that COVID-19 patients are more likely to form clots in the lungs. Developers need to take this into consideration when testing, and we're aware of some investigations that have not done so.

Are there any promising legitimate therapies for COVID-19?

Weiss: I think mesenchymal stromal cells for COVID-19 respiratory failure have a good chance of showing real benefits. We have to be extremely careful for the reasons I've discussed, but there are current trials addressing safety and efficacy and I'm very much looking forward to their outcomes.

Good Things Come in Small Packages

SCHOTT introduces an online shop with low minimum order quantities to help smaller companies overcome the challenges associated with conventional purchase order procedures for primary packaging.

With the prominence of small biotechs and start-ups in the biologics development space, the traditional big pharma business model is being disrupted.

In 2018, for example, 38 of the 59 new drugs approved for use by the FDA originated from small biotechs (1); however, many aspects of the supply chains in a pharmaceutical environment are still geared towards larger companies – including primary packaging. The complex and sensitive nature of biopharmaceuticals demands robust packaging solutions, which tend to be subject to minimum order quantities – a common practice in many industries. But for smaller companies developing a drug product for a niche patient population, "minimum" can mean burdensome.

Finding the right vendor is also a challenge for small businesses. A large variety of packaging solutions is available across different suppliers, and an easy comparison between various offers is sometimes difficult. Additionally, price negotiations with suppliers, reams of paperwork, and long lead times before receiving orders are commonplace. To keep up with the industry's trajectory, we need new, modern solutions to ensure suppliers can support the smallest – and arguably the most influential – companies in the biopharma arena.

The order process: simplified

To make it easier for smaller companies to order the packaging they need in the right quantities, SCHOTT has launched an online shop for its customers. With low minimum order quantities, the online platform provides customers with containers in desired quantities without lengthy manual ordering requests. The online shop stocks a range of premium ISO-certified borosilicate glass special vials, as well as ready-to-use containers. Options include a variety of filling volumes, coatings, and different blowback types for vials. All products are in stock and ready to ship quickly. Furthermore, pre-tested container-component systems in ready-to-use formats round off the offer. The latter are especially interesting for labs and start-ups looking for an easy way to order pre-sterilized containers and matching components in small quantities. The solution is called SCHOTT Fast Track Kits. The kits consist of adaptiQ® (currently available in 2R, 6R, 10R, and 20R formats, but the portfolio will grow) ready-to-use vials, and matching stoppers – everything required for fast and simple processing. Further product types, such as syringes, cartridges and COC Polymer containers can also be requested online. Offering these from stock is part of the shop's growth plan.

Regardless of the type of packaging sought by current and future customers, the user-friendly design of the online shop aids navigation and streamlines the purchasing process; existing customers will easily find their products and detailed information on packaging solutions. And new customers, who may be less familiar with the SCHOTT brand, can easily discover information on products that suit their needs. Of course, SCHOTT's customer service team is always available to help and respond to any questions. It is simple for customers to register themselves on the shop's website and they can place the order without the usual price and document exchange associated with traditional ordering processes negotiations (which can be difficult for smaller customers).

One key advantage of SCHOTT's range of products offered in the online shop is the ability to use them during the complete product life cycle of the drug. Order quantities can be easily scaled up and packaging registration stays untouched.

SCHOTT's pharma online shop is currently available within the European Union but will be available to customers in the USA and Canada in Fall 2020 – inquiries from other countries are welcome, too.

SCHOTT Pharmaceutical Systems design solutions to ensure medicines are safe and easy to use for people around the world. Because human health is of the utmost importance to SCHOTT, the company will continue to use modern technologies to support businesses on the front lines of drug development, regardless of their size.

Visit the online shop to find out how SCHOTT can assist with your primary packaging needs:

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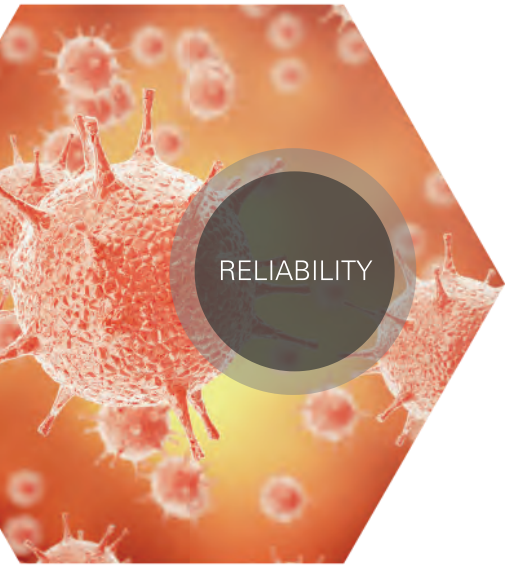
https://shop.schott.com/pharma/



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The Patient Voice

Pharmaceutical products are made for patients, so it is essential that drug development incorporates the patient view

By Sven Stegemann

Launching new products is a source of growth and sustainability for any industry, but innovation is particularly important for pharma, which thrives on discovering new molecules for the treatment of acute and chronic diseases. Because of the pharma industry, effective therapies exist for the major chronic illnesses and, increasingly, for more complex and life-threatening diseases as well. Life expectancy has grown along with therapeutic advancements, but so too has the number of patients living with multimorbidity and polypharmacy. In addition, downsides have surfaced, including a rise in medication-related hospitalization, medication errors, and, unexpectedly, poor therapeutic outcomes.

Medication-related problems are a major cause of unplanned hospital or emergency department admissions, especially in older patients, as well as a leading cause of premature death in US hospitals (1). Hospital admissions could have been predicted and prevented in over 60 percent of cases (2), and it is estimated that over 80 percent of medication problems occur on the patient level (3). Today, there is increasing focus on seeing the patient as an active partner in medication management and therapeutic effectiveness – and ensuring that pharmaceutical products are usable in the real world to help patients take their medicines as intended.

Design partners

When we buy a consumer product, our choice is based on value and perceived benefit – mainly ease of use, functionality, and expected outcomes. For products like smartphones, many different customized versions exist to cater to various user groups. Market research and consumer involvement have been established processes for many years. Including consumers in the development process makes them active partners and helps ensure products are designed to their needs.

This approach is slowly coming to the pharma industry; for example, the FDA introduced human factor and usability engineering in 2016 for medical devices to ensure they were safe and suitable for use by the intended patient population (4). The benefit of patient involvement in medical device development can be demonstrated by the optimization of a prefilled syringe for use by rheumatoid arthritis patients (5). Such patients can struggle to handle drug delivery devices, but an ergonomically designed syringe significantly eased the self-administration of injections.

For many years, non-adherence was regarded as poor patient behavior that could be solved with better instruction. But when the FDA started an initiative to collect direct patient feedback on treatments in early clinical trials – without the interpretation of healthcare professionals – it became obvious that patients often change or stop the regimen because they experience adverse reactions that interfere with their daily lives and outweigh the perceived benefit of the therapy. To understand patients' views on new drug therapies, the FDA has introduced a plan for "Patient-Focused Drug Development" guidelines. The guidelines describe "a systematic approach to help ensure

"Involving the target patient population in a drug development program is still far from common."

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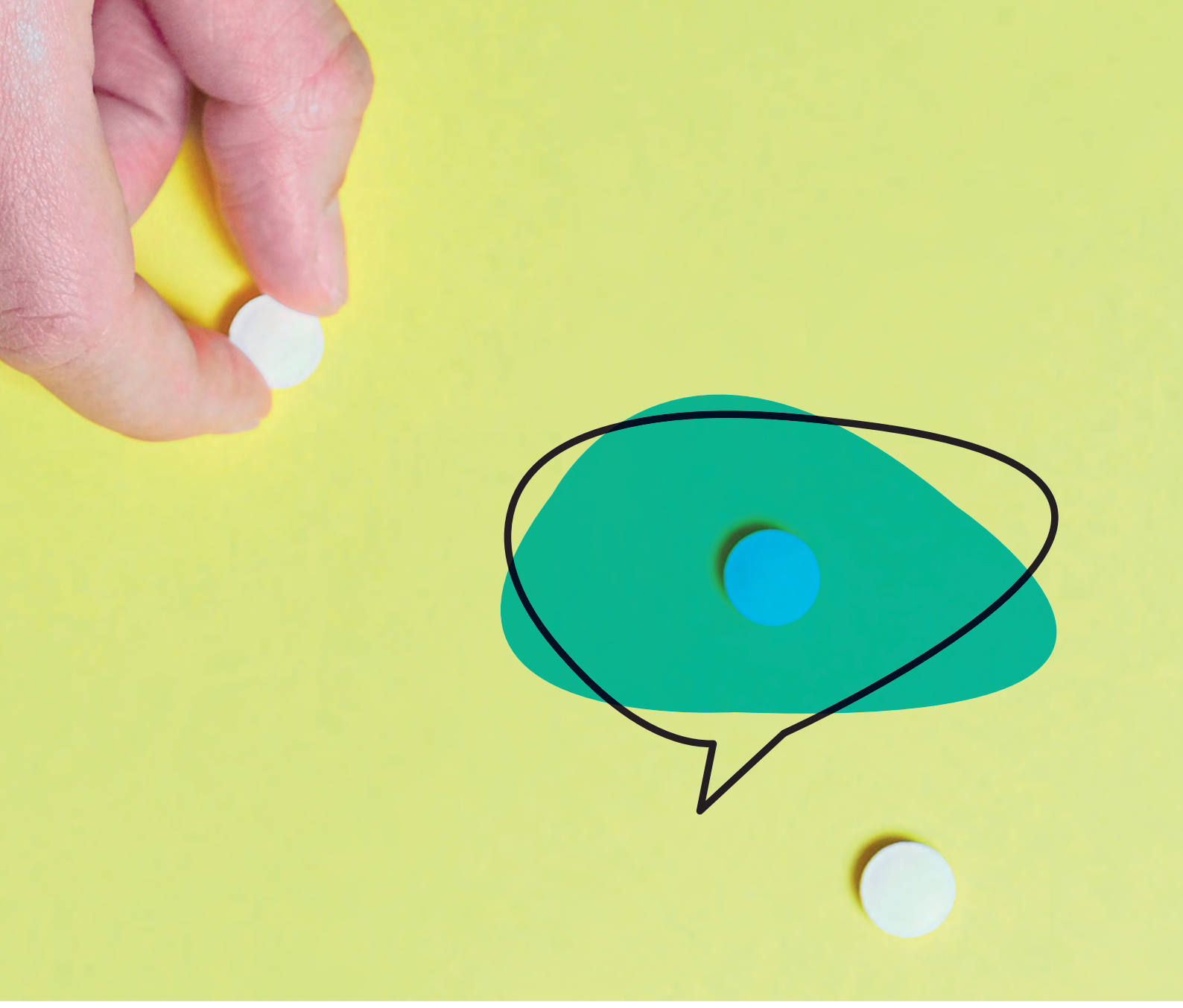
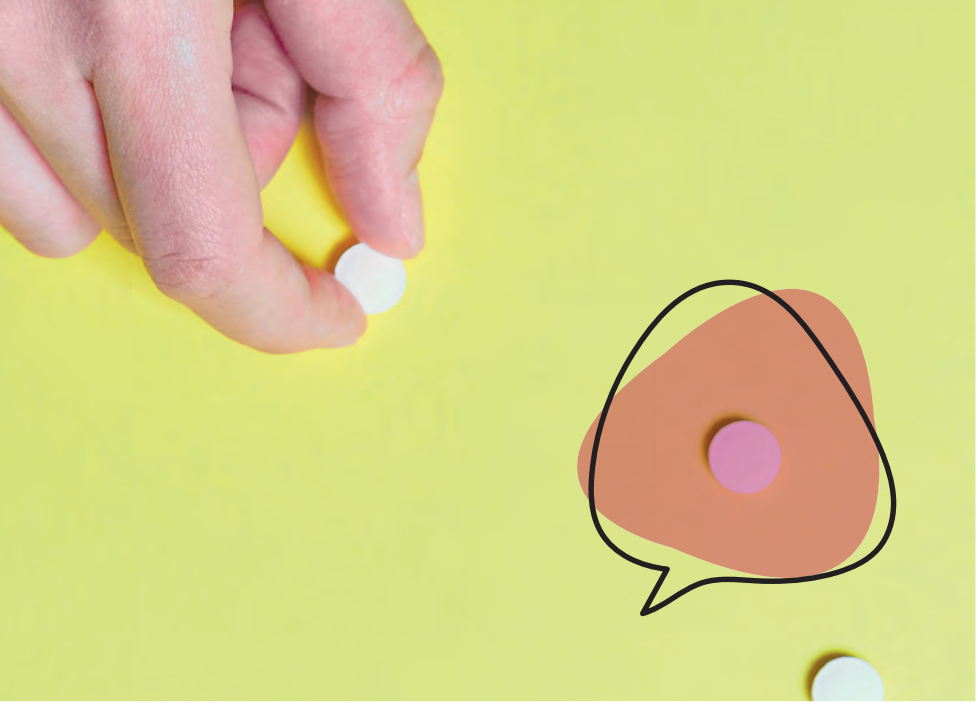


that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into the development and evaluation of medical products throughout the medical product life cycle." (6). As such, patient-focused development will, in the future, become part of the drug evaluation and approval process.

Involving the target patient population in a drug development program is still far from common in the pharma industry. There are good reasons for this; the early stages of drug development come with high attrition and high risks, coupled with uncertainties on the specific clinical indication, including dose regimens, timelines, and regulatory requirements. When clinical proof is established (around phase II), the market formulation has to progress very rapidly, leaving limited time for the pharma company to consider the patient voice in their established formulation and drug product development processes. Unsurprisingly, new drug products usually end up being repetitions of standard tablets that have not been tested for true usability by the target patient population.

Considering the needs of patient populations should not be a burden for a drug development program; it is simply a matter of selecting the right options at the start of commercial product development and understanding the needs of patients in real-world settings. Consider older or multimorbid patients; the medicines may prevent fatal events in the future, but could have a negative effect on the patient's present quality of life and plans. These patients also have more specific



needs than younger, healthier patients; for example, multimorbidity is often associated with the decline of functional capabilities like grip strength, dexterity, eyesight, hearing, and cognition (7). Increasing the number of drugs can also lead to complex treatment schedules difficult for even professional caregivers to compile as intended (8).

Recent studies reveal that patients deal with medicine usability issues in their own way based on learning with prior medications. Crushing or splitting larger tablets for swallowability reasons was seen as normal practice, without even considering that the leaflet instructions might not allow such procedures. Another important issue is product identification after a tablet has been released from the packaging into, for example, a multiple-compartment compliance aid. Many tablets are similar in size, shape, and color (9). There is limited guidance on what real patients can differentiate best, but identification of twelve different solid dosage forms was investigated in type 2 diabetes patients. The shortest identification times and lowest error rates were observed for colors, especially bichromatic forms, followed by shape and size. Color was recognized very easily (10), whereas shape depended on perspective. Size determination required direct comparison and a significant size difference. Most importantly, all volunteers used "semantic cues" to describe the search item (e.g., blue, yellow, round). Colors are learned from early childhood and have a clear name, unlike shapes, which are not always straightforward; descriptors like the "diet", "slim," or "funny one" were just some examples used (11). Other research groups investigating the acceptability of different acetaminophen dosage forms found that the most accepted oral dosage forms in older patients were capsules, closely followed by oral disintegrating tablets and powders (12).

Listen to the voices

The patient voice is a rapidly growing area of science – and collaborations are emerging to help translate research findings into better-optimized medicines for patient use. For example, the Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik (APV, Germany's working group for pharmaceutical process engineering) and the Geriatric Medicine Society e.V. have joined forces to create the "Patient Centric Medicine Initiative" (PaCeMe). PaCeMe groups experts from academia, industry, and regulatory science to develop a practical and meaningful roadmap to better incorporate patient needs in commercial drug development.

We cannot ignore the growing evidence that drug usability and acceptability by patients is a critical factor in achieving desired therapeutic outcomes (13). If patients do not take their medicines correctly, they will not get the therapeutic benefit. As human beings and patients, we act on learning and intuition. With consumer goods, we expect self-explanatory design and usability without any barriers – and it is common for these types of products to incorporate views from users during the development process. We need to do the same in pharmaceutical development.

As the pharma industry and its regulatory authorities begin to understand the importance of the patient voice, we can move toward a new, collaborative model of product co-creation. According to ICH Q8 (R2), "in all cases, the product should be designed to meet patients' needs and intended product performance" (14). The ideal co-creation process should capture what matters to the patient about their medicine, including what they expect from the product and how these expectations can be built into it. The process should include patients, the company, and its suppliers, who will need to develop scientific expertise beyond the excipient and its application. In some cases, there may be "easy win" solutions. For example, by observing how

"Recent studies reveal that patients deal with medicine usability issues in their own way based on learning with prior medications."

patients handle secondary packaging, you will likely find many ways in which the packaging can easily be optimized to meet patients' needs.

A more collaborative approach to drug developments that takes into account the patient view will result in optimized medicines with better usability for the patient and acceptability that will finally help to achieve the desired therapeutic compliance.

Sven Stegemann is Head of Global Scientific Business Development at ACG

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Charting the Rise of Single Use

Single-use systems have come a long way. Timothy Korwan, Director, New Product Development – Single-use, and Sean DeFusco, General Manager, both at Avantor, discuss biopharma's experience with the technology so far – and consider why it has become a popular choice for producing new drugs.

Take us back to the early days of single-use...

Timothy Korwan: During the late 90s, I started working for a biotech company that relied heavily on stainless steel, but we slowly began introducing single-use technologies where we could see immediate benefits; first in filtration to replace multi-use components in the transfer steps between tanks. We realized immediate benefits by removing cleaning steps and saw a faster turnaround for some applications. Over time, we began integrating single use for simple 2D and 3D bags, holding containers and for non-sterile application buffers.

Sean DeFusco: We've always been using single-use products in the industry; we just used to call them disposable products. For example, though they fit into a reusable metal housing, the filters themselves would be thrown out after one use. Items such as tubing tended to be single use as well. It was when we started combining these components into more sophisticated systems that single use took on the meaning it has today. There was early demand to integrate ready-to-use systems in stainless steel environments, but they required a device to mate with the stainless steel. That's when we saw the crossover begin, where single-use technology was introduced to a stainless steel system. As soon as those connectors were developed, uptake increased and the true benefits of single use began to be realized, making processes more efficient and cost-effective.

When did single use really start to take off?

DeFusco: One defining moment was the introduction of aseptic disposable sampling systems in the early 2000s, which fundamentally changed the way sampling from stainless steel bioreactors was performed. Previously, taking a sample required steaming of all the metal parts and glass bottles, and it would often produce a bad result. False positives were common and by the time you figured this out it could be too late. With the introduction of closed, single-use sampling systems, no one sampled the old way anymore. New metal bioreactor designs also helped eliminate steam drops, and plants were even built without the capability to operate in the old way. We don't have false positives anymore; we know the results are accurate. I think this highlighted the potential of single use – and from there, pharma companies began imagining other ways that single use could improve processes.

Korwan: Another significant milestone was the advent of the traveling wave single-use bioreactor, which was something that could not be easily scaled in stainless steel. The bag could be rocked to achieve the right oxygen transmission in the bioreactor, and it produced very good cell expansion.

Both the wave bioreactor and disposable sampling system fundamentally changed how biomanufacturing was conducted and inspired people to do things differently – without stainless steel. Single use led to a revolution in how to build and run a bioreactor, how to sample, and how to scale up production. Far more than just popularizing the use-it-once concept, the early adopters of single use changed the biopharma workflow at its core. And once the first single-use commercial-

scale bioreactors were born, there was a significant leap forward.

What were the early concerns?

Korwan: Initially, there were some concerns about cost, validation complexity, and regulatory reliability – in particular concerning the possibility of extractables and leachables. The main question was whether single use would negatively impact drug quality. There were also some early reliability problems and questions concerning leakage, but the main issue was trust: can you trust your highly valuable drug product to a plastic bag? Early on, I think many saw single use as an interesting concept with applicability to process development, but did not envision a future for the technology in commercial manufacturing.

But today, single use is prevalent throughout the biopharma industry. And it's now acknowledged that it can be scaled up quickly for commercial drug manufacturing. In the early days, it was restricted to unique applications in initial-stage product development areas, but now it's seamless across the entire scale and workflow. An entirely single-use facility is now possible.

DeFusco: In biopharma, early adoption of new technology is often not immediately seen as an advantage over competitors; people tend to take the "wait-and-see" approach.

People are more comfortable with single use today, largely because of big pharma's high-profile experience with the technology. Consider the Takeda facility in Lexington, Massachusetts, which was one of the first commercial-scale plants with no cleaning systems. It

Right, Sean Defusco; left, Timothy Korwan

was single use from beginning to end, and perfect for producing orphan drugs. Shire took the leap – under the close scrutiny of their competitors! The success of the company became a benchmark for others. The plant hosted many other drugs afterward, proving that single use was no longer theoretical, but a viable way of manufacturing medicines.

What are considered the biggest benefits of single use?

Korwan: Cleaning is one. Often, a stainless steel system must be disassembled when it comes to cleaning – and it's a tedious and time-consuming job. Cleaning obviously isn't required for single use so production is more continuous, meaning that a single-use plant can produce more batches per year than a traditional stainless steel facility. The lack of cleaning also comes with environmental benefits in terms of reduced water and energy consumption. On the flip side, however, stainless steel advocates point to the disposal problems with single-use systems, particularly unrecyclable plastics. The struggle to improve the recyclability of single-use systems used in biopharma manufacturing is an ongoing challenge.

Today, single-use products are used for the manufacture of the vast majority of drugs, particularly new drugs. The technology may not always extend to the bioreactor, but it is evident in sampling, fluid transfer and storage. The many fluid and material transfer interconnections between the different steps in drug production are rarely top of mind, but that's where facilities are looking to single use to solve production challenges.

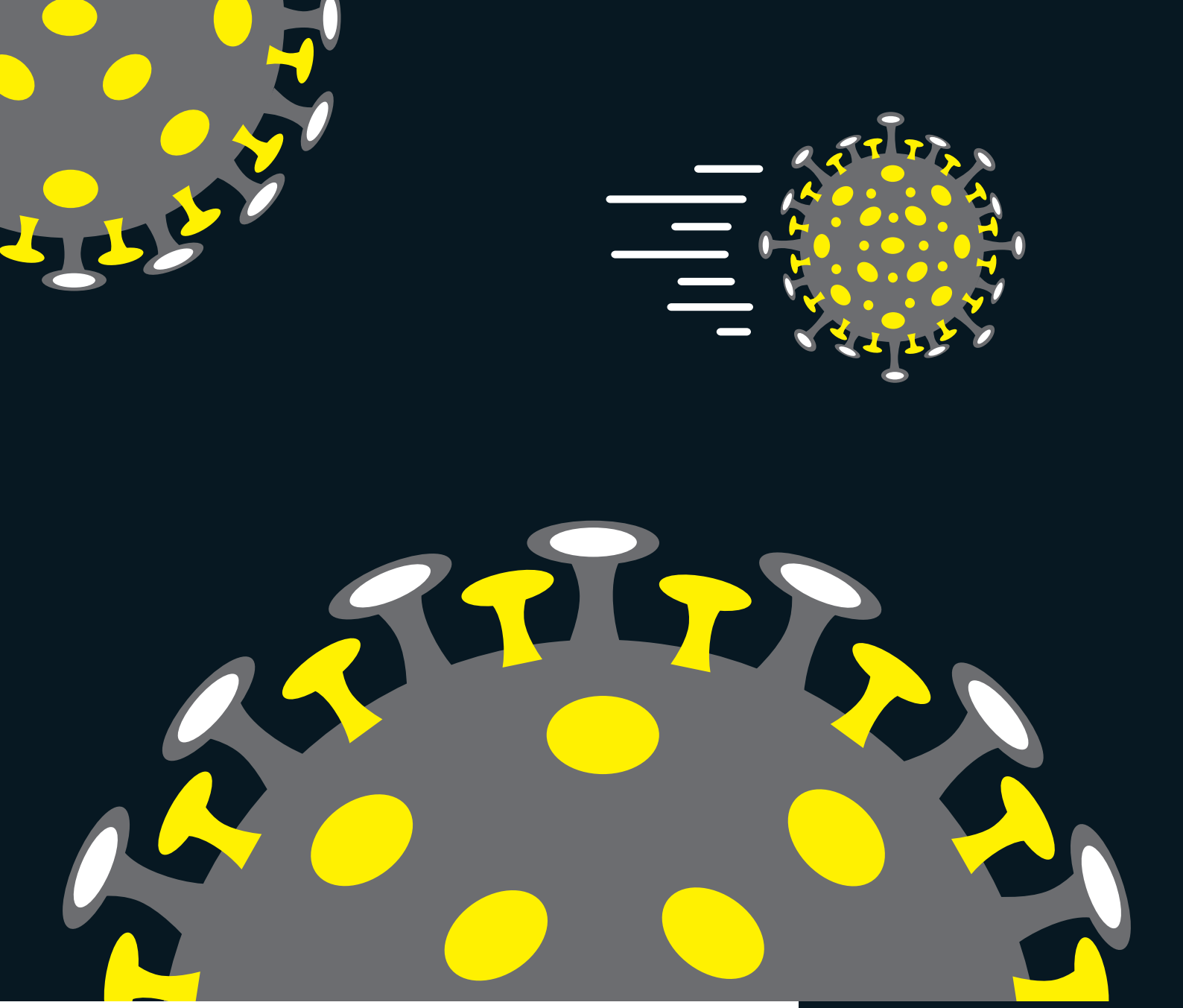
DeFusco: The lack of a cleaning requirement is a nice aspect of single use – certain features of a stainless system can be notoriously hard to clean! The reduced need for cleaning results in cost savings, but the broader economic picture of single use comes into play the most when building new facilities. A stainless steel facility can take years to build so the investment will be tied up for a very long time. Construction must begin early, but by the time the factory commences manufacturing it may already be out of date. Imagine buying a brand new car and then leaving it in a garage for eight years. It would still be new of course, but it would be very dated.

There is also the fact that many phase III drugs fail. There have been instances of facilities being built for a specific product, and then sold off or demolished before they are ever used – a huge waste of money. Single use plants are faster to get up and running, and the important build/not build decision can be delayed until there is more certainty about the future of the drug. If things do change after the facility has been built, it's fairly straightforward to change out the single-use systems (replumbing an entire stainless steel facility on the other hand would be far more difficult). In short, single use offers much greater flexibility.

What are the biggest lessons the industry has learned about implementing single use?

DeFusco: Facilities traditionally relied on a large engineering staff – internal or external – to design every detail of a facility, right down to the piping layout. Single use came along, and suddenly just a few people could do the job by sketching it on a notepad. There was a major loss of design rigor that caused considerable issues early on. Most companies today produce specifications with more detail than a mere sketch. Providing the necessary level of design rigor was a valuable lesson learned.

Another lesson we're still learning – and COVID-19 is a great reminder – relates to the logistics and supply chain attached to single use; either all or part of the manufacturing plant must be shipped in to make every batch of drug. This huge logistical undertaking involves a complicated supply chain that is vulnerable to interruption events, such as weather, a disaster, or pandemic. In such cases, whole countries might not be able to export or import goods. Most drug plants were not built with an attached warehouse for all the consumables that single-use processes require, but the need to obtain, inspect,



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sort and store these items is critical to an effective supply chain.

Korwan: The topic of supply chain logistics often goes unnoticed because we talk about the technology so much. But whether it's film chemistry or tubing or connectors or sensors, if you don't have it all packaged for delivery when you need it – and able to withstand typical and atypical transit trouble – it doesn't matter how good the technology is: it won't get there. This aspect is not considered enough in the single-use world. Vendors have to put a lot of work into establishing their supply chains and logistics processes. And if you're looking to adopt single use you need to take this into consideration early in your planning.

What's your advice for a company unable to decide whether to adopt single use?

Korwan: When designing or writing a specification for a single-use application, my advice is to design for the application – you should always try to be as agnostic as possible when it comes to components in your design. I've seen too many designs specify components by specific vendors and this limits the flexibility of that design. Of course, there will always be exceptions, but thinking first about the application and function is best practice and allows you to design for easy substitutability and second-sourcing where prudent. For instance, don't write a specification using vendor names, but select materials based on application. Including a particular vendor requirement in your specification can limit your capabilities if there's a problem with that vendor or the production process. Think more about the technology and what you're trying to achieve – and don't write specifications in a counter-productive way.

DeFusco: I've seen some mistakes when companies decide that adopting single use is their primary goal. The primary goal should always be to make every batch of drug product reliably and predictably. Single use can help achieve that goal, but some projects focus too intently on implementing single use. If you keep the real goal in mind, a single-use approach can work well and reduce costs. But ultimately it depends on what fits your business plan. Some companies may prefer to stick with stainless steel. The facility location and the intended scale of production will likely lead you in one direction or another. For example, in drier regions where water is less available, cleaning less frequently is a much bigger factor in decision making.

Is there room for improvement in single use?

DeFusco: There is plenty of room for improvement in materials and deliverability. In some emerging areas, such as cell and gene therapy, the industry is adapting products that came from the medical device industry. There are shortcomings there, but they are the only materials/approaches currently available. It's similar to where we were 15 years ago in biotech when we were using available industrial products and adapting them to the needs of the biopharma industry. But innovation led to big improvements – and the same will happen with emerging fields.

Korwan: Beyond improving the supply chain for single use, there are huge areas for improvement in the general capacity of the industry. Materials and construction continue to get better and more specific, especially at the molecular level.

What about the ongoing debate around standardization?

DeFusco: Most people are only interested in a standard product if it is their standard. We're a long way from having a true consensus standard, which would require that every drug plant be built the same. We can certainly make a standard assembly, but if the spacing between equipment isn't uniform in every factory in the world, it just won't work. Worse, too much standardization can stifle innovation. The opposite is also bad, where every new application needs a new set of drawings, assemblies, bags, and so on.

Modularity is the likely path forward. It may not lead to standardization across the industry, but it drives the process within each plant. A single facility may use many duplicates and redundant skews. There is an enormous opportunity to reap some benefits of standardization by reducing skews and simplifying supply chains, but still allowing each drug manufacturer to develop incremental process improvements.

Korwan: Standardization can also apply to the manner in which things are done, such as how to conduct audits, and how we request data and provide information. This topic has become prominent during the pandemic. For example, consider a situation where we are helping with a new COVID-19 therapeutic. The client requires an audit, but the auditors are quarantined and can't travel to the site. A standardized audit procedure would enable others to step in and do the job. I think there are no doubt many opportunities to standardize in areas like this, which would lead to increased efficiencies.

How does the vendor relationship change with single use versus stainless steel?

DeFusco: When purchasing stainless steel equipment, you are looking for a vendor that can deliver the product you need on time and in spec. Though some after installation support might be necessary, it is mostly a discrete project. When you choose a single-use process, you're choosing a partner – likely for the lifetime of that drug product, so choose carefully! It's a very different decision and involves different criteria, such as supply chain considerations.

Korwan: It's a fundamental difference in approach and a complete shift in mindset. You want a company that can manage a project really well and deliver worthwhile results. Trust and reliability are everything. You need people who can run a project properly and deliver consistently for as long as you make that product.

Candidate Commercialization: A Helping Hand

How to drive antibody drug development and manufacture forward safely and quickly

In today's busy biopharma market, speed is of the essence – and demand for COVID-19 interventions means that it's more important than ever to find ways to safely accelerate the development and manufacture of antibody drug candidates for multiple indications through immunotherapy. Here, Kenneth Lee, Head of Commercial Division, Americas, GenScript ProBio, explains how he helps biopharma, biotech and academic institutions to optimize their manufacturing processes.

At least in the media, development and commercialization typically take a backseat to discovery. What are your thoughts?

You are spot on – almost daily, we hear of promising novel drug candidates celebrated in newspapers. But in many cases, that ends up being the first and the last time we hear about them. Developing a latent breakthrough into a good business project is just as important as making the discovery in the first place. And process development and manufacturing play a key role in minimizing costs and optimizing quality attributes to transform the good science into a good business. At the end of the day, a medication should not just be safe and effective, but also affordable.

How do you help customers?

GenScript ProBio offers one-stop development and manufacturing solutions designed to get drugs to the market fast and affordably, while meeting necessary regulatory and quality guidelines in the US, EU, China, and APAC. We work with customers all the way from cell line development to process development to GMP production. In cell line development, we transfect plasmid DNA into a host cell genome and then screen a large number of clones to select the best one based on productivity, chronology, and stability. Once identified, each hit is confirmed, validated, and characterized using a variety of functional assays. Upon completion, we expand and scale up the single best clone, then optimize additional downstream processes before moving into GMP manufacture for clinical studies.

GenScript ProBio has performed around 200 elite optimization projects and 50 CMC projects, including projects that have obtained IND approval.

What are the main challenges faced during process development?

One clear challenge is maintaining productivity at scale. Better productivity means a high yield; a higher yield means more product per batch; fewer batches mean lower prices. Another challenge is batch failure and contamination. It is vital to have a strict and robust process over the entire course of manufacturing. Fed-batch cultures have a success rate of over 90 percent, whereas the spin filter perfusion approach has a much lower success rate due to the extended culture periods increasing the risk of contamination.

And, of course, cost is often a concern. In GMP production, my advice is to carefully gauge the quantities you need for each step of your development. For example, at the IND filing stage, you might want to manufacture just a bit more than you need for phase I, so that you can use that buffer for the PK/PD/tox studies. This way, you can hedge the risk of overproduction in case you don't succeed.

Every molecule is different. Although working with an established and proven set of cell lines and processes is considered best practice, it's important to be open to experimenting as much as possible when it comes to upstream process development like media and cell culture conditions, so that you can make informed decisions on maximizing productivity and robustness. GenScript ProBio offers "in process consulting" to ensure our clients make the best decision at each step based on data from previous steps.

What investments have you made to increase capacity?

From a production point of view, we will make an additional 2,200 L available by Q4 of 2020, and are building new global commercial production capacity that will be tens of thousands of liters in size by late 2022.

As well as conventional development and manufacturing services, we now offer regulatory consulting and documentation services that are not typically offered by CDMOs.

As a CDMO, it is important for us to grow with our customers. We have served our customers well throughout development and into clinical manufacturing, but the new capacity will allow us to help our customers be ready for global commercialization of their products.

How has COVID-19 affected business?

COVID-19 does not affect our supply chain as we have global operation in CDMO perspective and we keep up our promise to serve our customers as planned. We are also collaborating with many different companies on COVID-19 solutions and working on a number of drug development and manufacturing projects in this area.

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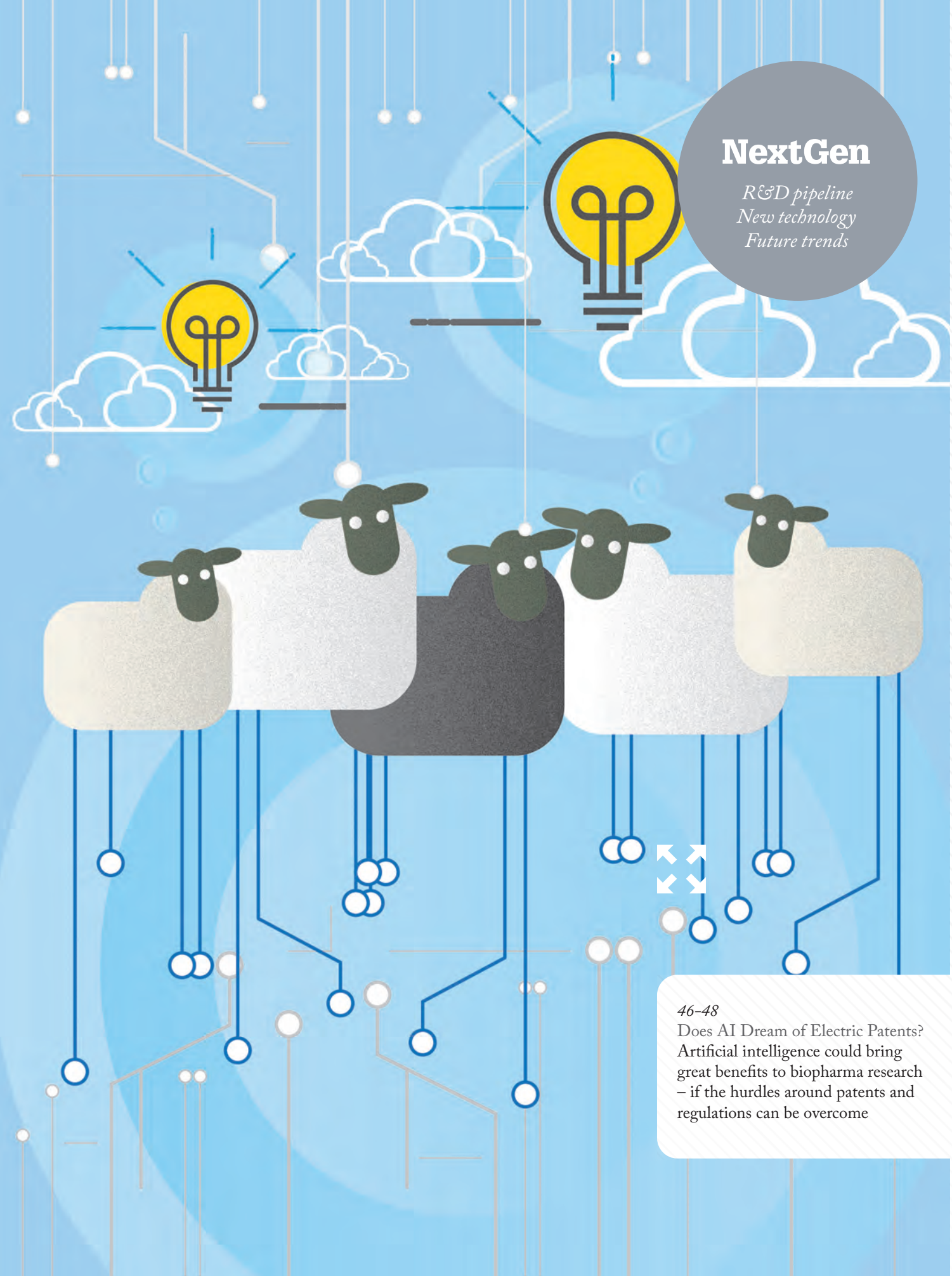

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Does AI Dream of Electric Patents?

To reap the rewards of artificial intelligence and machine learning, biotech companies must overcome the legal, regulatory, and commercial hurdles

By Amy Nick

Developments in artificial intelligence (AI) and machine learning (ML) are playing an increasingly influential role in the pharma sector. FDA approvals of AI algorithms have increased exponentially over the past few years (1), and the AI healthcare market is predicted to reach US$6.6 billion by 2021 (2). A 2019 survey of pharmaceutical and biotech professionals by ICON suggested that 80 percent of survey respondents were using, or planning to use, AI technologies (3). The trend has driven the formation of new partnerships between the tech and healthcare industries; for example, AI startup Concerto HealthAI is currently working with BMS, Pfizer, and Astellas, to support precision oncology initiatives, while Roche's acquisition of Flatiron Health and Foundation Medicine provided proof-of-concept that clinically meaningful insights can be generated through large-scale analysis of genomic and clinical data (4). Meanwhile, major tech players, such as Google, IBM and Microsoft, have all taken steps into the biotech space; among other developments, 2019 saw the announcement of several new healthcare-related collaborations by Alphabet-owned Verily (5), and a partnership between Microsoft and Novartis aimed at integrating AI across clinical development and commercialization (6).

AI and drug design

The use of AI in drug design is considered speculative right now. At the time of writing, no AI-designed drugs have been approved and very few have reached clinical trials. UK-based startup Exscienta was the first company to put an AI-designed drug into clinical trials (7). In collaboration with the Japanese pharmaceutical firm Sumitomo Dainippon, Exscienta succeeded in reducing the development time of its OCD drug to just twelve months. The drug is currently undergoing phase I trials.

The COVID-19 outbreak has created a new sense of urgency as researchers race to develop treatments. There is greater interest than ever before in accelerating the drug development process. With the spread of COVID-19 outpacing the capacity of global healthcare systems, alliances between the pharmaceutical and tech sectors have become more influential than ever in combating the spread of the disease. Though there has been great optimism about AI's potential to assist in drug development, the COVID-19 crisis may reveal which approaches can truly deliver.

Several companies are already employing AI-mediated approaches to combat the pandemic. BenevolentAI, for example, has applied its proprietary AI platform to the prediction of COVID-19 drug candidates (8). The software highlighted members of the numb-associated kinase (NAK) family as potential targets for treatment, and identified baricitinib, currently used to treat rheumatoid arthritis, as a potential therapeutic agent based on its antiviral and anti-inflammatory properties, and safety profile. Meanwhile, South Korean company Deargen's deep learning technology has identified the antiretroviral atazanavir, used for the treatment of HIV, as another possible candidate (9).

US-based biotech company Insilico Medicine has taken a different approach. Rather than attempting to identify commercially available drugs that could be repurposed for the treatment of COVID-19, the company employed AI to accelerate the synthesis and validation of new drug candidates. Their platform has identified six new small molecules, predicted to target a key viral protease, which they suggest could be synthesized and tested for efficacy. Meanwhile, Moderna, the first company to bring a COVID-19 vaccine into Phase 1 trials, suggested that its $100 million investment in digital technologies (including AI) was a key factor in its ability to push products rapidly through the development cycle. Indeed, the speed at which Moderna responded to the emergence of the novel coronavirus is considered unprecedented. Phase III trials have already begun for the company's mRNA vaccine.

"The COVID-19 outbreak has created a new sense of urgency as researchers race to develop treatments. There is greater interest than ever before in accelerating the drug development process."

The Risk of Error

So far, few drug development predictions made by AI have been validated, and the extent to which many of these technological solutions can be implemented in the real world remains to be seen. Critics have also alleged that, although AI may be faster than medicinal chemists at identifying novel drug candidates, the development process for these drugs does not necessarily lead to better outcomes. Nevertheless, the risk of failure is an unavoidable part of drug development and achieving the same outcomes at an accelerated rate now, more than ever, appears a goal worth pursuing. Validation of AI predictions is likely to be expensive and time-consuming, especially where they require the synthesis and trial of new compounds or large-scale clinical trials. Companies investing in this kind of research need to be convinced that the chances of success are worth the risks.

The challenges of using and validating AI can be emphasized by looking at the healthcare sector and diagnostics. Recently, an AI algorithm developed by Google Health in collaboration with Imperial College London made headlines for out-performing human radiologists in the diagnosis of breast cancer. A meta-analysis comparing the diagnostic performance of deep learning algorithms and healthcare professionals suggested that algorithms performed at least as well as human experts in diagnosing a wide range of diseases from medical imaging. However, the authors noted that very few of the studies they analyzed were carried out in conditions that realistically reflected clinical practice. And we must remember that the margin for error is low. Despite the interest in using AI to diagnose patients, the reality is that any mistake could cost lives. This risk is particularly problematic for unsupervised algorithms, which generally offer little insight into the processes underlying their final output, leaving healthcare professionals unable to determine whether anything critical may have been missed. Further work is needed to demonstrate the extent to which algorithm-based approaches to diagnostics could lead to tangible benefits for patients and healthcare systems. Even the most advanced machine learning models are limited by the quantity and quality of the datasets they are trained on, and in the healthcare sector, much of this data may still be inaccurate, incomplete, or biased towards specific populations. Furthermore, algorithms cannot yet take the full clinical picture into consideration in the way that a human doctor would, nor are they able to account for the wider context of a problem, such as its emotional or economic impact.

Although new collaborations between tech giants and biotech or healthcare companies have the potential to drive significant technological progress, they also give rise to a new set of legal, ethical and regulatory issues, which must be resolved soon if progress is to be made at the speed envisaged by the tech sector.

AI meets IP

When it comes to using AI in the drug development process, companies need to consider how they create and protect their intellectual property (IP) – especially with the trend towards personalized medicine. With some products being applicable to just a handful of patients, there is likely to be a greater emphasis on patents that capture the potential value across all stages of the clinical development process – not only the final product. In particular, patents will need to protect novel strategies for accelerating drug discovery, improving patient selection, and enabling treatment optimization, as well as methods of data capture and the analytics underpinning them.

Obtaining such protection will not be without its challenges. In Europe, for example, the approach of the European Patent Office (EPO) to patentability in this area is still evolving. In 2018, the EPO updated its Guidelines for Examination to include, for the first time, specific guidance on how the patentability requirements for algorithms and computer programs should be understood in the context of AI and ML. Meanwhile, in decision T 0694/16, the EPO's Technical Board of Appeal acknowledged that a claim directed to the use of a known drug in a purposively selected patient subgroup could be considered novel, even where the identified subgroup overlapped with the previously treated patient group (10). This decision paves the way for patentability of existing drugs that have been identified by AI and ML platforms, such as those used by BenevolentAI and Deargen, as potential candidates for repurposing.

In addition, broader questions arising from the use of AI are likely to impact approaches to IP in biotech. Standards for inventiveness may need to be revised, as AI interprets and processes information in an entirely different way to a human inventor. Under current law, to obtain a patent, the invention must not be obvious to a person of skill in the relevant field, on the basis of publicly available information. Yet questions will arise as to how this standard should be applied in the context of AI-generated

"These are fundamental issues and navigating them will be complex, requiring careful consideration and close collaboration with stakeholders across the pharmaceutical and tech industries."

predictions. While it could still be argued that Insilico's novel protease candidates are within the scope of what could be achieved by a skilled synthetic chemist, for example, this type of algorithm could conceivably identify drug candidates that are entirely non-obvious to a human expert, but nevertheless an obvious outcome of the application of AI. The more commonplace these methods become, the more difficult it may be to determine the inventiveness exclusively by reference to the perspective of a human inventor.

Such applications of AI also raise issues around the nature of inventorship. Currently, inventorship is generally considered to reside with the person who developed the AI. Yet this situation is likely to become increasingly complex as the capabilities of AI develop and the role of human supervision becomes less prominent. There are currently no specific legal provisions addressing the notion of AI as an inventor. And most jurisdictions require the named inventor to be a natural person (11). Both the UK Intellectual Property Office (UKIPO) and the EPO recently rejected applications because the named inventor was an AI named DABUS, despite acknowledging that the criteria for patentability were met, and the UKIPO has now updated its Manual of Patent Practice to explicitly exclude the AI being named as an inventor.

But this is unlikely to be the end of the issue. As technologies developed by unsupervised learning algorithms become more prominent, we're probably going to see more cases where the extent of the developer's oversight is increasingly insufficient to justify human inventorship – bringing the issue back to the fore.

As more companies switch to AI- and ML-driven approaches, the case law will necessarily develop to take account of such issues and ensure that AI-driven biotech inventions do not risk slipping through the gaps in current IP law. Drug development is a notoriously costly process, and the chance of not being able to obtain a return on investment is likely to significantly disincentivize innovation. The field also needs a balance between ensuring companies can protect the value of their investment and making sure that the monopolies do not unduly limit the potential for progress. Ensuring that a consistent approach to patenting AI and ML inventions will also be important here. Patents require public disclosure; without robust systems for protecting IP, companies may increasingly choose to protect novel AI and ML processes as trade secrets – depriving the research community of the opportunity to build on their progress.

These are fundamental issues and navigating them will be complex, requiring careful consideration and close collaboration with stakeholders across the pharmaceutical and tech industries. Addressing these uncertainties surrounding the role of AI within the biotech field will be essential to move towards an era where the industry can truly embrace technology.

Amy Nick is Technical Associate at Intellectual Property Firm, Mathys & Squire

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If You Build It, They Will Come

Sitting Down With… Kelly Chibale, Neville Isdell Chair in African-centric Drug Discovery & Development, South Africa Research Chair in Drug Discovery, and Director, H3D, University of Cape Town, South Africa.

Why chemistry?

Chemistry is one of those things that people either love or hate. For me, it was more than a subject studied at school or even a profession – it was a calling. I was always fascinated by chemistry as a schoolboy, but I truly fell in love with the logical nature of organic chemistry while studying for my undergraduate degree at the University of Zambia. And everyone knows that when you fall in love it's impossible to control the feeling! I was entranced by the fact that organic molecules, no matter how simple or complex, could be modified and manipulated to create a whole host of products – including pharmaceuticals.

Who inspired you?

One of the most influential people in my professional life was my PhD supervisor at the University of Cambridge, the late Stuart Warren. I'll always be grateful to him for taking a chance on a young student from Zambia, and laying the foundation for much of my future work. I began my studies at Cambridge in 1989 after being awarded a Livingstone Trust scholarship to work in Stuart's lab, where he was developing new synthetic methods for optically active molecules.

What stood out to me about Stuart was his patience and kindness – he always gave me room to grow and learn. Based on my work in his lab, I secured my first post-doctoral position and moved further north to the University of Liverpool. I then joined the Scripps Research Institute in La Jolla for my second post-doctoral position.

These early experiences and opportunities gave me some insight into the types of people who inhabited the scientific arena – not just bench scientists, but entrepreneurs and thought leaders who were creating companies and driving progress. I was inspired to create similar opportunities for scientists on the African continent. Though the continent is often viewed through a lens of poverty and disease, I knew that there were many African scientists who wanted to contribute to the life science community in their home nations and build the infrastructure necessary for improved drug discovery and development. In 2010, this inspired me to found H3D, a drug discovery research center at the University of Cape Town.

What is the premise behind H3D?

To produce medicines for diseases that predominately affect Africans while also creating jobs and African-specific patient models, so the drugs used by African patients are tailored to their needs – improving patient outcomes. Too often drugs are developed abroad and introduced to African countries, despite never being tested in African people. Given the genetic diversity of Africans, that is an important commission, and I felt it important to address the issue through the center.

As an academic, I always thought big – I wanted the center to hold its own against any pharma company – but I knew that I lacked the practical knowledge of the industry to make it a reality. I turned to my friend and mentor, Tony Wood, former Senior Vice-President at Pfizer and now with GlaxoSmithKline, for help. He arranged for me to visit the Sandwich Pfizer site in the UK to learn more about the practicalities of pharma. He even flew out to Cape Town to read and discuss the business plan my team and I had put together. Tony's support was one of the greatest assets we had. He eventually became the first Chair of our Scientific Advisory Board.

Since then, many experts from the industry have passed through our doors and contributed to building our pharmaceutical infrastructure. We've been able to deliver on multiple projects and currently have a phase II trial underway for one of our patented antimalarial drugs. It's amazing how easily my initial fears for the center were put to rest once I learned to lean on those around me with the expertise and skillsets that could help us make a difference.

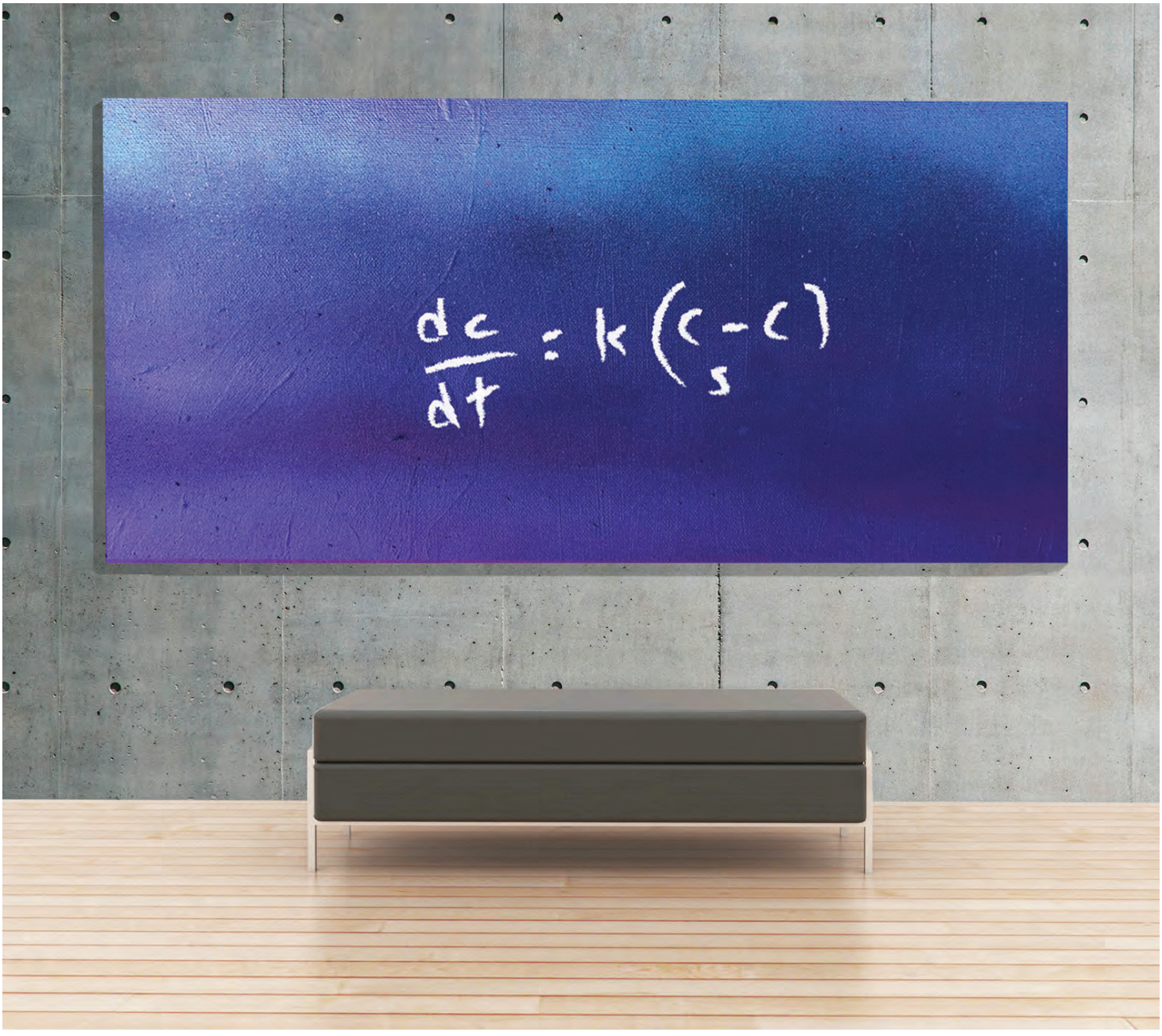
What challenges did you face in getting the center up and running?

H3D is unique in that it is embedded in an academic environment – it isn't an off-site operation but rather like a pharmaceutical company or small biotech integrated into the university's infrastructure. In the center's early days, we had to learn to navigate institutional bureaucracy and work within an environment that wasn't originally intended for pharmaceutical drug discovery. We also had to recruit the talent that would get H3D off its feet. Though it was challenging to find the right people at first, we were able to assemble a team of talented chemists, biologists, and others. They, like me, wanted to see the center thrive and helped us to bring in more talent from around the continent and beyond – we now have an 80 person-strong team made up of scientists from around the world.

Our multi-national team proves that with the right framework in place, people will travel to and work in the African drug discovery ecosystem, in the same way that people are attracted to pharma companies in the West.

What advice do you have for other entrepreneurs?

Be humble. The people that you meet along the way could open doors that you never knew existed! That said, it's important not to be swayed by opinions or people you're not entirely comfortable with. Influence and experience shouldn't intimidate you. As a business-minded person, you will undoubtedly have a vision of what you want to achieve. Don't let anyone steer you along a path that causes you to lose sight of your goals. We all have unique life experiences that we can draw on; use yours to make the best decisions for your company!



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