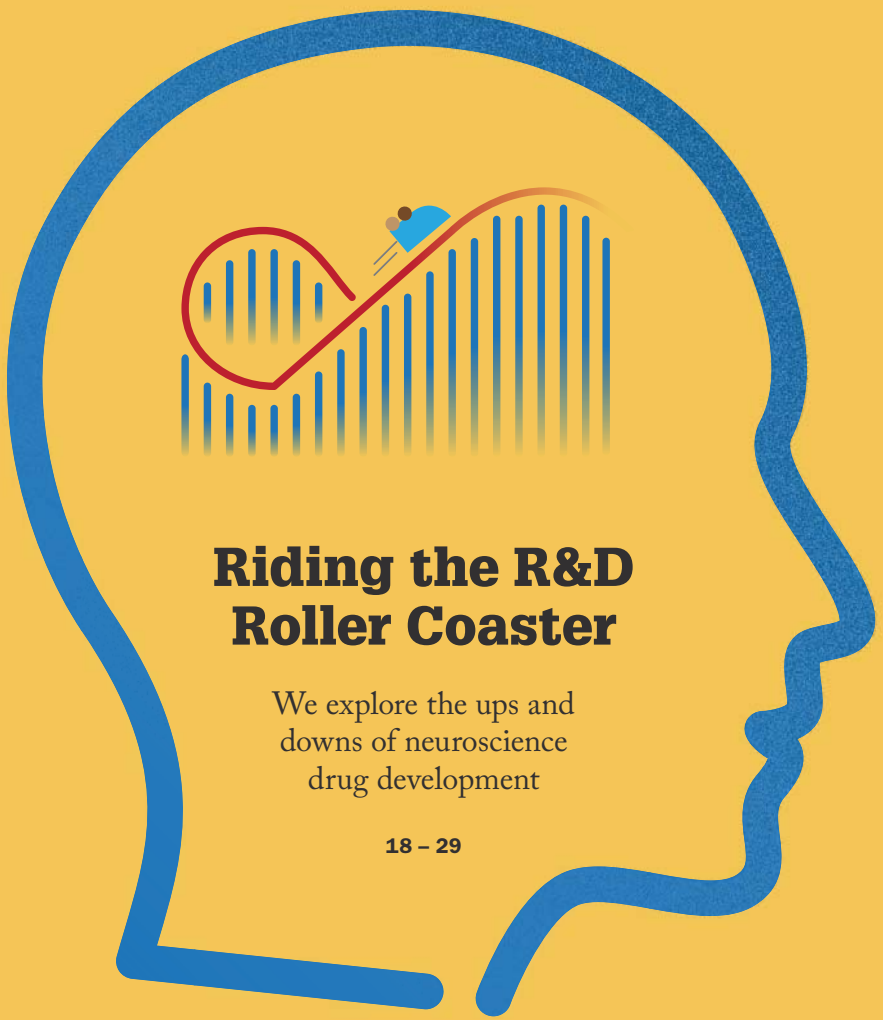
MARCH 2021 # 73

the Medicine Maker®



Riding the R&D Roller Coaster

We explore the ups and downs of neuroscience drug development

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Selfishness and Stupidity?

We have vaccines. Now, pharma's mission is to address novel variants – and vaccine hesitancy.

The end of February saw the FDA approve another COVID-19 vaccine: Janssen's single-shot vaccine – developed using the company's AdVac platform (1). Janssen has also applied for conditional marketing authorization with the EMA.

What the scientific community has achieved in terms of COVID-19 vaccine development over the last 12 months is incredible, but it's not over yet. A number of SARS-CoV-2 variants could affect the efficacy of current vaccines; for instance, the Oxford/AstraZeneca vaccine was reported to be less effective at preventing COVID-19 cases caused by the "South African" variant of the virus – and roll out has been halted in South Africa (2).

But action is being taken. Pfizer and BioNTech recently commenced a study looking at a third dose of its vaccine and how it protects against newly emerging SARS-CoV-2 variants (3). The FDA has released policies to guide developers addressing variants and the EMA has issued guidance that outlines requirements for vaccine manufacturers that are planning to modify their vaccines (4,5).

I'm not worried about the science or vaccine success. The pharma industry has already proven it is up to the task.

I am concerned about the public. Though many people applaud the speed at which pharma has moved, others are suspicious that the vaccines are rushed and unsafe. COVID-19 vaccine conspiracy stories are rife. For a person of average intelligence, conspiracy theories are often mildly entertaining works of fiction, but the anti-vaccination movement is downright dangerous. Outbreaks of measles in recent years in the US have been linked to anti-vaxxers. And during the COVID-19 pandemic, doctors and healthcare workers advocating for vaccination have even received death threats (6).

A UK survey conducted at the end of 2020 found that most British people consider anti-vaxxers "selfish" and "stupid" (7). But experts have also warned that negative attitudes towards anti-vaxxers are part of the problem and will do little to persuade doubters to change their views. A UK university is currently setting up a global taskforce to examine the issues of vaccine hesitancy – and has received £2.7 million (around US$3.7 million) under the EU's Horizon 2020 program (8). The taskforce will "systematically" investigate vaccination attitudes among healthcare workers and analyze the arguments made by anti-vaccination activists to develop tools and techniques to challenge and refute such claims.

Stephanie Sutton
Editor

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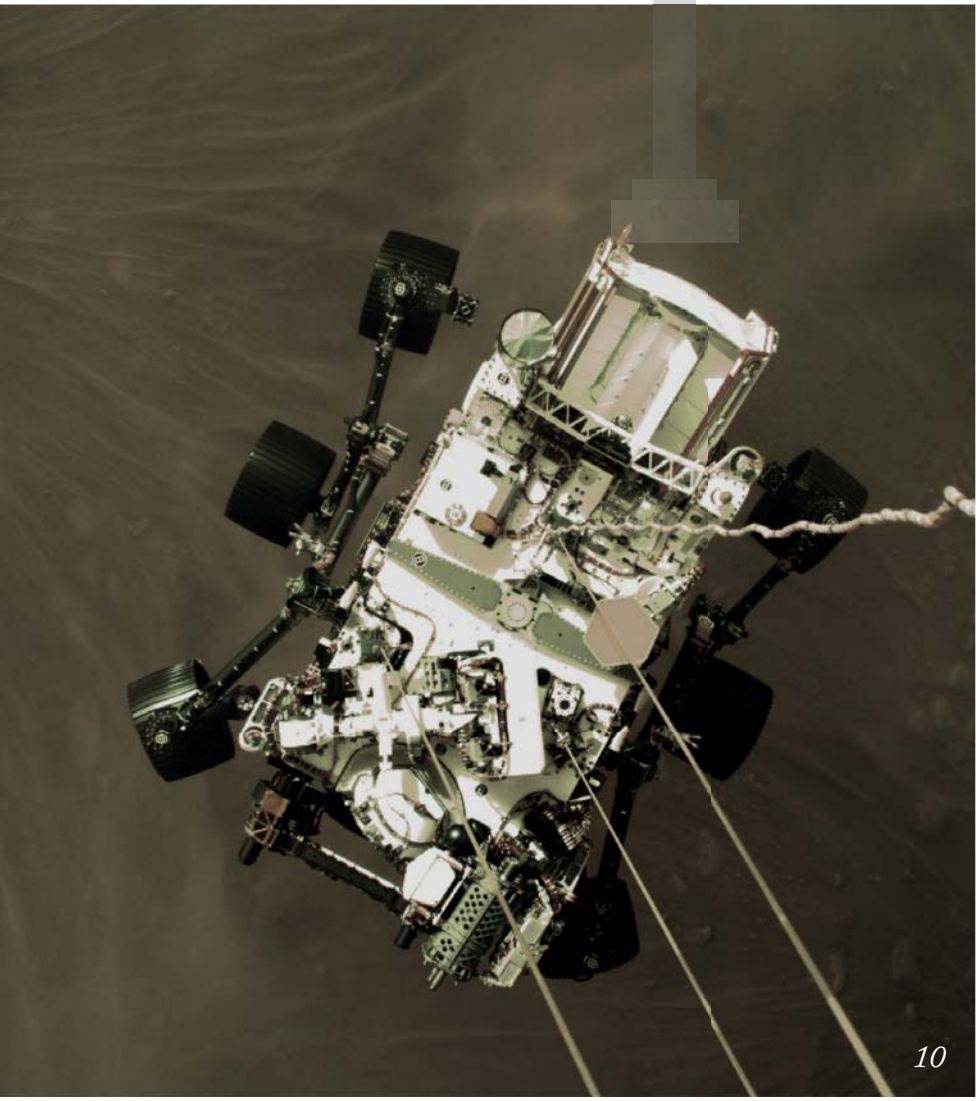
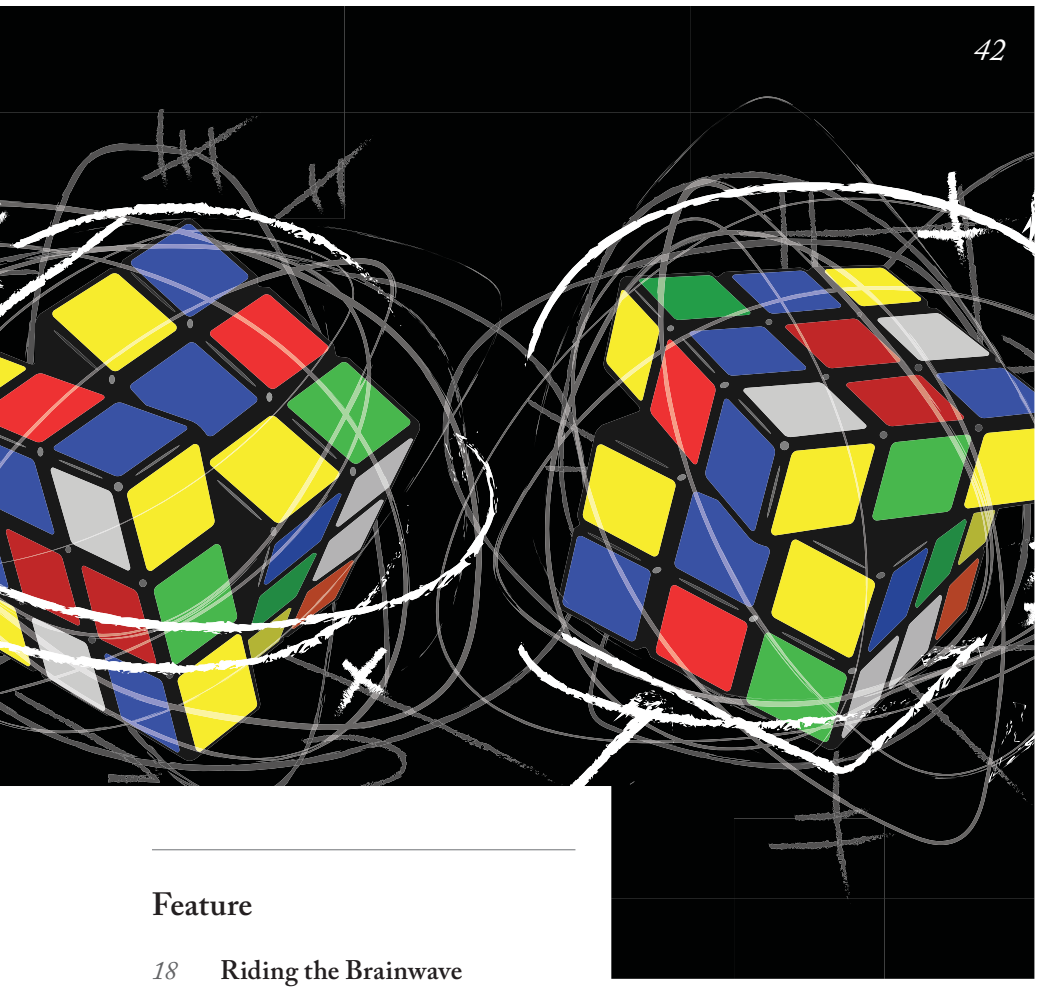


On The Cover

The ups and downs of neuroscience drug development – when will the roller coaster end?



Feature

Business

NextGen

Sitting Down With

the Medicine Maker

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Upfront

Research
Trends
Innovation

Let's cHAT About Drugs

How can we reduce the cost of pharmaceutical intermediates?

Modern synthetic chemistry comes at a high price. Most catalysts used to convert alkenes into pharmaceutically relevant compounds are costly – with rare noble metals such as gold, palladium, and rhodium commonly used to drive reactions. But could cheaper, earth-abundant elements replace them? Julian West, a chemist at Rice University, certainly thinks so. In a paper published in the Journal of the American Chemical Society, he and his colleagues outline a method – cooperative hydrogen atom transfer, or cHAT – to help change the status quo (1).

"The reason noble metals are often used is that they reliably drive reactions that happen two electrons at a time," says West. This makes them suitable for hydrogenation – a chemical reaction used to reduce organic compounds. But the same can't be said for earth-abundant metals like iron, manganese, and cobalt. In previous studies, West and his team found that, when compared with noble metal catalysts, large quantities of both reductants and oxidants are needed to drive the process. "This always struck us as strange because, as a reductive reaction, hydrogenation doesn't typically require the presence of an oxidant." The team then discovered that, because the cheaper catalysts only use one electron of the two-electron reductant, the oxidant soaked up the remaining electron before the reaction turnover.

To make the process more efficient, the team developed cHAT – which allows two catalysts to be used together, donating electrons to the reaction in succession. "Our approach boils down to basic addition: 1+1 = 2. Because earth-abundant elements like to do one-electron reactions, why can't we just add up two one-electron elements to make two?" West says.

The Rice University researchers combined iron and sulfur catalysts, discovering that they had similar properties to palladium. In fact, West highlights the method's additional benefits for the production of intermediates. "We've managed to eliminate the stoichiometric tert-butyl hydroperoxide oxidant required for previous hydrogenation methods – simplifying the reaction system and removing this compound from the waste stream."

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INFOGRAPHIC

The Rise of Vials

The pandemic has triggered a surge in demand for vaccine packaging – which means big growth for the future

Source:
Future Market Insights, "Vaccine Packaging Market," (2021).

Key numbers

Vaccine market to surpass **$1.15 billion in 2021**

Forecast to exhibit **13.1% CAGR between 2020 and 2030**

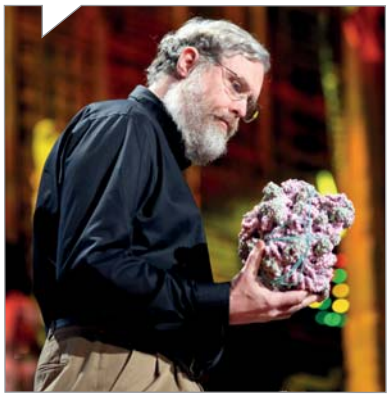
Common formats?

- Vials and prefilled syringes
- Vials are expected to account for four fifths of vaccine packaging
- But prefilled syringes have sustainability and safety benefits – and may take over in the future

ADVANCED MEDICINE IN BRIEF

Skin grafts for addition, cloaking AAV, and lentiviral treatment on hold pending cancer investigation… What's new in advanced medicine?

- Researchers from the University of Chicago have tested a skin graft to treat cocaine and alcohol addiction in mice – with positive results. Previously, the team used CRISPR to genetically engineer mouse epidermal stem cells, which they grafted onto mice to deliver genes. Here, they used the platform to deliver the GLP1 gene to mice, which resulted in attenuated development and reinstatement of alcohol-induced cocaine-taking and seeking, as well as voluntary oral alcohol consumption.
- BlueBird bio notified the EMA that they are suspending marketing of the beta thalassemia treatment Zynteglo as a precautionary measure, after a recipient of their related bb1111 gene therapy for sickle cell disease developed acute myeloid leukemia (AML), and another developed myelodysplastic syndrome, a cancer-like disease of the bone marrow. The cases are currently being investigated. But, as Stat News reports, the situation is complicated as the patients in the trials also received a carcinogenic chemotherapy called busulfan to "condition" the bone marrow.



- AAV vectors trigger an immune response through Toll-like receptor 9 (TLR9), which can prevent therapies from working and pose a potential risk to patients. Now, an international team of researchers have developed a "coupled immunomodulation" strategy, involving short inhibitory DNA sequences that antagonize TLR9 activation and "cloak" the AAV containing the therapeutic gene from detection. The researchers administered the modified vectors in mice and pigs, which resulted in reduced innate immune and T cell activation, and improved gene expression. Two of the study's authors, George Church and Ying Kai Chan, are seeking to commercialize the tech with new spinout Ally Therapeutics.

The Powder Problem

A new technique assists improve deagglomeration processes

What happens when the same batch of powder gives different results when tested with different laser diffraction machines? It's a common problem in pharma development, but Hovione Technology says it has patented an improved method for particle size analysis by laser diffraction.

The method is based on understanding the process of powder particle deagglomeration prior to laser diffraction analysis. Deagglomeration is a precise technique that requires correct sample preparation. According to Hovione, equipment wear decreases the efficacy of deagglomeration techniques. Their new method compensates for wear to deliver an ideal sample for every particle size test. The company explains that this is particularly important for drugs with a particle size less than 10 microns µm or that are prone to agglomeration.

"Drugs known to agglomerate, particularly fine powders used for inhaled pulmonary delivery, were a problem to test. We have implemented the improved method in different machines of different analytical laboratories and everyone is now getting the same test data," said Hovione Director of Analytical Development, Constança Cacela, in a statement.

Top markets for 2021

US: worth
$248 million

UK: worth
$62 million

Other countries to watch: France, Germany, Japan, South Korea, and China

Key players

Gerresheimer, West Pharmaceutical Services, Beckon, Dickinson & Company, Schott, Catalent, and Stevanato, Nipro, Piramal Glass, and UDG Healthcare

Key players will supply
20-30% of the global demand

An Inspector Calls?

The FDA is under fire from the US GAO after the pandemic lengthened its already long inspection to-do list…

The US Government Accountability Office (GAO) has aired concerns about the FDA's ability to oversee pharma's increasingly global supply chains since 2009, but the challenges have been further intensified by the backlog caused by the pandemic. From March 2020 to the end of the fiscal year, only three inspections were conducted. Instead, the FDA is using alternative tools and approaches to oversee drug manufacturing quality, including inspections conducted by foreign regulators, requesting and reviewing records and other information, and sampling and testing drugs. But these efforts are not equivalent to a full FDA inspection, according to the GAO.

The GAO has issued a report discussing the number of FDA foreign inspections; the FDA's response to the pandemic and impact on inspections; and persistent foreign inspection challenges that have been an issue for years (1).

As of February 2021, the FDA has resumed some foreign inspections but no date has been set for resuming routine foreign surveillance inspections in all countries. Clearly, if inspections continue to be postponed, the backlog can only grow. The GAO has recommended that the FDA develops inspection plans for future fiscal years that identify, analyze, and respond to the issues presented by the backlog. But even prior to COVID-19, the FDA faced challenges in conducting foreign inspections, including inspection staff vacancies, preannouncing inspections (which could allow companies to cover up problems), and translation barriers.

"Over the years since we first examined this issue, FDA has made significant changes to adapt to the globalization of the pharmaceutical supply chain and has greatly increased the number of inspections it conducts of foreign establishments," the GAO report states. "However, we found in December 2019 that the agency faced many of the same challenges overseeing foreign establishments that we identified over the last two decades. Subsequently, the outbreak of COVID-19 has added a layer of complexity. Therefore, it will be important for FDA to utilize lessons that it has learned during the COVID-19 pandemic to improve its foreign drug inspection program, including efforts to identify alternative mechanisms to satisfy foreign inspection requirements and plans to address its growing backlog of inspections."

Reference

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A Weighty Loss

Diabetes drug repurposed for obesity

A trial of Novo Nordisk's semaglutide involving 1,961 obese patients has shown that the drug can help cut body weight. Three-quarters of patients receiving semaglutide lost more than 10 percent of their body weight, and over one-third lost more than 20 percent (1). Patients also showed improvement in cardiometabolic risk factors and a greater increase in self-reported physical functioning compared with placebo. The drug works by interfering with the brain's appetite-regulating system, leading to reduced hunger and calorie intake.

One of the principal authors of the paper, Rachel Batterham, Professor of Obesity, Diabetes and Endocrinology at University College London, UK, said, "No other drug has come close to producing this level of weight loss – this really is a game changer. For the first time, people can achieve through drugs what was only possible through weight-loss surgery (2)."

Semaglutide is already approved as a treatment for type 2 diabetes in numerous countries, but Novo Nordisk has also filed for FDA and EMA approval to use the drug in weight management.

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IMAGE OF THE MONTH

Found in Translation

An international research collaboration captures ribosomes translating messenger RNA expressed from the maternally inherited mitochondrial genome using cryo-electron microscopy. The group discovered a novel mechanism that mitochondrial ribosomes use for the synthesis and delivery of newly made proteins to prevent premature misfolding.
https://bit.ly/3kwyskR Credit: A Amunts and D Nowakowski

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

QUOTE of the month

"Five years ago, the prospect of correcting a single base pair in a living animal that causes a fatal genetic disease, with a one-time treatment of an engineered molecular machine, seemed like science fiction."

David Liu of MIT and Harvard University
in the Guardian newspaper https://bit.ly/2O99NGX

V for Victory?

Controversy-ridden vaccine, Sputnik V, (finally and definitely) starts rolling review with the EMA

The EMA has started a rolling review of Sputnik V, developed by Russia's Gamaleya National Centre of Epidemiology and Microbiology.

Sputnik V was approved for emergency use in Russia in August, but the approval was met with some criticism; large-scale trials had not been conducted at that time. However, data released in recent months appear to confirm that the vaccine has over 90 percent efficacy. The decision to start the rolling review is based on studies that support the vaccine's ability to trigger antibodies and immune cells that target SARS-CoV-2 (1).

Russia's sovereign wealth fund, RDIF, which is responsible for marketing Sputnik V abroad, actually reported in February that the vaccine had already been submitted to the EMA for rolling review, but the EMA later tweeted that it had received no such submission. It has since been reported that the dossier may have been accidentally submitted to the Heads of Medicines Agencies (HMA) by mistake (2).

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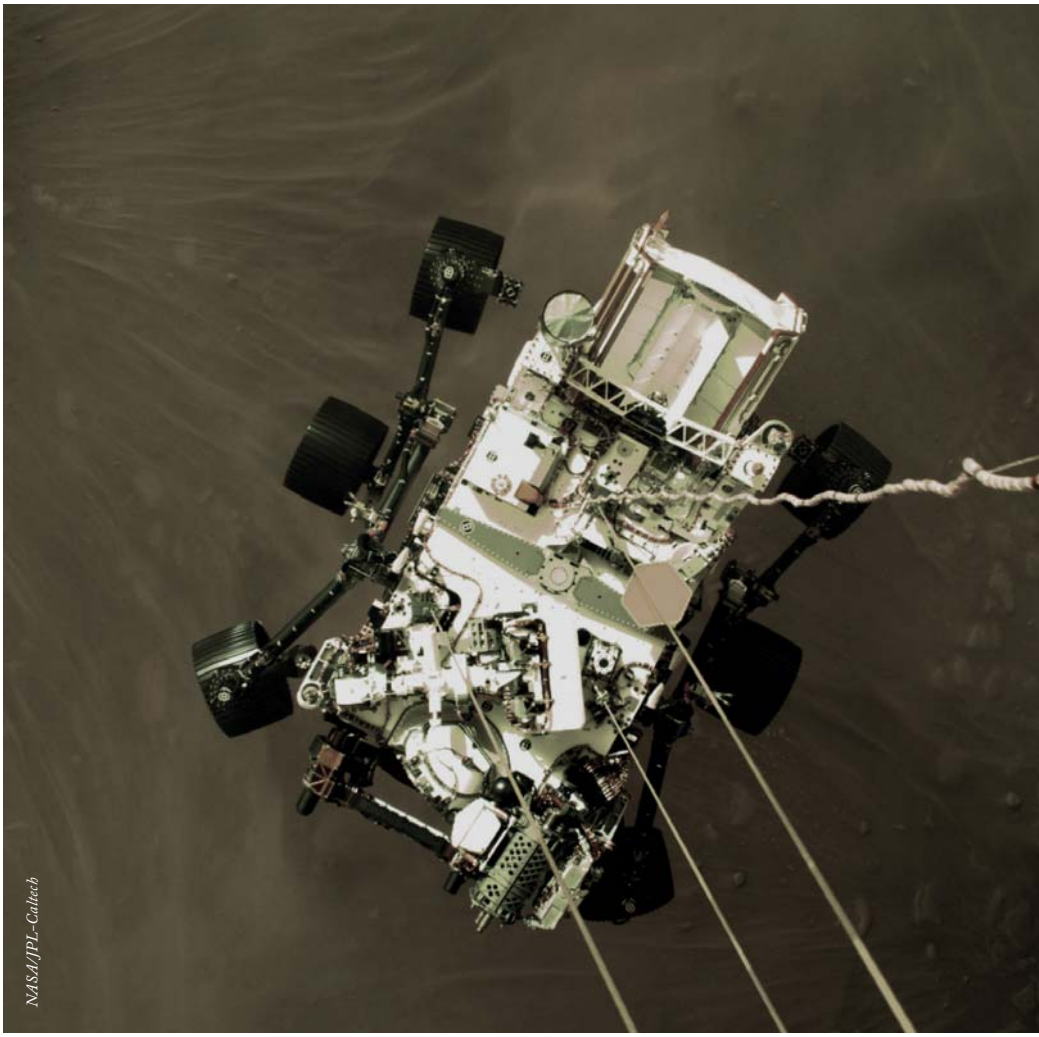
Medicine Making on Mars

When astronauts are eventually sent to Mars, what will they do about medicine needs?


NASA/JPL-Caltech

NASA's Perseverance Rover touched down on Mars on February 18 after a 6-month journey – and has provided some stunning visuals from the Red Planet. A key objective of the rover's mission is to search for ancient signs of microbial life, characterize the planet's geology and past climate, and pave the way for human exploration.

When humans are eventually dispatched to explore Mars, they are going to need many supplies: including medicine. But it won't be feasible for the astronauts to take large quantities of medicine with them. Instead, scientists are exploring how medicines can potentially be made on demand in space or on Mars.

Lynn J Rothschild is a senior research scientist at NASA's Ames Research Center who has been working with Phil Williams, a professor of pharmacy at the University of Nottingham, UK, to create an "astropharmacy" system for astronauts to create biologic drugs on demand. The work combines pre-programed cells in spore form, genetic engineering, and a small volume system adapted from standard laboratory protocols.

Rothschild says: "There are plans for a long-term human presence on the moon and, eventually, to send humans to Mars. With current technology, it would take around six months to reach Mars and the astronauts would have to stay a year and a half for the planets to realign to minimize the journey time home. For such a long trip, you cannot possibly pack every potentially useful medicine. It would take up too much mass – and most medicines also have a limited shelf life, which would render them useless part way through the journey."

Space can also affect how the body responds to medicines. According to Williams: "Studies on the SpaceLab (the laboratory that flew in the bay of the Space Shuttle), for example, have shown that the rate of absorption (measured in saliva) of paracetamol and scopolamine/dexedrine from tablets were double after one day of space flight, and almost halved after two. Longer term changes caused by microgravity include muscle atrophy, insulin receptor desensitization (astronauts can be clinically diabetic after 30 days of spaceflight), retinopathy, and decalcification of bone (and the consequent deposition of calcium elsewhere, often as kidney stones)."

The concept of making medicines for astronauts and future journeys to Mars is incredibly exciting, but Williams also points out that any technology developed to make medicines on demand in space, could also be applied to remote regions on Earth – so any work in this field could have huge benefits for patients all over the world.

More about our coverage on space medicine: http://tmm.txp.to/1220-space

Who's the Winner?

Announcing the Grand Winner of The Medicine Maker 2020 Innovation Awards

The many, many votes for The Medicine Maker Innovation Awards have been counted and we can finally reveal the winner for 2020: the Smart Container, from Schott Pharmaceutical Systems. Congratulations to the smart brains behind the Smart Container!

Our annual Awards celebrate the top technologies released each year for pharmaceutical development and manufacturing. The finalists for the 2020 Awards were published in our December issue and the grand winner was decided via votes from visitors to our website.

Smart Containers can potentially facilitate the move to "Industry 4.0" by allowing companies to improve reject management and line clearance, reduce the risk of mix-ups, optimize lyophilization processes, and support container-based targeted recalls. The bottom of the container is laser-marked with data matrix code, allowing each vial to be traced throughout the fill-finish process – and beyond. The code can be as small as 1 x 1 mm, which equals 14 x 14 dots, and remains stable during the entire fill and finish process. It also resists abrasion and avoids the risk of particle contamination.

You can look forward to reading the story behind Schott's innovation in an upcoming issue of The Medicine Maker.

The two deserving runners up for 2020 are:

- GPEX Boost Technology from Catalent Biologics – cell line expression technology for improving titers and cell-specific productivity
- AdhereIT 360 Base and AdhereIT Clip from Noble and Aptar Pharma – a system that integrates with self-injection devices to support patients during treatment

Looking ahead, entries for the 2021 Innovation Awards will open soon. Nominations will be collected through an online form and the finalists will be published in our 2021 December issue.

Sign up for our newsletter at www.themedicinemaker.com for updates.

In My View

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

Many Hands Make Light Work

Effective lung cancer treatment requires industry collaboration and good timing

By Camille Hertzka, Head of US Medical Affairs at AstraZeneca, a founding member of the Lung Ambition Alliance, Gaithersburg, Maryland, USA

When I started my career in pharma 15 years ago, lung cancer was a fatal disease. Most patients (around 85 percent) were diagnosed at stage IV. This meant that the disease was no longer limited to the lungs, but had spread throughout the body. With limited treatment options, life expectancy was approximately 12 months. The seriousness of the condition also led many patients to believe that testing and treatment were futile. Today, we have a better understanding of cancer biology.

"Despite improvements, the five-year survival rate for lung cancer remains among the lowest of all cancer types."

Now, more patients are diagnosed early, before the disease has spread. The introduction of personalized medicine is also transforming patient outcomes.

Despite these improvements, the five-year survival rate for lung cancer remains among the lowest of all cancer types. Last year, more than 140,000 people in the US alone died from the disease, representing nearly 25 percent of all US cancer-related deaths (1) And although precision medicine and biomarker testing have been important, their adoption isn't widespread. Universal biomarker testing, for example, is not yet the standard of care. Recent data indicates that only 7 percent of non-small cell lung cancer patients receiving care in community oncology practices received comprehensive testing for all biomarkers recommended in the

"The industry and its regulators are proactively working to identify and progress novel solutions, but we need to ensure that this focus is maintained."

National Comprehensive Cancer Network guidelines (2). We must ensure that all eligible patients receive appropriate testing and that oncology providers know to collect samples for all patients – even those with early-stage disease.

As part of its Major Pathologic Response Project, the Lung Ambition Alliance is validating surrogate endpoints to accelerate drug approval in early settings. We are also using our understanding of the molecular features of cancer to identify patients at high risk of early relapse and those who may benefit most from therapeutic intervention. As we make strides in developing new diagnostic tests and targeted therapies, provider education is essential to ensure eligible patients receive timely testing and treatment.

Ultimately, no progress is possible alone. In my opinion, collaboration and the ability to ensure that medicines get to patients at the right time are crucial factors in our continued progress. Through partnership, we can better understand all aspects of the patient journey, hear the patient's voice, and holistically address cancer care and treatment disparities. And companies across the industry are beginning to respond to our call to engage in this important battle. The Lung Ambition Alliance, which is led by AstraZeneca, the Global Lung Cancer Coalition, and the International Association for the Study of Lung Cancer recently announced that five companies would join on as project partners (Bristol Myers Squibb, Eli Lilly and Company, Genentech, Merck, and Novartis). A strong collaboration like this will help bring treatments to patients faster – but is it enough to realize a future without lung cancer?

Though I cannot accurately predict this, I can share my aspirations. Lung cancer is not one single disease; rather, it is multiple. If we can develop targeted therapies for each of them and ensure that patients enjoy the best quality of life during treatment, then, in my view, we will have made considerable progress. I want us to work together to redefine the treatment landscape and, one day, eliminate lung cancer as a cause of death.

When it comes to facing lung cancer, there is more hope than ever. From the potential to screen and diagnose early to treatment options tailored for each patient to holistic quality care – we've already seen important advances. But we can't stop now. My mantra is, "No rest until no lung cancer!"

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Purifying Gene Therapy

The gene therapy industry must maximize the amount of therapeutic gene payload being delivered with each vector to reduce the risk of immune reaction and, ultimately, cut costs. How? High-level purification.

By Akash Bhattacharya, Senior Application Scientist at Beckman Coulter Life Sciences

Most would agree that gene therapy holds enormous potential for treating, preventing, and even eradicating disease – and we are starting to see real results. The first gene therapy product was approved in the US by the FDA in 2017 but, since then, approvals have come rapidly. To date, there are nine approved therapies in the US, including treatments for several cancers, spinal muscular atrophy in young children, an inherited form of blindness, and certain genetic disorders in which the body is unable to make a protein or enzyme.

Creating safe products that can be scaled up – and retain their safety – is key. The important element in manufacturing gene therapy products is purity, which refers to the efficiency of "packaging" for delivery into the cell. Poor packaging can lead to less effective therapy. And giving higher doses of therapy to offset poor packaging risks triggering an allergic reaction in the patient. The FDA has issued guidance for clinical trials that addresses the importance of this very issue (1).

As a quick recap, gene therapy typically involves inserting genetic material into cells via a harmless viral vector that "infects" the cell and delivers the genetic payload. One of the most popular vectors for packaging is the adeno-associated virus (AAV), which has two key benefits: efficiency as a gene delivery vector and low pathogenicity. The virus has been modified from the wild type to optimize its efficiency as a therapeutic gene carrier and minimize its potential to cause disease. Recombinant AAV is the leading platform for gene therapy today.

Although the AAV itself is harmless, it is a foreign substance, so it can trigger an immune reaction in the patient. Packaging efficiency greatly affects this consideration, especially if a larger dose of the payload gene is injected in hopes of a greater therapeutic effect. For instance, if the packaging efficiency of the packaging is very poor, eight out of 10 viral packages might be empty or only partially loaded. Logically, then, to deliver the desired dose of the payload gene, you might have to dose the patient with a proportionately higher amount of total vector. This process may trigger an elevated allergic response, so gets no marks for safety (in fact, just the opposite).

To minimize risk, the obvious solution is to maximize the amount of therapeutic gene payload delivered with each vector – in other words, high-level purification. The strategies employed have been the subject of my own research over the years. Two related methods are ultracentrifugation and analytical ultracentrifugation (AUC), which can, respectively, purify and characterize a gene therapy product.

Ultracentrifugation has been around for decades, but has advanced rapidly in recent years. The machine itself is a fraction of its previous size, with many more capabilities: spinning at 100,000 rpm or greater and delivering 100,000 g. The ultracentrifuge can separate compounds of similar size, but different densities, based on a density gradient – which means it does an excellent job of isolating filled AAV vehicles from partially filled or empty vehicles. The ultracentrifuge is a method for arriving at a product of high homogeneity and purity.

Once you've isolated your product, a quality check is in order. Analytical ultracentrifugation (AUC) can be used for this purpose, because it is very good at characterizing the purified product. In short, a very small amount of the sample is run on the AUC, which employs sophisticated detectors and highly complex mathematics to determine the percentage of filled vehicles. Combining ultracentrifugation with AUC to achieve – and evaluate – a good drug product could minimize patient risk.

Gene therapy technologies are fast advancing and close interdisciplinary collaboration makes it all possible. Our virology colleagues, for instance, are working on ways to modify and scale up triple transfection, the elegant process by which the AAV itself is made. The classic method uses human embryonic kidney cells, known as HEK-293. But a newer strategy employs an insect cell line system, Sf9 , which holds a great deal of promise.

On our end, we will continue to streamline the instruments and workflow until the entire experiment and analytic process conform to current good manufacturing practices. We also hope to further reduce time and costs with the ability to analyze "dirtier" samples closer to the bioreactor and before multiple rounds of purification. Another goal is to make some of the elements fully disposable, which is important from a

biohazard perspective.

Gene therapy is a powerful step in the direction of eradicating a disease – something that has only happened a few times in history. Eliminating diseases that affect a large percentage of the population or are particularly devastating – such as macular degeneration or neurodegeneration – would be an enormous advance, but one I believe will someday be achievable through simplifying workflows and increasing purity and safety. These steps will ultimately allow us to distribute gene therapy safely and affordably to much greater numbers of people.

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Digital Overdose: The New Academic Reality

E-learning and e-communication has swept science amidst the pandemic, but are they worthy substitutes for their physical counterparts?

By Victoria Samanidou, Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece

The COVID-19 pandemic has changed our daily routines. Distancing has put our social lives on hold; remote working has invaded our homes. This is the "new normal": a digital life and a virtual reality.

Few foresaw the rapid spread of the pandemic. But all of us soon faced the reality – and the resulting lockdowns. These lockdowns had far-reaching effects. The impact on academia was obvious, with campuses becoming ghost towns and terrified professors wrestling with unfamiliar online teaching platforms. Sitting at home and speaking into a screen, wondering whether your students are even listening, is quite an experience. And, on the other side, students may struggle to connect to these often very impersonal presentations.

Though teaching from home may sound cozy, it is actually quite tiresome for all involved. The biggest challenge is the lack of interaction with the audience. There's no way for presenters to immediately assess whether the information is being absorbed. And, if it is, to what extent? My own students have admitted that they are easily bored when attending online lectures and webinars; attractive topics or lectures delivered by notably charismatic professors may be exceptions, but they are rare.

Then came the conference changes. Most were postponed for one or two years (the latter currently sounding a little more feasible), but some organizers opted for a digital format. Others opted for a hybrid of physical and digital elements. Unfortunately, those that went fully digital received some

negative feedback – particularly from senior scientists. Why? Because virtual events cannot offer the opportunity for connection and collaboration that physical conferences do. After all, we cannot replicate the atmosphere present at coffee breaks and social events, and no one can say for sure when those may return. Yet nobody can deny that digital events have their benefits. If nothing else, we at least save time and money on transport.

Before 2020, I viewed online events with trepidation. But, since March, I seem to have magically overcome this. Now, I find myself not only attending webinars, but even organizing my own events and e-conferences. In fact, 10 days ago we organized a virtual, three-day conference with 18 sessions (some running in parallel), with an audience of over 100 participants from Greece and overseas. Over 200 oral and poster presentations were included, and participants readily asked questions. All admitted that the event was very successful (though we missed coffee breaks and informal chats). It was an awesome experience under current circumstances.

All things considered, remote education is a powerful tool. Take webinars, for example. These events are usually free and anyone can attend – regardless of the locations of hosts or other attendees. With the issue of distances eliminated for the time being, scheduling is also simplified. Nonetheless, I cannot help but wonder to what extent an audience can take in all of the information presented through a computer screen.

I consider myself very lucky that I've had the opportunity to meet many a scientific guru throughout my career – most of whom I encountered at conferences. Their words and lectures have had a significant, positive impact on my career. Perhaps it is still too soon for us to have a clear view on the topic. However, I optimistically think that we should take all the advantages that technology offers us to transform this difficult situation into a positive experience. After all, some changes will likely remain long after the pandemic. So, the "new normal" is truly upon us. Time will tell what impact the lack of these encounters will have on us, and especially on early-career scientists, in the coming months.

Digital Discussion

To give patients timely access to novel and effective therapeutics, we must use artificial intelligence – but changing industry attitudes is no mean feat

By Jaleel Shujath, VP Marketing at Absorption Systems, Exton, Pennsylvania, USA

As our global supply chains grow in reach and complexity, so too does the potential for quality control and safety issues. The problem has been compounded by COVID-19, with newly imposed supply chain restrictions causing product shortages and disruptions to production and distribution. It has become common for patients, governments, and even health organizations to stockpile medicinal supplies – sometimes in substantial quantities. Pharmaceutical hoarding has resulted in massive price hikes for raw ingredients. For example, the price of ingredients for hydroxychloroquine, a malarial drug, recently rose from US$100 to $1,150 per kg in Pakistan (1), resulting in some companies' trying to source alternatives. This current crisis exacerbates an ongoing problem: creating new risks for supply chains and exposing patients to substandard or falsified products. Other issues, such as geopolitical crises and fraud, remain constant threats to pharmaceutical supply. Is there a way to address the disparate problems that plague our industry?

Advanced technologies, such as blockchain and artificial intelligence (AI), may hold the answer. These technologies offer the resilience, agility, and supply chain visibility essential to maintaining consumer access to potentially life-saving therapies – and pharma must implement them for the sake of not only the supply chain, but also patients' health and wellbeing.

Blockchain is one of the more popular track-and-trace technologies used by pharmaceutical stakeholders. As a substance or product travels through the supply chain, each step generates data and adds an unchangeable code to the entry (an "immutable ledger" system). If one step is broken, the system can flag for investigation and stakeholders within the supply network can assess the accuracy, traceability, and authenticity of every product and process step – easily identifying and addressing weak areas in the chain. Blockchain also allows for data sharing while protecting sensitive and proprietary information.

The data blockchain technology gathers can, in turn, feed AI-powered analytics and solutions. AI tools can predict where a supply chain is likely to be disrupted and preemptively reroute medicine deliveries. Such tools could also be leveraged in exploratory or diagnostic ways to protect supply chains. By modeling whether orders could be consolidated in the production and distribution chain, AI-based tools for logistics and fulfillment can identify areas where increased efficiency can protect

profit margins and improve performance. AI can also help protect against fraud in vulnerable parts of the supply chain by identifying potential weak points. Finally, AI's modeling and analytics capabilities can enable more informed decision-making – a critical factor in managing risk and product quality, as well as harmonizing and optimizing supply chain management.

But despite their promise, these solutions have not yet seen widespread adoption. Many life science companies take a "wait and see" approach to adopting innovation or are forced to consider it by emerging regulation. This has affected the extent of AI use across the industry. And with technology outpacing regulators' ability to set clear guidance for use, the compliance landscape is continually growing in complexity and cost to implement – another concerning factor for pharma stakeholders. Data integrity is also an important consideration. The pharmaceutical industry generates data in vast volumes and at differing qualities. How can organizations manage such large amounts of information with confidence that each data point is reliable? How do we determine which data are useful to collect and which are not? Although information is undeniably valuable, not every data point must or should be retained – and those who fall into this trap run the risk of making their systems more challenging to manage and optimize.Also unclear is which data may be useful in the future, which can result in data hoarding. To produce robust data models and unlock the full predictive potential of AI, we must use high-quality data – poor data will lead to poor analysis.

Data collaboration could provide businesses with the high-value data needed to support the validation and refinement of novel AI tools, but pharmaceutical organizations have historically been hesitant to share relevant datasets with "competitors." Blockchain offers the industry an open, decentralized model for data collaboration that could allow organizations to build and share the verified, high-quality datasets AI solutions need.If the industry can more widely embrace these technologies, we will all have a fuller understanding of the dynamics and processes at play across our ever larger and more complicated supply chains – better equipping us to foresee and proactively overcome complex challenges. The faster we adopt AI, the better we can use it to protect our patients.

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Riding BRAINWAVE

Are we at the advent of a new era in neuroscience R&D?

By Maryam Mahdi

The 1990s is sometimes referred to as the "Decade of the Brain" (1). During this period, several well-known drugs, including the antidepressants Zoloft and Prozac, were commercialized. But eventually, a shift in the industry saw many companies withdraw from the field – the complexity of neurological conditions and the inability to convert discoveries into viable treatment being major drivers in a changing landscape.

Brain disorders are now the cause of a worsening healthcare crisis. Neurodevelopmental, neurodegenerative and neuropsychiatric diseases are all intrinsically linked to high societal and economic costs. The WHO claims that these conditions are a "major cause of lost years of healthy life (2)" and, in 2014 alone, the US dished out roughly US$800 billion to cover the cost of patient care and the loss of productivity caused by these diseases (3). As our societies age, these challenges are expected to worsen. United Nations statistics suggest that 16 percent of the world's population will be over the age of 65 by 2050 (4). And with a lack of treatments to halt – or even slow – these broad and varied conditions, there are significant hurdles to overcome.

Fortunately, an increasing number of companies appear interested in tackling the issue. Reports estimate that the market has a compound annual growth rate of 6.4 percent, with the sector expected to generate US$520.8 million per year by 2025 (5). But, questions arise as to whether the renewed interest in the field will mark the start of long lasting change both for neuroscience programs and the patients waiting for treatment options.

We've brought together industry experts to discuss the past and current state of the field and the progress that will inform the future.

Nitin Joshi

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Meet the Experts

Neuroscience R&D covers a broad spectrum of indications, from highly prevalent diseases, such as Alzheimer's, to rarer disorders like Huntington's disease (see "Understanding the Burden"). Here, our experts share the reasons behind their interest in brain health and highlight the contributions they are making to the field.

Nitin Joshi, Associate Bioengineer at the Center for Nanomedicine in the Brigham's Department of Anesthesiology, Perioperative and Pain Medicine

"I am an engineer and my lab focuses on developing biomaterials-based drug delivery solutions for unmet medical needs in different diseases. Neurological diseases and drug delivery to the brain is one of the major focus areas of my research. Over the past few decades, scientists have identified promising therapeutic agents that can target the biological pathways involved in brain diseases. Unfortunately, clinical translation of these therapeutics is limited by their inability to cross the blood brain barrier (BBB) and enter the brain at therapeutically effective levels. My goal is to develop drug delivery technologies that can facilitate and maximize the penetration of these promising molecules across the BBB, thereby enabling their clinical translation."

Arthur Roach, Director of Research at Parkinson's UK

"I've spent many years working in neuroscience R&D and now head up Parkinson's UK Virtual Biotech. I oversee the charity's research efforts. We're striving to better understand Parkinson's and help people living with the condition lead better lives. And, of course, one of my main goals is to find treatments (and a cure) for the condition!"

Bill Martin, Global Head of Neuroscience, Janssen

"I have the privilege of leading Janssen's global neuroscience program, which covers everything from new biology all the way through to late development. My interest in the field began during my undergraduate degree. I was fascinated by the brain and its rich complexity. My interest only grew as I started working in the laboratory and carrying out research. It was the idealistic thought that I could help change the world through science and therapeutics that helped steer my career path."

Arthur Roach

Bill Martin

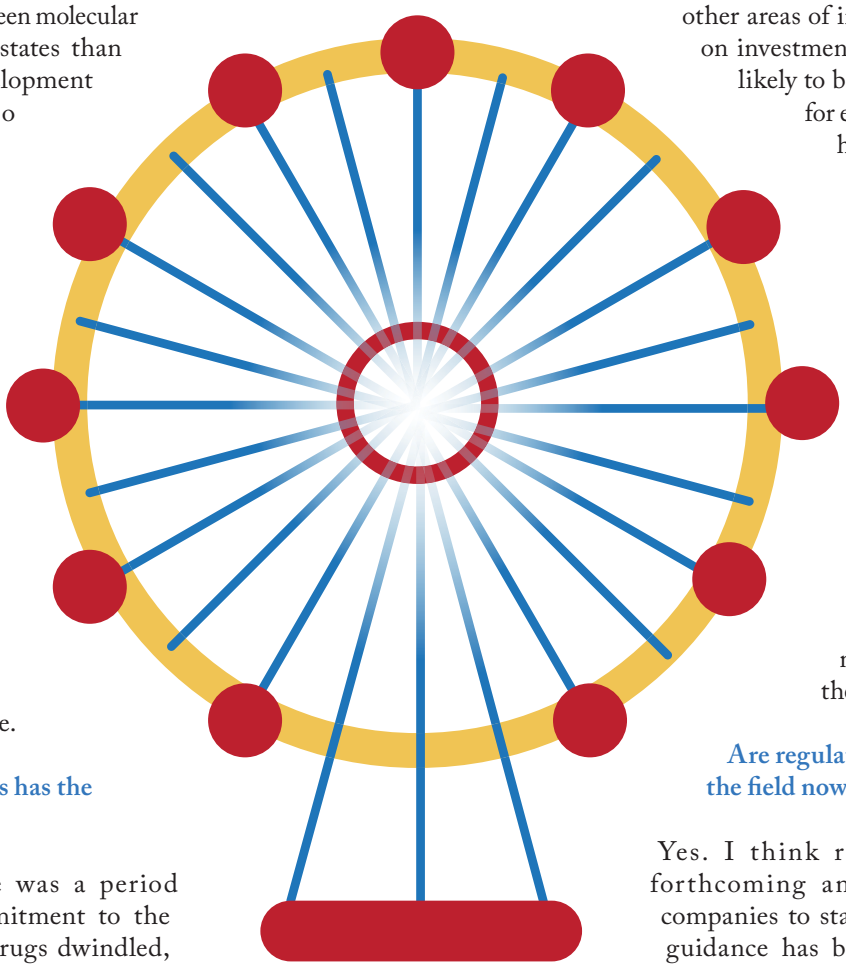
On the Cusp of Change

Though neuroscience R&D has faced setbacks, a renewed interest in the field is helping companies draw closer to solutions for patients living with brain disorders

Janssen's Global Head of Neuroscience, Bill Martin, sits down with The Medicine Maker to discuss the current state of the sector and the steps that need to be taken to drive its future success.

How has pharma's involvement with neuroscience R&D evolved?

Pharma's relationship with neuroscience has matured and changed over time. We're now at the cusp of understanding the very complex neuropsychiatric and neurodegenerative diseases that affect patients' lives. This progress has been defined by the advances made in our understanding of human genetics. We now have a clearer picture of the relationships between molecular pathways and disease states than ever before. The development of biomarkers to support diagnosis and treatment has also furthered our progress. These factors, coupled with the increased use of data-driven solutions, have enabled the industry to tackle long-standing historical challenges. In my view, these changes have led us to the point where we are now and have helped usher in an era of new precision in neuroscience.



What sort of challenges has the industry experienced?

Unfortunately, there was a period where pharma's commitment to the development of new drugs dwindled, due largely in part to the rich complexity of the central nervous system (CNS) and the challenge in accessing it, among other reasons. The complexity of these disorders means that translating drug candidates from bench to bedside is a significant hurdle. Understandably, this created a sense of uncertainty for some of the players involved. The path to overcome these challenges wasn't clear either. Moreover, the regulatory guidance available wasn't robust enough to help them push past the issues they experienced. Times are now changing, but wavering commitments by companies over time have had a lasting impact on the field.

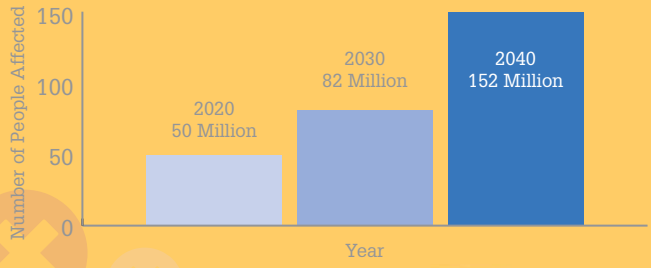
At the time, companies had to consider the economic factors of investment, risk and return at an R&D portfolio level. Investing in neuroscience R&D, without a deep understanding of the mechanisms behind these diseases, led to assessments in which products could not be developed with a high enough likelihood of commercial return given the clinical and regulatory risks. And that led to tough decisions being made as to where to deploy resources. There are other areas of industry where a return on investment was considered more likely to be made (take oncology, for example, where funding has rapidly increased in the last 10 years). On a positive note, we are uncovering more about the ways these disorders work and ultimately closing the translational gaps that have hindered the industry in the past. It will take time, but I'm optimistic that recent advances will guide us in developing the next generation of therapeutics.

Are regulators more engaged in the field now?

Yes. I think regulators are more forthcoming and this really helps companies to stay the course. Specific guidance has been issued and there

Understanding the Burden

Alzheimer's and Dementia



10 million new cases every year

Alzheimer's accounts for **60–70%** of all cases

- *Memory loss*
- *Poor cognitive function*
- *Loss of mobility*
- *Incontinence*
- *Weight loss*
- *Pain*

Headache

50% of adults have had a headache within the last year

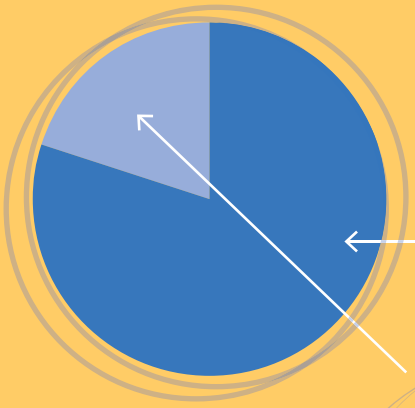
30% have experienced migraine in the last year

1.7-4% are affected by headaches 15 or more days each year

<50% of British and American sufferers have seen a doctor

Epilepsy

Where is the most significant patient burden?



80% Low- and middle-income countries

20% developed countries

50 million people worldwide

0.5% of the global burden of disease

139 people in every 100,000 diagnosed each year in low- and middle-income countries

Schizophrenia

20 million people affected worldwide; 2–3 times more likely to die early than the general population; 69% of schizophrenic patients not receiving adequate care

- *hallucination*
- *delusion*
- *disorganized speech*

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Big Pharma, Big Plans

The big pharma companies in neuroscience drug development are casting a wide therapeutic net to help address patient needs, exploring the potential of small molecules, biologics, and gene therapies to treat diseases that affect patient populations both large and small. Here, we present a snapshot of just some of the drugs moving through the clinical pipeline as well as those with the regulatory stamp of approval.

Drug name	*Indication*	*Drug Type*	*Clinical Phase*
Branaplam	Huntington's disease	Survival motor neuron protein	Phase I
Branaplam	Spinal muscular atrophy	Survival motor neuron protein	Phase II
MIJ821	Depression	NR2B Inhibitor	Phase II
Ofatumumab	Relapsing multiple sclerosis	CD20 Antagonist	Approved filing in the USA
OAV201 (AVXS-201)	Rett's Syndrome	MECP2 gene therapy	Phase I
OAV201 (AVXS-201)	Spinal muscular atrophy type 2/3	MECP2 gene therapy	Phase II
Aimovig	Pediatric migraine	Selective CGRP receptor antagonist	Phase III
Mayzent	Stroke	S1P1 Modulator	Phase II
Mayzent	Pediatric multiple sclerosis	S1P1 Modulator	Phase III
BLZ945	Amyotrophic lateral sclerosis	CSF-1 Inhibitor	Phase II

Table 1. Novartis' current neuroscience pipeline

Novartis

From depression to multiple sclerosis, Novartis' neuroscience programs cover both neuropsychiatric and neurodegenerative disorders. Several of its treatments are also being explored for multiple disease indications. For example, branaplam, a large molecule drug, is currently under investigation for spinal muscular atrophy and Huntington's disease (1).

Roche

Roche has a considerable number of neuroscience treatments in its pipeline. The company expects to begin regulatory filing for human monoclonal antibody drug gantenerumab in 2022. Preventing the build-up of beta-amyloid plaques in the brain, the mAb aims to reduce cell dysfunction and improve outcomes for Alzheimer's patients (2). Tominersen, an antisense drug developed in collaboration with Ionis, is also predicted to face regulatory scrutiny next year. The drug targets the mutant variant of huntingtin protein (mHTT), which is associated with the onset of Huntington's disease. mHTT causes the progressive deterioration of brain function, causing patients to experience symptoms like depression, lapsed concentration, and difficulty in moving (2).

Eli Lilly

Eli Lilly's neuroscience pipeline focuses mainly on neurodegeneration. The company has five drugs at various stages of clinical development to address Alzheimer's disease, and several others to tackle other forms of dementia including a gene therapy for patients with frontotemporal dementia and a small molecule, which modulates dopamine receptor D1 to help treat symptomatic Lewy body dementia (3).

Johnson & Johnson

Johnson & Johnson's Spravato was the first FDA-approved nasal spray designed to address treatment-resistant depression – a form of major depressive disorder that is defined by patients' unresponsiveness to two or more antidepressants. Another treatment for the condition, seltorexant, is also moving through the clinical pipeline, with the company hoping to file regulatory applications for the small molecule by 2023 (4).

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"Times are now changing, but wavering commitments by companies over time have had a lasting impact on the field."

are efforts to harmonize international standards on the development of drugs for neurological disorders. We're also seeing an increase in the number of meetings between regulators and innovators in the field, which is certainly positive. However, there's always work to be done; that's just the nature of the field!

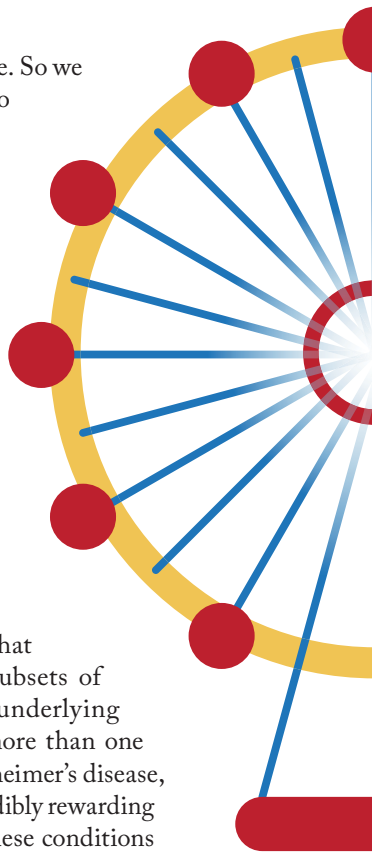
We also have to wonder whether these efforts are enough to maintain commitment. I think it comes down to a social contract. Other fields have been incentivized to help keep companies working on new therapeutics – just think of the initiatives available for orphan diseases, antibiotic resistance, and pediatric disorders. It would be great to have similar opportunities for those of us working in the neuroscience field.

So what are the main motivational factors for the companies that remained in the field?

First, it's the patients. The unmet needs remain high. Second, the breakthroughs we're beginning to see are great motivators. We now have digital tools at our disposal that give neuroscience companies across the industry a unique edge. Using them, we can measure patient well-being, for example. Though that may sound unusual, advances in neuroimaging – for example - mean that we have a window into the brain, allowing us to push the boundaries of knowledge and the application of this knowledge for medical advances.

The precision of the technologies that are now available also means that we are able to get molecules into the CNS to better treat patients. We've seen advances in our ability to penetrate the blood-brain barrier and have expanded our horizon past the use of small molecules alone. There are many researchers and companies who are assessing the power of biologics and other therapy types for treating diseases. It's an incredibly exciting time for the industry.

For Janssen, neuroscience is part of our origin story. Almost 60 years ago, we started to develop our first neuropsychiatric drug for patients living with schizophrenia. This was during a time when few treatment options were available. So we have a long-standing commitment to this specific area of R&D. Though we've had initial successes in the discovery of new molecules, there are still so many patients whose needs remain unaddressed. By staying in the field, all of us focused on brain health can actively search for solutions for all the people living with neurological disorders today.



What about the companies entering the field for the first time?

Part of the reason we're seeing companies drawn to the field is that they can really focus on small subsets of patients. Many diseases have underlying subtypes. For example, there is more than one type of Parkinson's disease, or Alzheimer's disease, or even depression. I think it's incredibly rewarding to explore the different facets of these conditions and reduce the heterogeneity that has previously defined them. Their work will certainly help in addressing the specific needs of patients.

What change still needs to happen?

Neurological disorders don't only impact patients. The lives of their caregivers are also significantly impacted. There's not a day that goes by when somebody doesn't call me to discuss the effects of a CNS disorder on a loved one. If we keep these experiences in mind, it helps us to recognize that the science we're pursuing is helping to improve outcomes and the quality of life of patients worldwide. The tremendous need should be enough to catalyze people and companies to contribute to the progress being made in the field.

I was drawn to neuroscience because of the potential there is to change lives. It's been a tremendous privilege to see how the industry has changed for the better. Looking ahead, I'm optimistic that we will continue to see breakthroughs happen – some more quickly than others. What's important is that they are durable so that we can achieve sustained improvement in areas that have previously been difficult to characterize. We've already overcome so many hurdles and it is exciting to imagine what the next 60 years of innovation will bring!

R&D Without Borders

Without the constraints of brick-and-mortar sites and employees, virtual biotechs could help in bringing the next generation of brain drugs to market

A new dawn seems to be approaching for neuroscience companies and researchers. From studies exploring nanocarriers that bypass the blood-brain barrier to the use of monoclonal antibodies to treat a plethora of conditions including migraine, multiple sclerosis, and myasthenia gravis – the broad scope of discoveries holds huge potential. However, for people living with Parkinson's, treatment options to address many of the condition's non-motor symptoms (see sidebar: Understanding Parkinson's) remain scant. The condition affects approximately 10 million people worldwide (1), and the numbers are set to increase as the global population ages (2).

"There are many treatment options available to deal with some of the early symptoms of the condition, like stiffness and slowness," says Arthur Roach, Director of Research at Parkinson's UK. "But after five years or so these drugs are rendered ineffective, so the need for new options is urgent."

Though stakeholders in pharma and academia are working on the development of new treatment approaches, funding is a significant stumbling block. Without the appropriate investment, good ideas can fall by the wayside. This challenge prompted Parkinson's UK to launch its pioneering Parkinson's Virtual Biotech initiative in 2017 to plug the funding gap in the drug development pipeline and fast-track the development of new treatments for people with Parkinson's. There are no large teams of scientists or expensive labs to run. Instead, the model works by seeking out the best and brightest innovations emerging in Parkinson's research. By partnering with institutions and pharmaceutical companies worldwide, the most promising discoveries can be developed into plausible new drug treatments.

Entering a world of virtual R&D

"The industry is changing, and where companies have previously pulled their neuroscience programs or put them on hold, there is now a renewed interest in the brain disorder space," Roach says. However, as some companies have spent a significant period of time without engaging in this area of industry, they lack the connections and resources to find the right backing and support. "It's important to acknowledge this issue and recognise that there is a need to support companies and research groups at the intermediate stages of clinical development."

The Parkinson's Virtual Biotech provides companies and researchers with the investment required to push projects forward – giving them access to funds to advance their Parkinson's research at each stage of the development process. Right now, there are projects at the non-clinical, preclinical and early clinical development stages. The model also makes use of the infrastructure and resources that are already in existence – avoiding unnecessary costs. But how are the right projects selected? Roach explains that the biotech team made up of the charity's in-house experts, operates like venture capitalists – assessing the need for particular drugs as well as the projects that hold the most promise. The charity is driven by the needs of people with Parkinson's and continuously seeks input from the patient community to guide and inform the programme. Another key factor in the decision-making process is the potential to attract future investors. "If a project is attractive to other funders, it means that we can step away from it after some time and redirect our efforts into other exciting research," he says. The not-for-profit will use any financial return made to support other research projects.

The virtual approach typically allows R&D to take place anywhere around the world, but like many areas, it has been affected by the COVID-19 pandemic, particularly when it comes to clinical trials. "We've had to spend time thinking about how we could get patients to trial centers and hospitals, bearing in mind they may only be allowed to stay there for short periods," says Roach. "We also found ways to mitigate the impact of coronavirus and ensure partners like UCL who are leading on a clinical trial funded by us, had the right support to adapt the trial. We've been involving people with Parkinson's in that process, as ultimately we need people with the condition to feel safe, comfortable and supported to participate if we are going to be successful. We've also had to make major changes to studies which has included reducing the number of in-person assessments, and replacing these wherever possible with telephone calls or video conferencing. Drugs will also be couriered directly to participants' homes and they will be given thorough instructions on how to take the pills. Though there have been some delays, our activities haven't come to a halt. There is still progress being made!"

Collaboration for a better future

The Parkinson's Virtual Biotech is currently supporting several projects. One of the most recent is investigating how mitochondria can be rescued to prevent the progression of Parkinson's. Normal functioning cells have protective mechanisms that help defend against damage or trigger

Understanding Parkinson's

With Arthur Roach

What impact does Parkinson's have?

Parkinson's is a chronic, progressive condition that affects almost every aspect of day-to-day life for patients. There's a misconception that Parkinson's only affects older people and causes tremors, stiffness, slowness of movement and a shuffling gait. The reality is that there are more than 40 symptoms and it affects a broad range of people. It's also important to note that Parkinson's is, to a degree, an invisible condition. The non-motor symptoms aren't noticeable to an observer but significantly impact patient wellbeing and their quality of life. These symptoms can include chronic pain, sleep problems, and cognitive impairment as well as mental health problems like depression, apathy and hallucinations.

What have been the most exciting breakthroughs?

Almost a decade ago, a lot of progress was being made to understand the genes that contribute to the onset of Parkinson's. We discovered that though the condition could be attributed to a single faulty gene in some people, for others it couldn't be defined as a genetic disorder; many genes were shown to play a role in the cell death that led to the onset of the condition. Back in 2004, research supported in part by Parkinson's UK identified a gene called LRRK2. Changes in this gene are the most common cause of genetic forms of Parkinson's and may also be a good target for people with the sporadic form of the condition. Today a number of companies are testing exciting new drugs targeting LRRK2 in clinical trials.

What has prevented the success of drugs for the later stages of the condition?

We know that Parkinson's is a progressive neurological condition for which there is currently no cure. It develops when nerve cells that are responsible for producing dopamine die. By the time an individual reaches the mid-stages of the condition, they may have already lost more than 50 percent – sometimes up to 80 percent – of some dopaminergic cells. The underlying pathology, therefore, makes it difficult to treat the condition and means that most drugs will lack the capacity to holistically address patient needs.

And even though the newer drugs work to address the issue of cell loss, they may only be able to elicit a weak effect or one that isn't significant enough to make a substantial difference in patient lives. But the most critical issue here is the way that we test drugs. A lot of contemporary clinical research is influenced by earlier studies where scientists were developing dopamine replacement medicines. These drugs were known to have strong and rapid effects. So, when we started testing newer drugs, we had the expectation that they would have the immediate effect that we had seen in the past. But many of these next-generation medicines begin to work over the course of months. It's hard to prove that they are viable options for patients when we so heavily subscribe to an older approach to testing. Attitudes are changing, as can be seen in the work of the many researchers who collaborate with Parkinson's UK.

reparative responses. However, research suggests that these triggers happen slower in people with Parkinson's and, therefore, allow greater levels of damage to occur. The charity is working with a UK-based researcher to investigate how medicines can be developed to lessen this impact.

"The protective mechanisms we're investigating work almost like sprinklers. In the event of a huge fire, sprinklers will turn on and immediately help to reduce damage," Roach says. "However, in the case of Parkinson's, instead of a full-blown fire, the stimulus is not large enough to set off the sprinklers so it smolders – affecting people living with the condition for a longer period of time. So, if our drugs can prompt a faster response, it will make a huge difference to many lives."

Although the charity's projects are making headway in the Parkinson's research space, Roach argues that it will require industry-wide collaboration to continue to develop new and successful treatments. "We're uniquely positioned in the fact that we prioritize the needs of the Parkinson's community. Though big pharma companies, regulatory agencies, and health care systems may have different areas of focus, progress will happen fastest when we work together to help support this growing patient demographic."

For more information visit https://www.parkinsonsvirtualbiotech.co.uk/

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Bridging the Barrier

Pharma has always had its sights set on the lofty goal of traversing the blood-brain barrier. Could nanoparticle technologies bring the industry a step closer to success?

By Nitin Joshi

Traumatic brain injury (TBI) is driving a silent epidemic. The condition, which is initially caused by mechanical impact to the brain, affects sixty-nine million people each year and is a leading cause of death and disability in children and young adults. Though initial symptoms can include headache, nausea, and fatigue, they can gradually worsen as a result of secondary injury and lead to the onset of neurological dysfunctions including Alzheimer's and Parkinson's disease. But treatment remains a challenge. After the event of a TBI, the blood-brain barrier (BBB) is physically breached for a short period of time. Treatment through it would be ideal, but the extent to which the barrier is compromised varies among the patient population. Another challenge is the short window of time for treatment, which prevents repeated dosing that might be required over the long span of secondary injury that can last for months to years. Previously used approaches for treatment of TBI were rendered because of these limiting factors.

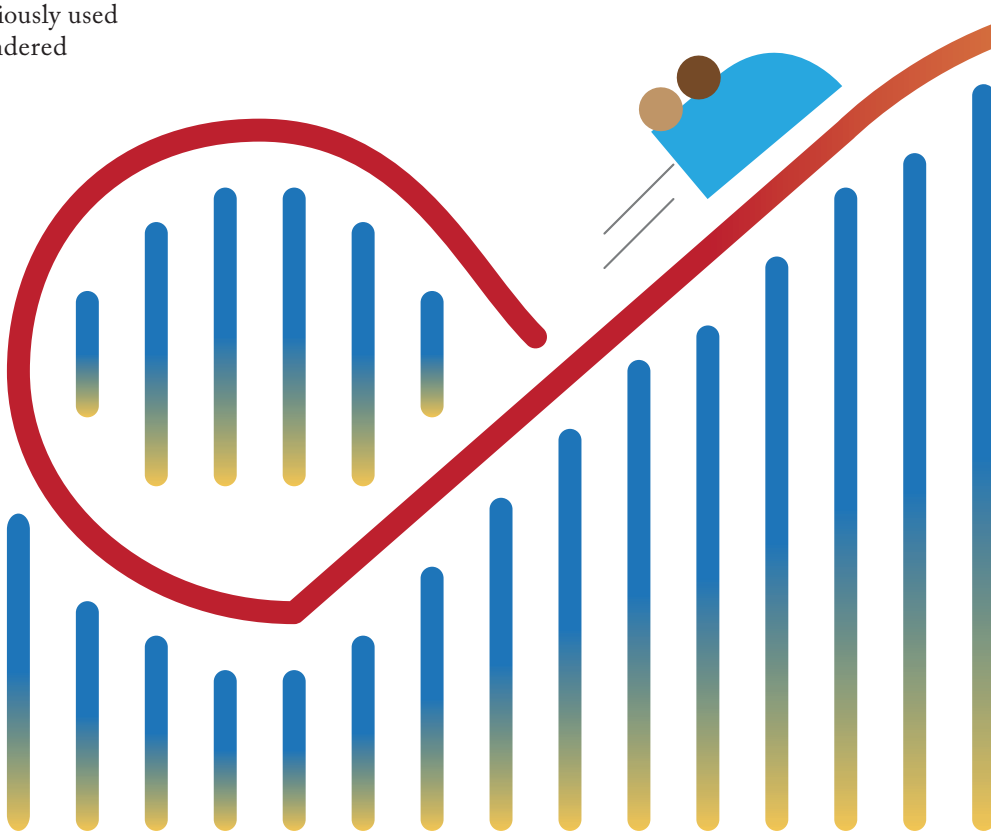
But beyond TBI, the BBB has been historically difficult to penetrate. This barrier prevents molecules in the circulating blood from non-selectively crossing into the brain tissue – preventing the translation of many promising drugs. Though this challenge may be considered difficult to contend with, I believe that they are not insurmountable. Nanotechnologies are emerging as pertinent drug carriers, enabling the penetration of therapeutic agents across the BBB.

Molecular Trojan Horses

Using a Trojan Horse mechanism, nanoparticles can be engineered to encapsulate therapeutic agents. Their size and surface properties can be fine-tuned to enable them to cross the BBB, thereby delivering therapeutic agents into the brain. These ultrafine particles can also prevent the degradation of labile agents, such as siRNA, in blood and facilitate their entry into the target cells, without premature degradation. At the Center for Nanomedicine at Brigham and Women's Hospital, we have developed a platform that can therapeutically deliver drugs into the brain, across both physically breached and intact BBB – which could prove important in the treatment of TBI and its related conditions.

Our platform relies on the precise engineering of the surface properties of nanoparticles – helping to maximize their transport across the BBB. Poly (lactic-co-glycolic acid), or PLGA – a biodegradable and biocompatible polymer – was also used as the base material for nanoparticles. This platform was then used to encapsulate a siRNA designed to inhibit the expression of tau protein – a microtubule-associated protein, which is thought to play a key role in neurodegeneration. It is also involved in the progression of secondary injury following TBI.

In collaboration with Jeffrey Karp from Brigham and Women's Hospital and Rebekah Mannix from Boston Children's Hospital, we tested the coated particles in both



"There are several issues that can arise, either due to the therapeutic agent itself or due to the associated technology."

healthy mice and those with TBI. Our investigation in the healthy population allowed us to identify a unique nanoparticle design that maximized the transport of the encapsulated siRNA across the intact BBB and also significantly improved uptake by brain cells. Using this information, we intravenously administered the nanoparticles across the BBB of TBI-affected mice. This resulted in a three-fold higher delivery of siRNA to the brain when compared with non-engineered nanoparticles – an improved delivery that occurred irrespective of whether the nanoparticles were infused within or outside the window of physically breached BBB.

Compared to TBI-affected mice treated with saline, our engineered nanoparticles loaded with anti-Tau siRNA (a proof-of-concept drug) showed a 50 percent reduction in the expression of the protein. As the next step, we want to explore potential targets for several neurological diseases. In this study, we used the TBI model to develop the technology, but our approach can be useful for other neurological diseases that require drug delivery to the brain. Our technology has the potential to deliver large molecule biological agents, such as proteins, which are typically challenging to formulate. I'm looking forward to seeing where this can best be applied. Beyond our own discoveries, it's important that the industry continues to work towards the goal of treating neurological disease.

Moving forward

Though many pharmaceutical companies have neuroscience programs that cover various neurological disorders, the majority are focused on the discovery of novel targets. It would be great to see more efforts towards the amalgamation of novel target identification with technologies that can enable the translation of promising therapies to improve their therapeutic efficacy.

Regulators must also contribute to these efforts. They already play a crucial role in facilitating the translation of novel therapeutic approaches into viable products. But they could be involved right from the beginning and through all stages of drug development; after all, the process of developing therapeutics is lengthy, complex, and extremely costly. There are several issues that can arise, either due to the therapeutic agent itself or due to the associated technology. An expert regulator can guide the early development process to avoid any potential regulatory hurdles and can therefore help companies and researchers to find the most appropriate regulatory path forwards.

Ultimately, all aspects of industry need to work together seamlessly to help bring novel solutions to the fore. Patients are waiting, so we must all strive to create drugs that work effectively for them.

Nitin Joshi is an Associate Bioengineer at the Center for Nanomedicine in the Brigham's Department of Anesthesiology, Perioperative and Pain Medicine and an Instructor of Anesthesia at Harvard Medical School.

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Suggested Reading

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Business

Economic drivers
Emerging trends
Business strategies

Saving the World, One Vial at a Time

SiO2 Materials Science joined Operation Warp Speed in the summer of 2020 to produce its plastic-glass hybrid vials for the COVID-19 vaccine rollout in the US. Lawrence Ganti, Chief Business Officer, explains how they quintupled their workforce and increased production capacity 12-fold in just a few months.

Tell us about the history of SiO2...

SiO2 Materials Science dates back to 1910. In those days, the family business, led by Mauri Abrams, worked on accounting systems and various new technologies for the US government. In the 1950s, his son, Bobby Abrams, took the helm and built one of the largest dairy manufacturing plants in the US. Over the years, Bobby has invented a number of products, such as the first private labels for the dairy industry to desiccated plastic vials for diabetic strips, the infant sippy cup, and airtight vials for drugs of abuse testing. In 2012, Bobby – who remains our CEO – was approached by the Children's Hospital at Stanford University. They were unable to save the lives of 20–25 premature babies each year due to adverse reactions to sub-visible particles found in traditional glass syringes and vials used with their medicines. Bobby then set out to invent an inert container to house modern biological drugs – and that was the birth of SiO2 Materials Science.

How do your vials and syringes differ from traditional glass-based technologies?

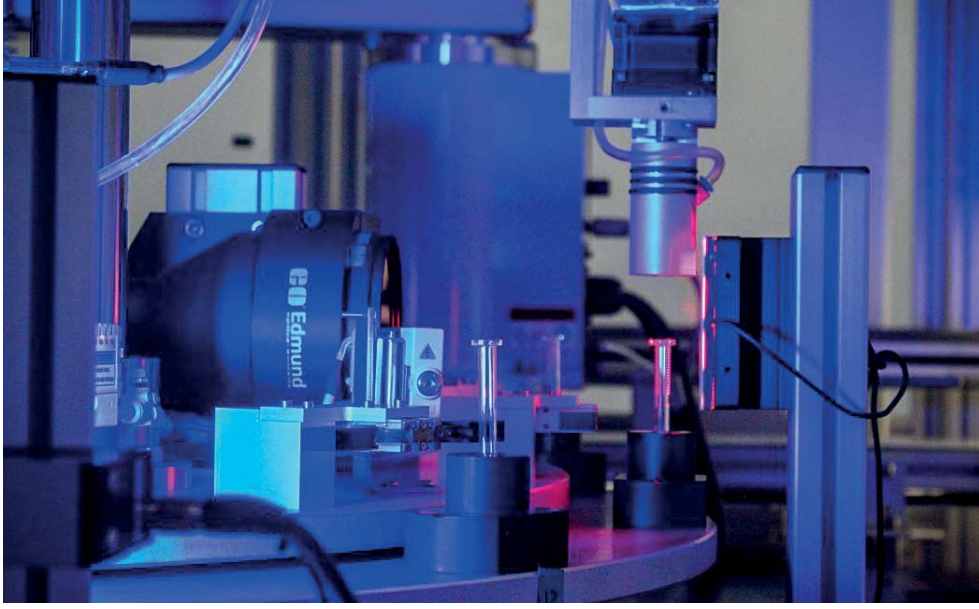
We've spent the past decade, and more than $500 million in research and development, to invent a technology that fuses plastic and glass. The technology we've invented looks and feels like plastic, but on the inside they have a nanoscopic layer of pure glass (SiO2), which keeps the oxygen and moisture out of the plastic container. Unlike regular glass, there's no delamination – the appearance of visible flakes or glass lamellae, which can be a risk to patients if undetected. You can also freeze these vials to cryogenic temperatures.

Then the US government got in touch…

We were using the hybrid material to make syringes, mainly for biological and advanced therapy products. Then, when the pandemic hit, the US government were looking for glass vials that were outside of the existing glass supply chain, and could also meet certain requirements around protein aggregation, interaction with oil, ability to withstand low temperatures, and so on. They got in touch to inquire about our technology – and our ability to scale. We ended up being a good fit and set about increasing production – rapidly. We had to go from making 10 million vials per year, to 10 million vials per month for the COVID-19 vaccine rollout in the US.

"We had to go from making 10 million vials per year, to 10 million vials per month for the COVID-19 vaccine rollout in the US."

The pharma industry has been dealing with glass shortages for a number of years now. Usually when a company develops a drug, they have a period of five-plus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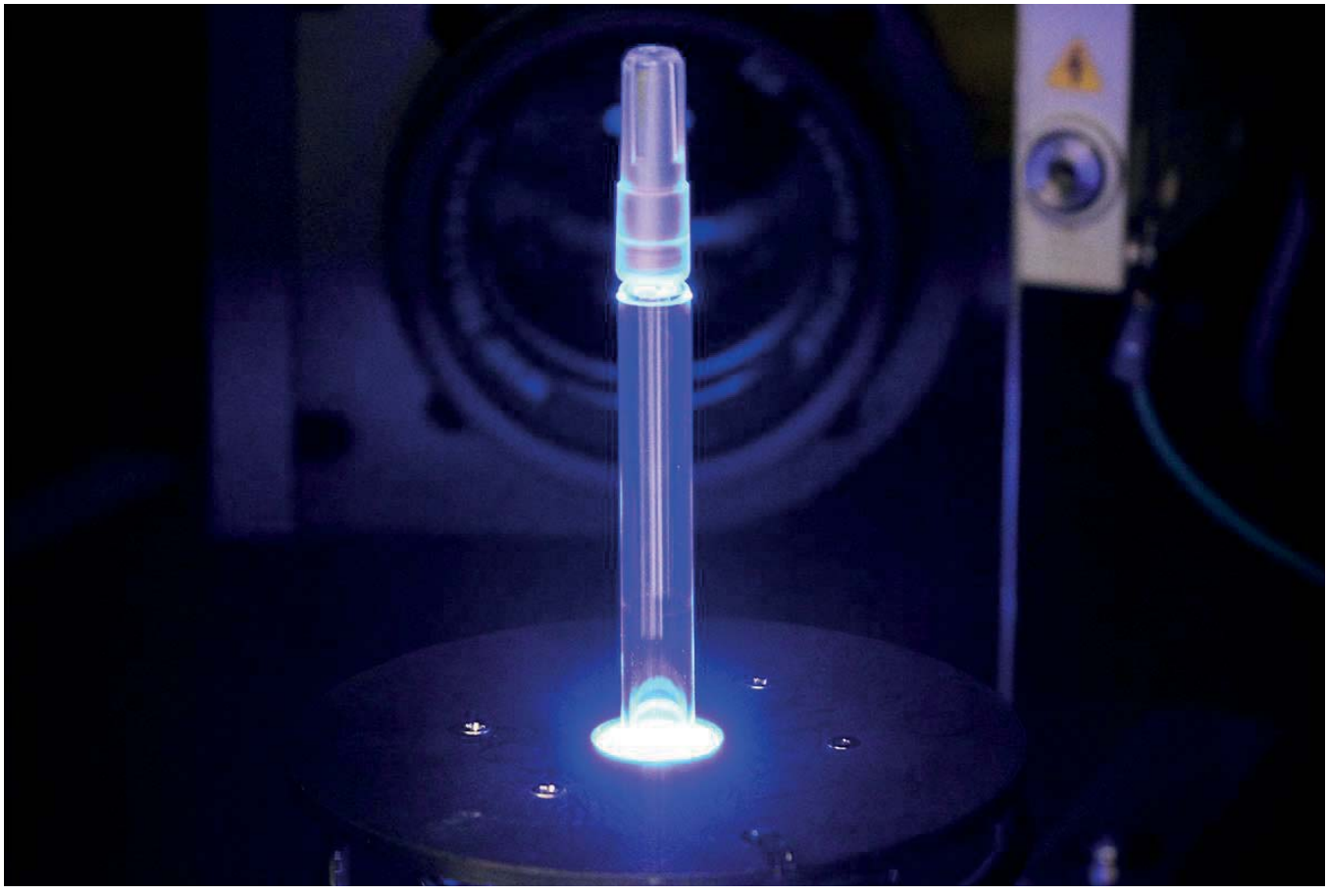
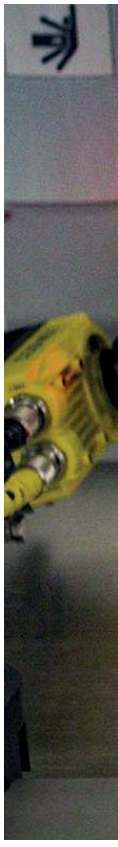
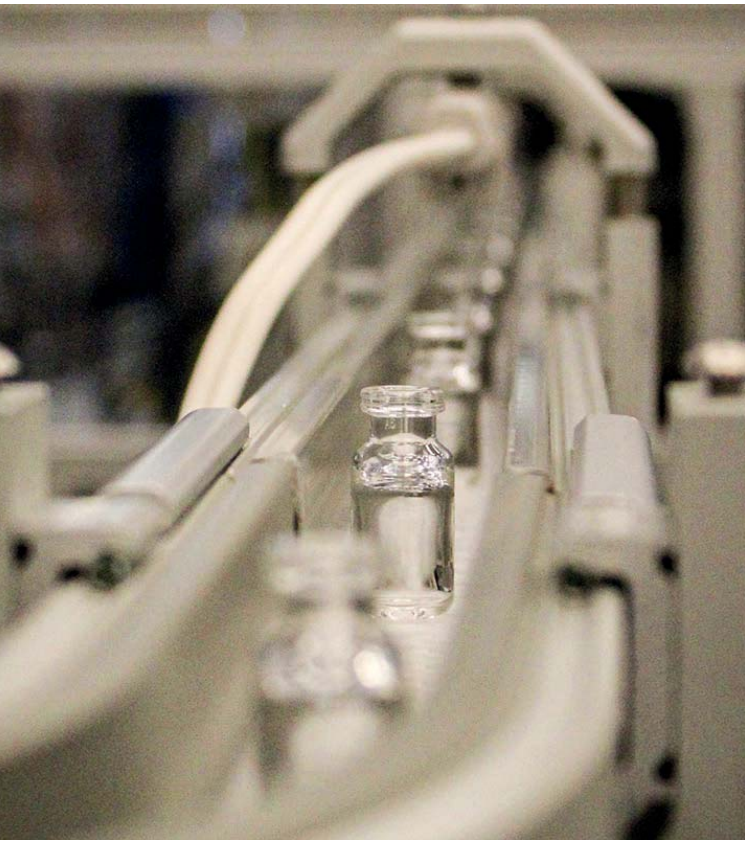
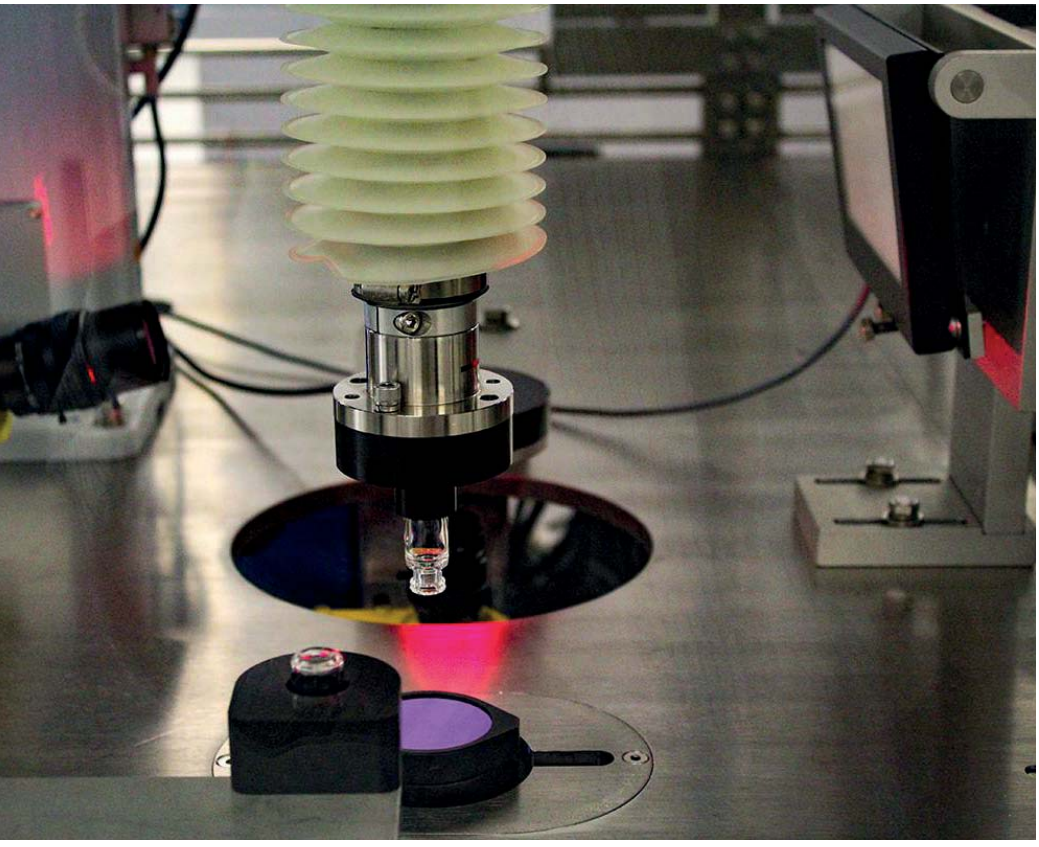








"Whenever you increase capacity, there's a lot of paperwork involved."

years to plan and ensure they have all the supplies they need. But the COVID-19 pandemic suddenly raised the demand for glass, with manufacturers needing to produce millions of vials in a matter of months. For traditional glass vial manufacturers, it might take 18–24 months to achieve what we were able to do in four because they're all using the same raw materials. We're outside of that supply chain because our technology is predominantly plastic.

It also helped that we were already working with several large pharma companies prior to the pandemic. We had our technology being used in close to 20 clinical trials and had launched a syringe with Novartis for Lucentis.

What were some of the challenges involved in increasing capacity 12-fold in just a few months?

The technology itself is inherently scalable – so there weren't many problems from a scientific perspective. Rather, the challenges were logistical in nature. Pharma, as we all know, is highly regulated. So whenever you increase capacity there's a lot of paperwork involved. And scaling at the pace we did, we found the sudden uptick in the amount of documentation we had to fill out slowed things down quite a bit – though we did, of course, appreciate why it had to be done. Another perhaps more challenging aspect of the scale up was recruitment. Under normal circumstances, you might hire 100 people over the course of a few months. And of those 100 people, five might not work out. But when you shrink that timeline to a week or two, that 5 percent might rise to 10 or 20 percent. In the end, we had to over hire knowing that there would be some attrition.

There are several additional challenges associated with quadrupling your staff. For example – and I sometimes joke about this – you don't think about potato chips! Where will everyone park? Where is everyone going to eat their lunch? Where will they take their breaks? Our break room was set up for 100 people – not 500. Add to that the need for social distancing and you quickly run into some real logistical challenges. In the end, we had to set up tents and tables outside (luckily it's warm enough to do that here in Alabama). We also had to secure parking places with the local town to ensure we weren't creating any problems with our employees parking by the street on the grass. Many of these things get taken for granted – I could add cyber security and database scaling to the list – but they are essential to supporting a sudden increase in production. We had to be flexible, and from a management perspective, decisive. It's about moving forward quickly in a coordinated fashion.

Finally, we faced challenges rapidly procuring the required hardware. We were working with a number of different partners on the equipment builds, all of which had to be coordinated to ensure everyone was on the same page – they're scaling too and our timelines need to match. We also had to ensure our

"I think COVID-19 has forced companies to adopt new – or perhaps 'emerging' – technologies and ways of working."

partners understood the importance and urgency of what we were doing.

Where are you up to now in terms of production?

In terms of doses, we reached the 100-million dose milestone. So that means we've shipped more than 10 million vials (they each hold 10 doses). We're now averaging around eight to nine million vials per month, so we're really rocking – producing and shipping and producing and shipping... But we're not just supplying vials for the mRNA COVID-19 vaccine in the US, we also have customers in Europe, Asia, and South America that are testing the vials for their vaccines. And of course, we are also still producing syringes and other vials for key biological drugs in clinical development.

How did your staff rise to the challenge?

The effort that people have put in has been nothing short of inspiring. It's been 24/7, working 80-90 hour weeks, with some working through Thanksgiving, Christmas, and New Year. The people on the production line, in the quality teams, the program managers who look after the schedules – and all their related supervisors and managers – have been, I would say, maxed out. We have a team that physically build the manufacturing technology, as well as testing and validating them. Normally, it might take six months to get a machine up and running, but they've had to shrink that timeline to a matter of weeks – days even. But it isn't just the manufacturing staff who have put in extra hours. Going back to staffing, consider the HR manager who had to send out offer letters to hundreds of people, facilitate criminal background checks, ensure their benefits, 401Ks, and healthcare plans are set up. Everyone has had to pull together to scale up so fast.

Given the sheer number of vials, how do you deal with sustainability?

Once used, our vials are considered medical waste, which means they're not recyclable; however, I will say that the process we use to make our vials is more sustainable than traditional glass vials. Making glass uses a tremendous amount of water and heat – energy, in short. Our process is "dry", so there's very little water involved and much lower temperatures. So our carbon footprint is relatively low.

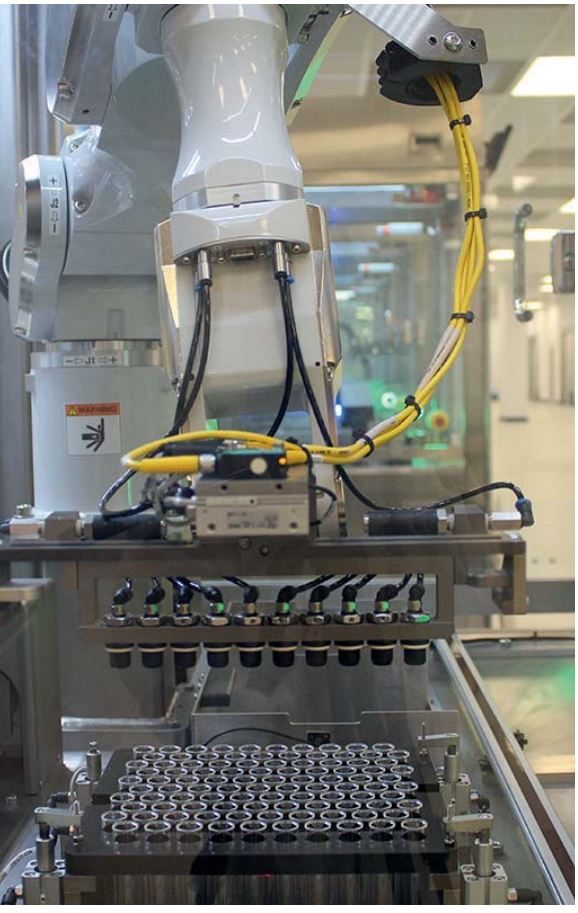
How has COVID-19 changed the pharma industry – with particular regard to glass vial usage?

The pharma industry is always slow to adopt new technologies. But sometimes it just takes one or two trailblazers to make everyone realize, "Oh, it does work!" We've seen that with the initial success of immunotherapies, which prompted hundreds of companies to work on them. I think COVID-19 has forced companies to adopt new – or perhaps "emerging" – technologies and ways of working. Working from home is the obvious example of a trend that has been hugely accelerated by the pandemic, and I think the adoption of our technology fits into the same category.

But just as working from home was already prevalent before 2020, we were already in discussions with many companies. And most – I'd say 70 or 80 percent – of large pharma companies had already tested our technology with positive results. Under normal circumstances, it might be another 5–10 years or so before we might see that translate into a much larger market share. But with companies like those leading the COVID effort now using our vials at scale, we expect to see that timeline reduced considerably – just as many people will probably spend some time working from home once we can all safely return to the office. Plus, there are other pre-existing trends working in our favor. We see many companies moving into the "bioengineered" or biological space, such as antibody drug conjugates, cell and gene therapies and other protein-based therapies. These are all technologies that are more sensitive subvisible particles, silicone oils, and metal ions- all traditionally associated with glass. Our technology is well suited to those kinds of therapies and we are already seeing an uptick in interest from companies developing gene therapies and bioengineered therapies for oncology and immunological diseases. So, in short, yes – I think COVID-19 has changed things for good.

What does it mean to everyone at SiO2 to be involved in the COVID-19 vaccine rollout?

As I've discussed, there have been huge efforts – and sacrifices – made across the company. But I think everyone understands and takes a great deal of pride in the role we're playing in ending a deadly pandemic – "saving the world one vial at a time," I sometimes like to say. Leaders often talk about the importance of having a clear purpose to what your organization does. We certainly have that and I think that's been the key to our success so far.

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PWR ION HV NDL
CAUTION! / ATTENTION!
- Hazardous voltage, Risk of electric shock.
- Tension dangereuse, Risque de choc électrique.

No Deal; No More: How Is the UK's Brexit Deal Working for Pharma?

Did the pharma industry get everything it wanted from a UK-EU Brexit deal? Were worries over border delays and shortages of medicines warranted? After years of speculation, we reveal what Brexit really means for pharma – so far.

By James Strachan

A deal between the UK and the EU was struck on Christmas Eve 2020. The text – running to 2000 pages – allows for "zero tariff, zero quota" goods trade now that the UK has left both the single market and customs union at the end of the transition period (1). The EU-UK Trade and Cooperation Agreement contains a wide range of provisions, including fishing, aviation, nuclear energy, dispute settlement – but what about medicines?

The text contains (a welcome) annex on medicinal products, which provides for mutual recognition of Good Manufacturing Practice (GMP) inspections and certificates, meaning that manufacturing facilities do not need to undergo separate UK and EU inspections (2). Richard Torbett, Chief Executive of the Association of the British Pharmaceutical Industry, described this provision as "a huge benefit" in his evidence to the Lords European Union Committee (3). He also thought the commitment to regulatory co-operation in future was a good signal. "We do not know exactly what it will look like yet, but the principle is very welcome," he said. The deal also gives the UK the option to continue to participate in Horizon Europe – provided both parties can agree on the terms.

However, the medicines annex notably does not provide for the mutual acceptance of batch testing certificates – one of the UK government's stated aims for the negotiations (4). This aspect was a "big source of concern" for Torbett. "Every batch of every medicine and every vaccine has to be tested, which means that a certain number of doses are taken out of the supply chain and put through laboratory processes of various sorts to test purity, toxicity, and so on," he said. "It is a costly and difficult process; it takes time and resource, and it takes chemicals. If you think about the scale of that, we have 12,000 types of medicines going to the NHS, and we have multiple batches per year for each of those 12,000."

"We were disappointed not to find a commitment to the mutual recognition of batch testing," says David McClelland, Head of EU Biologics Operations at Merck. Interestingly, the US and the UK agreed in 2019 to roll over the US-EU MRA. And that means UK medicines exporters must now factor parallel batch testing when exporting to the EU, but not the US – a complete reverse of the situation prior to the full implementation of the US-EU MRA in 2019. The same also applies to the CETA agreement.

"This will be an ongoing cost for us," says David Jefferys, Senior Vice President at Eisai Medical Research. "Having to qualify for each and every batch twice will obviously double the cost in that area."

The batch testing of finished drug products is not a major concern for Merck, according to McClelland. "Finished product testing is often done in house by manufacturers or more specialist testing houses and tends to be

"Having to qualify for each and every batch twice will obviously double the cost in that area."

fairly straightforward analytical testing or microbiology testing," he says. "The core of our business is further upstream, and involves more intensive and complex biological methods, such as cell line characterization. While this is a smaller part of our business, it is still a concern because we want to be able to offer all aspects of testing, at all stages in the process for our clients."

In addition to the cost concerns, one comment from an audience member during the ABPI and BIA's Brexit webinar painted a worrying picture for the delivery of CAR T cell therapy. "I am unclear what the expectation is to be able to batch release a CAR T, for example, which may be a batch for one unit per person," she said. "We don't have the technology transferability in the UK, we don't have the testing that would be required to test these products, and it would be really difficult to transfer a bag of cells to an independent laboratory. Given the supply chain for a CAR T is a matter of days in some cases, introducing batching testing in this way without some kind of exemption for cell therapy could end up with products not being sold here or delays that could ultimately result in a patient death."

Jason C Foster, CEO of Ori Biotech, a cell and gene therapy manufacturing technology company, was also concerned about processes for QC release of autologous products. "QA and QC are already huge bottlenecks in the process today," he says. "The same level of quality control and batch release are required for a single dose of an autologous cell therapy as are required for a whole batch of small – and to some extent large – molecule drugs." However, Foster also points out that some autologous therapies are manufactured in Europe and distributed as far as Australia – though companies will have factored in batch testing requirements early on.

"For now, the UK has agreed to unilaterally recognize batch tests certified in the EU – at least until 2023."

For now, the UK has agreed to unilaterally recognize batch tests certified in the EU – at least until 2023. "That is helping the industry to avoid an immediate impact on products flowing into the UK," says McClelland. "But the industry as a whole needs more certainty about what's going to happen in 2023 – creating adequate UK-based testing is not something that's going to happen overnight."

And it's an area that represents another "big source of concern" for Torbett and the ABPI. "We would very strongly urge the Government to reconsider [ending unilateral recognition]," he said. "It would lead to a huge amount of cost, complexity and, ultimately, delay in the supply chain, which nobody wants. It is of no benefit, it is entirely duplicative, and those resources could otherwise be spent in other areas."

Jefferys was pleased that there was a deal, but described it as "thin," as far as the sector goes. Jefferys also highlighted the range of issues associated with Brexit that were never going to be addressed by the deal, given both side's red lines during the negotiation. "The UK is now a "third country," which means EU rapourterships are now handled by the EU27, the MHRA is now out of the system and does not have access to EU databases, the reference member states have been moved, sponsorships of clinical trials have changed, and QPPVs have moved to the EU (in our case to Germany) – these were all already in place and have been carried forward."

Eisai has spent approximately £10 million in direct costs in preparing for Brexit and another £10 million in indirect costs, according to Jefferys. "That includes money we've spent on new licenses, new labels, extra people, people's time and so on; making these changes doesn't come cheap."

The immediate impact

Another inevitable consequence of the UK's departure from the single market and customs union is an increase in the workload required to manage the activities linked to customs clearance (payments of tariffs and taxes, processing of paperwork, and so on). And even if pharma exporters aren't directly impacted by a newfound bureaucracy, they share the same roads and ports as other industries – making the consequences of Brexit difficult to predict. With this in mind, has there been any shortages of goods so far? At the time of writing, almost three months have passed since the deal came into effect, and the verdict is decidedly mixed.

According to Steve Bates, CEO of the BIA, security of supply wasn't an issue during the first weeks of January. "It feels as if the planning that has been put in place with the government is working effectively," he told members during a webinar in January.

Merck had been building up additional safety stocks of raw materials and finished goods in both the EU and UK in case of border delays. Concurring with Bates, Frithjof Holtz, Senior Expert Regulatory Intelligence, at Merck Life Science, says that the first week of January was "very quiet" and

An Alternative Ulster

Another Brexit-related issue is the new customs and regulatory border between Great Britain and Northern Ireland, which has special status as part of the EU's customs territory and single market for goods to prevent border checks on the island of Ireland. There is a 12 month phasing in period of regulatory requirements for medicines to avoid disruption to the flow of medicines from Great Britain to Northern Ireland, and there is some controversy over what is required of companies today – and what will be required in 2022.

During a later joint BIA/ABPI webinar, Mogford noted how there were some snagging issues related to Northern Ireland in the first weeks of January. And for 2021, Mogford wanted to make clear that the requirement for a Northern Ireland EEA importer, QP, and batch testing, plus the uploading of a new unique identifier code will not apply. "We will issue UK-wide and UK-only licenses for GB and Northern Ireland," he said, while recognizing there is some "controversy" about that.

One audience member of the webinar was worried about the end of the phasing in period: "Every single company on this call knows we probably cannot do what needs to be done by the 31st of December." He went on to argue that industry needs to say to the UK government: "You're telling us to be ready for something, but we don't know what it is. Can we please start working on this now?"

David Jefferys also highlighted that the industry is awaiting further guidance on Northern Ireland. "We understand that we will have to supply documentation for Northern Ireland to MHRA and then, supposedly, again for Great Britain – which is a potential problem," he says.

For Merck, the new arrangements have already prompted changes to supply chains. "Previously we would have shipments of raw materials and products moving from mainland Europe through the UK to the Republic of Ireland," says Holtz. "But we have had to reroute some of those supply chains to ship directly from France or Germany, for example, to Ireland to avoid crossing the border twice, which would come with potential delays."

that everything went smoothly. But then things became more difficult – "All parties are adjusting to new paperwork requirements at the borders," he says. "We've also had some challenges booking trucks." Another tricky issue is providing proof of origin to qualify for zero tariffs. "You need to have the right systems in place, along with IT support – this adds to the overall workload."

Jefferys also highlighted some initial difficulties with tariffs: specifically, new rules of origin requirements. "While there are no tariffs on medicines themselves, there is an issue whereby if the country of origin content of a shipment – of clinical trial material for example – is above 50 percent, then it may be subject to tariffs and additional border checks," he says. "This is an ongoing issue and will need to be resolved."

"We're going from a situation where there were no – or very limited – customs controls at the border to customs checks on both sides," says Holtz. "And it is taking some time for the customs officers and companies to get used to the new processes." He gives an example of a shipment of a product that must be kept at a low temperature with dry-ice. Prior to the new arrangements, Merck might use a shipper with the ability to keep the temperature for two or three days. Now they must use a shipper that can maintain the low temperature for five-to-seven days to be on the safe side.

Any delays or difficulties facing companies like Merck are inevitably compounded by the COVID-19 pandemic – and isolating the effects of one or the other is tricky according to McClelland. "Under normal circumstances, we'd use air freight for many items, but there just aren't as many planes in the air, which is forcing the use of more road and sea routes."

That said, McClelland's overall assessment of the situation is positive. "Merck has been able to get materials through borders without too much difficulty," he says. "It probably hasn't panned out as badly as we expected. This is in part down to Merck beginning early preparations for Brexit and assuming a no deal scenario, it has helped ensure our business continuity.

Kate Ling, Senior European Policy Manager at NHS Confederation, also gave evidence at the Lords European Union Committee. "So far, we have not heard about a lot of problems or, at least, no disasters," she said. "We have heard, for example, from a couple of research institutes that it has been touch and go for some of their temperature-sensitive deliveries, things such as ingredients for cell cultures that have to be delivered on dry ice." She also mentioned that some research organisations are incurring extra costs (for example, paying couriers) to guarantee speedy delivery of

medicines or ingredients or equipment.

However, border delays have had a significant impact on Pedro Silva Couto's work at University College London, where he is studying the expansion of mesenchymal stem cells as a PhD student. "First we noticed a global shortage of basic items such as gloves or sterile tips (mostly being used for PCR tests for COVID-19) – obviously working in a sterile environment requires the use of gloves, so without this, it is literally impossible to work," he says. "We have also experienced significant delays in some key products such as culture medium or even culture supplements (things like IL-2 or dynabeads for people who do CAR-T cell research)."

Ori Biotech also faced some initial problems with supply. "We've seen some initial shipping delays of materials coming from Europe or from the US," says Foster. "This includes raw materials, cells and cell culture media, virus and some of these other components that we use in our processes. We believe these are Brexit-related, but it could also be related to COVID-19 – it is difficult to separate their effects."

The future of UK pharma

Jefferys points out that Brexit has increased the cost of doing business in the UK. "It is slightly more difficult today than it was a few months ago," he says. With that in mind, will the UK pharmaceutical market continue to thrive outside of the EU single market and customs union?

"We wanted a close relationship with the EU, but we prepared for the worst. In the end, we didn't get everything we wanted and there are issues that must be managed carefully," says McClelland. "However, we have over 1500 people in the UK across 12 different sites, which includes production, sales, distribution. and contract testing – Brexit is not going to change the fact that the UK is, and will remain, a very important market for Merck."

"We wanted a close relationship with the EU, but we prepared for the worst."

For Massimo Dominici, scientific founder of Rigenerand, an Italy-based biomedical company producing disposable bioreactors for diagnostics/exosome manufacturing and cell-gene therapies for cancer "Nothing has changed to my eyes," he says. "The UK has shown a positive vision for the cell and gene therapy industry. And in terms of investment in capital projects, nothing has changed from my perspective as a result of Brexit – in fact, there may be some facilitation in terms of attracting foreign investments." Dominici has also been impressed with the knowledge of the MHRA. "For cell and gene therapies, the experience, knowledge, and flexibility of the regulators is a key factor – and I have always been impressed by the UK authorities having interfaced with them while consulting for several companies."

Marc Martinell, co-founder and CEO of Minoryx Therapeutics, a clinical stage biotech company focused on orphan drug discovery and development, doesn't see Brexit having much of an impact in the near future – but that may change as his company moves to commercialize products. "Brexit means separate approval processes for the EU and UK," he says. "And this will likely create staggered approvals as companies prioritize the most commercially important market – especially for smaller companies with more limited resources."

"There is a lot of great research happening in the UK and the support available from organisations like Innovate UK or the Cell and Gene Therapy Catapult – this isn't going to change as a result of Brexit," says Foster. From the cell and gene therapy sector specifically, Foster sees a drive to become a leader in the field, but the UK's success or failure will depend on other factors. "It is difficult to know whether advanced therapies will be subsumed by other priorities post-Brexit, but if money continues to be invested I can see the UK maintaining and even further establishing itself as a leader in the field."

The speed at which the UK is vaccinating its population against COVID-19 is to some an encouraging sign for the pharma industry. The UK invested heavily in vaccine development and the MHRA was the first regulatory agency to approve the Pfizer/BioNTech vaccine. Can the UK replicate its vaccine success for the wider pharma sector?

Jonathan Mogford, director of policy at the MHRA, also detailed some of the work that the MHRA has been doing to support innovation in the pharma sector during a joint BIA/ABPI webinar. On the international front, the UK is now a full member of the Access Group, which is a consortium of regulators in Australia, Canada, Singapore, and Switzerland. Mogford noted that all members have very strong links to the health systems, which he highlighted as being particularly important in light of the COVID-19 pandemic. "We've also been actively involved in exploring links with the FDA on Project Orbis," he added. Project Orbis is an initiative of the FDA Oncology Center of Excellence, which provides a framework for concurrent submission and review of oncology products among international partners.

"The UK joining the Access Consortium and also Orbis is extremely exciting," says Jefferys. "There may also be opportunities for the MHRA to be more rapid in its approvals." He notes that the MHRA is looking into innovative approaches to clinical trials in the future, as well as building the Innovative Licensing Access Pathway, which is aimed at reducing the time to market for innovative medicines through enhanced coordination and monitoring. "Brexit is by no means a disaster," he says. "In business you have to work with plusses and take care of the downsides."

There is also the question of whether the UK and the MHRA can exert an equal – or greater – influence on the global pharmaceutical regulatory environment now that is independent from the EMA. "The UK was a leading player within the EMA and the EEA, which remains a significant economic and regulatory force," says Jefferys. "It will be interesting to see whether the UK will go down the route of recognizing what is done at the European level without having a voice," he added. "That being said, there are new opportunities to work with agencies across the world and to act independently within global regulatory bodies, such as the ICH."

Steve Bates also argued during the BIA webinar that the UK could help "move the global regulatory agenda forward," while ensuring its processes are as efficient as possible – without completely changing approach. On the question of divergence, he said that the sector isn't keen on a "sudden regulatory handbrake turn," and that the BIA has argued for close cooperation throughout the negotiations.

"I think a close relationship between the regulatory agencies is going to help the industry in general – we don't want to see significant deviations in regulatory approaches," says McClelland. Holtz concurred, adding, "Though we now must submit registrations for the UK and EU markets, we hope that the regulations themselves, the forms and documents required, remain as aligned as possible."

Finally, in what may feel like deja vu for those following The Medicine Maker's Brexit coverage over the past few years, Merck, the BIA, and the ABPI are all hoping for a mutual recognition agreement on batch testing in the near future. The medicines annex of the Brexit deal will be reviewed by the UK-EU Working Group on Medicinal Products, which may provide an opportunity for the industry to push for closer ties in the coming months and years.

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NextGen

R&D pipeline
New technology
Future trends

Biopharma Trends to Watch

Five trends that will shape the future of biopharma manufacturing in 2021

By Priyanka Gupta and Amélie Boulais

The COVID-19 crisis showed us more clearly than ever that faster biopharmaceutical manufacturing saves lives. But to reach the level of efficiency needed to respond to the world's greatest health challenges, biopharmaceutical manufacturers need to invest in novel tools and strategies that will enable them to intensify and automate their bioprocesses. Here, we discuss the top five factors that will contribute to greater efficiency in biopharma manufacturing in 2021 and beyond.

1. Process intensification

Manufacturers have discussed the potential of "process intensification" for decades, but 2020 generated renewed urgency in implementation. Intensifying a bioprocess means increasing efficiency by reducing manufacturing timelines and using fewer input materials and less complex workflows in a smaller space – all while increasing productivity. We've already seen some biopharma companies embrace the benefits of process intensification in response to the pandemic. But, even after the pandemic is over, the industry will continue to face demand for less expensive products delivered quickly. Today, there are a variety of technologies available for process intensification. For example, advances in rocking motion and stirred tank bioreactors give manufacturers a choice of flexible upstream single-use seed train options that not only enhance flexibility but also lower the cost of goods. Also, using high cell density to inoculate a seed train enables one to inoculate at higher volumes. Finally, the use of multi-column chromatography systems in downstream bioprocessing can significantly lower resin cost, reduce timelines and also save on buffer volumes and cost.

2. Bioprocessing 4.0

Another popular approach that leads to a streamlined bioprocessing workflow is the concept of "bioprocessing 4.0", which allows manufacturers to measure and adjust process parameters more quickly and easily. A key element of bioprocessing 4.0 is the introduction of automation, where all of the tools and equipment within a workflow are connected digitally, from end-to-end, to reduce human error. It also improves the process by incorporating sophisticated feedback loops and machine learning to automatically introduce improvements. Today, bioreactor technologies exist that incorporate in-line sensors that report data in real time, to help scientists measure critical quality attributes and make modifications to the workflow while it's running. It is also possible to replicate bioprocesses digitally to run simulations for optimization. This method can shave weeks off manufacturing timelines and would reduce the time needed for testing data off-line and for cleaning equipment.

In our view, bioprocessing 4.0 is the most impactful way of accelerating biopharmaceutical development and processing.

3. Flexible manufacturing

Speed and efficiency will not only enable faster drug and biologic development, but will also help manufacturers produce a wider diversity of pharmaceutical products based on novel modalities, such as complex drug conjugates, viral vectors, nucleic acids, and fusion proteins. To accommodate these new modalities, biopharmaceutical companies will need the flexibility to easily adopt the necessary new manufacturing platforms and transition to new indications as needed.

The COVID-19 pandemic, for example, showed us the true value of flexibility. As biopharmaceutical manufacturers were able to transition almost immediately to SARS-CoV-2 vaccine development, we've seen the first wave of vaccine approvals in record time. Even more incredible; the Pfizer and Moderna vaccines are based on mRNA technology, which had not been implemented successfully prior to

SARS-CoV-2. Despite the novelty, the industry was able to innovate quickly, with flexibility enabling the efficient adoption of processes for manufacturing mRNA vaccines.

mRNA technology is a truly versatile platform. The same process that was used to develop an mRNA vaccine for SARS-CoV-2 can be used to produce vaccines for other indications by simply switching out the nucleic acid sequence. This platform makes it easier for manufacturers to transition from one vaccine to another in the same facility, enabling faster and more efficient vaccine development in response to future public health threats. Additionally, an mRNA platform makes the process of vaccine development easier, to the point where these vaccines can be developed in local facilitates all around the world, potentially helping developing nations gain better access to vaccines. Flexibility can also be achieved via single-use technologies These technologies can be implemented much more quickly than stainless steel technologies, and in the case of COVID-19, vaccine developers can leverage existing facilities to save time and cost. For example, before COVID-19, there was no large-scale capacity for mRNA production, but with the adoption of single-use technologies, existing CDMOs have been repurposing facilities to produce mRNA-based vaccines.

4. Demand for biosimilars in emerging markets

Biosimilars are in high demand worldwide because they are cheaper alternatives to their corresponding innovator drugs. According to McKinsey, global biosimilar sales are set to more than double to $15 billion by 2025, with roughly $5–8 billion of these sales predicted to come from emerging markets (1). And yet, though biopharmaceutical companies race to capture their share of this growing biosimilars market, they also face several hurdles.

First, dozens of biopharmaceutical companies are competing to produce biosimilars for the same 10 to 15 biologics. At the same time, producers of innovator drugs are adopting more streamlined approaches to biologic development so they can produce biologics at a lower cost. And that makes it even harder for biosimilar developers to be competitive.

In the race to be first, cost becomes the major bottleneck. To receive approval for their biosimilars, manufacturers must spend a great deal of time and money proving their molecule's biosimilarity to the innovator. Also, though these companies may ultimately seek a share of emerging markets, they must achieve approval in the US and EU – both regions impose high regulatory standards on biologic development.

"To receive approval for their biosimilars, manufacturers must spend a great deal of time and money proving their molecule's biosimilarity to the innovator."

All of which makes efficiency even more important; manufacturers must build facilities that can produce multiple biosimilars simultaneously. Additionally,

manufacturers must build redundancies into their workflows that will enable them to adapt to new public health threats. Efficiency and flexibility are related and essential.

5. Cellular and genetic approaches

Only a small handful of cell and gene therapies have been approved by the FDA so far, but more than 1,000 different therapies are in the pipeline, with more on the way. By 2025, the FDA anticipates that it will have approved 10–20 more cell and gene therapy products (2). And in the next decade, the gene therapy market is expected to grow at a 30 percent compound annual growth rate (3). Some FDA-approved advanced therapies are already showing success, including a gene therapy for spinal muscular atrophy (Zolgensma from Novartis/Avexis). The future is bright, with biopharmaceutical companies looking to expand beyond rare diseases to oncology and other chronic conditions.

As the cell and gene therapy pipeline grows, the need to produce clinical material will increase. And as developers begin producing therapies for a wider range of indications, including cancer and chronic diseases, more patients will become eligible to benefit from these therapies. These two factors will produce a shortage in manufacturing capacity. This means that manufacturing facilities not only have to grow in number, but developers will also have to intensify production.

Facing the future

The COVID-19 pandemic has intensified an already competitive race to streamline biopharmaceutical development. By embracing process intensification and the tenets of bioprocessing 4.0, biopharmaceutical companies can optimize their workflows to produce more with less. Such approaches mean shortened development timelines and the ability to produce vaccines and other crucial products more cheaply. As a result, the industry is better equipped to handle current and future health threats. The development of a SARS-CoV-2 vaccine so quickly might seem like an exception, but it is likely a sign of things to come in the biopharmaceutical industry in 2021 and beyond.

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Amélie Boulais is the Head of Market Entry Strategy, Virus Based Therapeutics at Sartorius.

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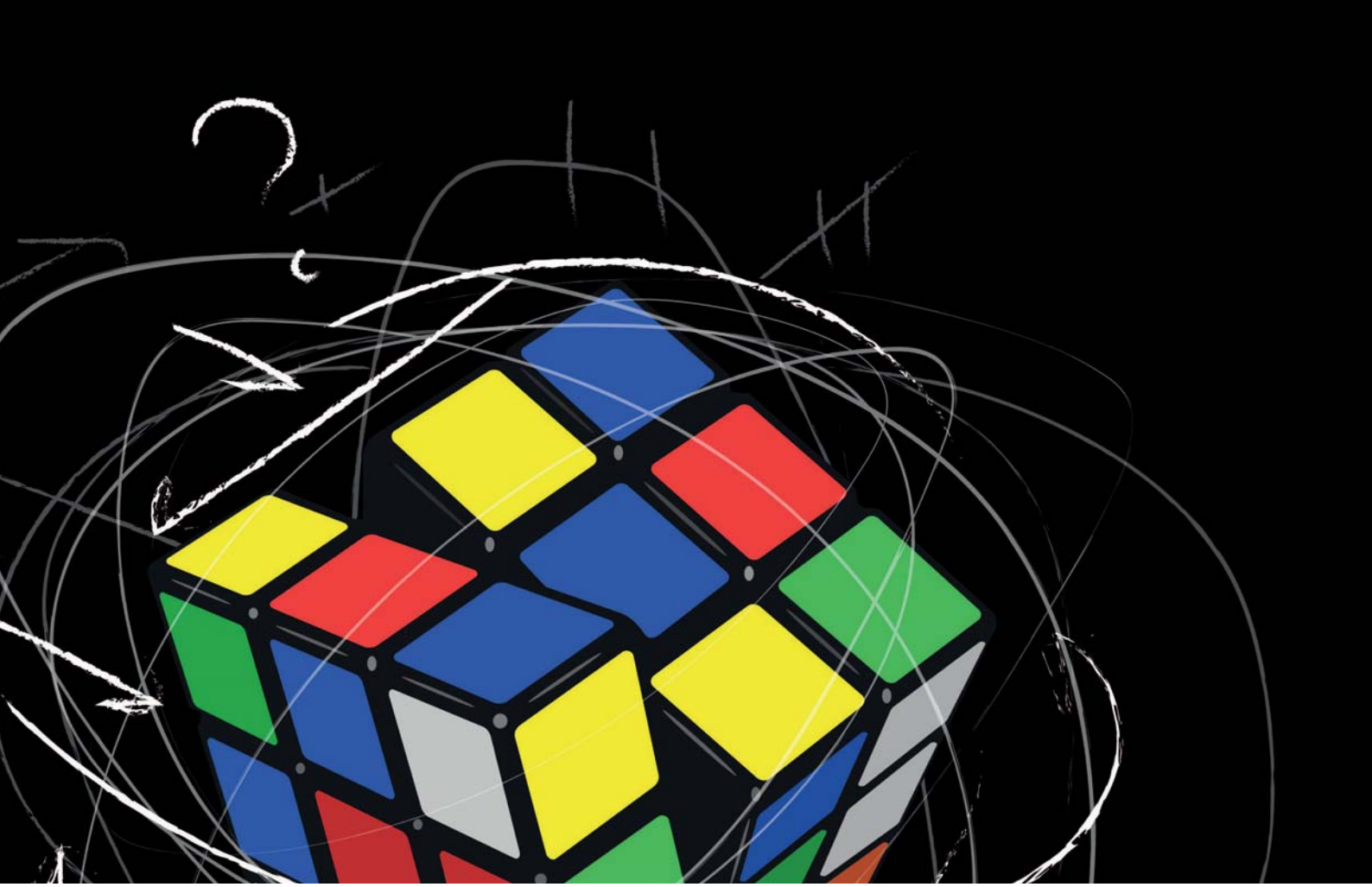


Two Grand Challenges for Pharma

A pair of medicines manufacturing initiatives are using digital technologies to improve continuous direct compression and make clinical trial supply more efficient

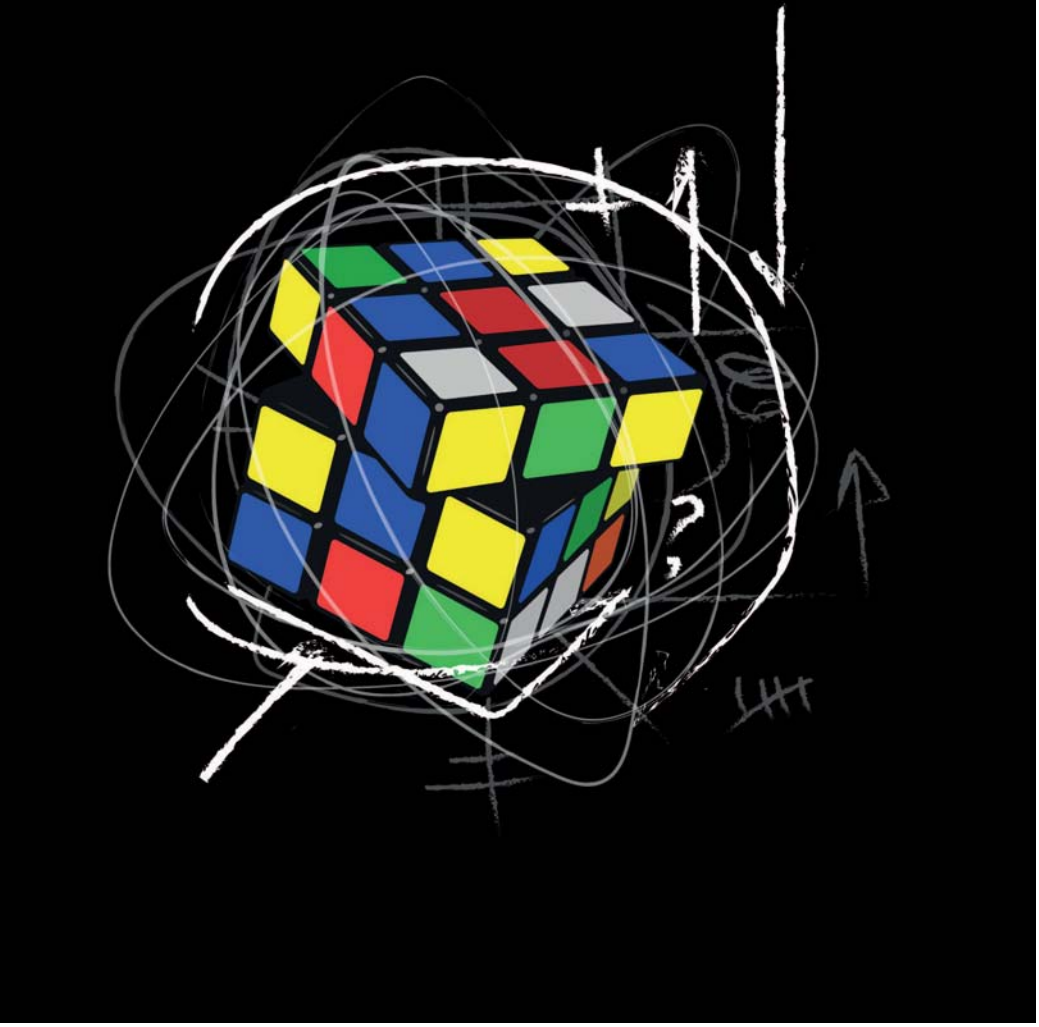
The growing, aging, and increasingly comorbid population is relying on the pharma industry for more personalized medicines and advanced treatments, all at lower costs. New approaches to manufacturing and supply will be essential.

In the UK, partners across industry, government, and academia have come together to form the Medicines Manufacturing Innovation Centre. As part of a collaboration between CPI, the University of Strathclyde, GSK, AstraZeneca, and with funding from UK Research and Innovation and Scottish Enterprise, the center has set out two 'Grand Challenges' to address in medicines manufacturing: producing tablets more efficiently using continuous direct compression, and reducing waste and improving agility in clinical supply with a "just-in-time" approach.

Here, we speak with John Robertson, Principal Investigator at CMAC Future Manufacturing Research Hub, about the development phase of Grand Challenge 1. And we chat with CPI's Dave Berry – Grand Challenge 2 lead – to find out how exciting new initiatives could transform the future of drug manufacturing.

Tell us about the two Grand Challenges…

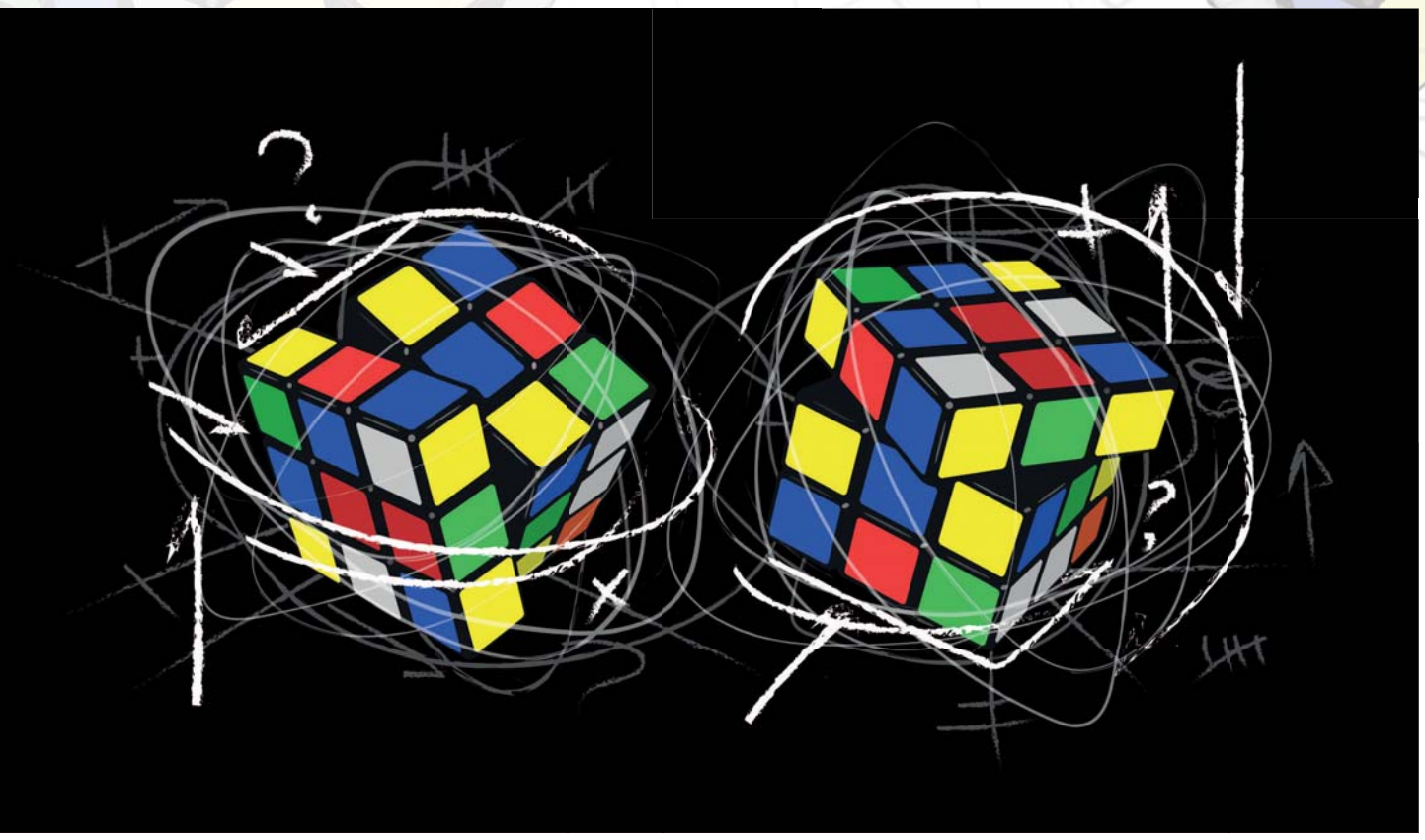
John Robertson: Grand Challenge 1 involves the creation of a continuous direct compression (CDC) platform that will enable oral solid dosage medicines to be formulated more easily. When compared with traditional "batch" manufacturing, continuous



"The platform will enable multiple medicines to be produced on a single line, along with individualized packaging and real-time quality checks."

manufacturing allows for more efficient use of time and expensive materials due to the flow of production without interruption. We will further build on this process efficiency by developing a digitally-twinned CDC platform and workflow, enabling scientists to better understand and optimize their formulations in a digital space. Existing CDC models are often inflexible and specific for individual equipment manufacturers; the digital twin will help us adapt and improve processes, while reducing development times.

Dave Berry: Grand Challenge 2 will deliver just-in-time medicines supply for clinical trials through an automated supply chain system, which we call the Pharmacy Automation for Clinical Efficiency (PACE) platform. The PACE platform consists of a collection of robots connected digitally to a dashboard that provides quality information to qualified persons who certify batches of medicines and send them to patients. The platform will enable multiple medicines to be produced on a single line, along with individualized packaging and real-time quality checks.



Grand Challenge 1 and 2 were officially announced in 2019. What are the updates since then?

Robertson: One of the most exciting updates over the last year has been the addition of several new partners to help support the Grand Challenges, including Siemens, Perceptive Engineering, and Process Systems Enterprise (PSE). Over the past year, we have also been working on the development and evaluation of the digital twin, which will allow us to understand and optimize the CDC platform in a digital space.

In October 2020, we officially broke ground on the Medicines Manufacturing Innovation Centre building in Renfrewshire, UK.

Berry: As John said, the addition of these new partners is certainly exciting. Siemens will also be providing digital manufacturing support to Grand Challenge 2, along with Applied Materials, which will be integrating its SmartFactory Rx automation software into the PACE platform.

We are also pleased to report that the PACE platform is now 90 percent built, and we are on track to finish in 2021. Originally, the plan was to finish the PACE platform in the new Medicines Manufacturing Innovation Centre building, which is the state-of-the-art facility that will house the Grand Challenges and future programs. However, COVID-19 forced construction to pause on the center. Interestingly, however, this hurdle has forced us to think more critically about the platform's portability. Through this disruption, we realized that some of the design features and IT infrastructure should be incorporated into the platform, rather than into the building, to allow the platform to be transferred with more ease – theoretically, across the world to be used for clinical studies.

How were the first two Grand Challenges chosen?

Berry: The challenges were selected and defined to tackle areas of medicines manufacturing where there are known inefficiencies – and because of the potential of advanced technology to reduce the waste associated with current processes.

Robertson: Despite improvements in medicines manufacturing, the way we make tablets has remained static for about a century. Grand Challenge 1 looks at how we can improve one of the simplest ways of making tablets: direct compression. The first step of Grand Challenge 1 looks to address the

"Despite improvements in medicines manufacturing, the way we make tablets has remained static for about a century."

direct compression process itself; the second step incorporates continuous manufacturing into the process. By leveraging continuous manufacturing, we can reduce waste while also reducing batch-to-batch variability. With these improvements, we hope to reduce drug waste from 30 percent – associated with today's manufacturing methods – to less than 5 percent. Not only can this offer a huge economic benefit, but reduced development times and API consumption can also provide significant environmental benefits.

Berry: The manufacturing of medicines for clinical trials is also very wasteful. Drug companies are potentially discarding upwards of £15-20 million ($20-27 million) of medicines for clinical trials per year. And that's not because anyone is doing anything wrong, but because clinical trial planners and manufacturers are forced to use a "just in case" approach to ensure a sufficient supply to clinical trials. Right now, the long lead times associated with manufacturing mean that clinical trial supply volumes must be predicted up to two years in advance of a clinical trial, leading to an over-production of drugs. Delayed or canceled trials can also result in expired drugs that will not be used. As a result of this waste, clinical trials are incredibly expensive, and these expenses are carried through pharmaceutical companies, impacting the development of other drugs. Making clinical trials cheaper and more effective will create a cascade of positive effects for both pharma companies and patients.

How could these initiatives help accelerate the adoption of personalized medicines?

Berry: Grand Challenge 2's PACE platform includes a number of features that allow for the creation and distribution of personalized medicines that are made just in time for clinical trials. The design of the platform allows for multiple drugs to be packaged on the same line without cross-contamination. Additionally, bottles can be filled with custom amounts of drug compounds, and then sealed and sorted with customized barcodes for rapid labeling and distribution. The platform enables the flexible production of clinical supply, produced for specific trials and even specific patients.

Robertson: The CDC platform associated with Grand Challenge 1 occupies a slightly larger scale than the PACE platform. At the moment, it cannot tailor medicines to individual patients. Instead, the Grand Challenge 1 technology will be able to respond to and tailor medicines for specific patient groups – e.g., pediatric or geriatric dosing regimens – through improved manufacturing processes. The improved speed and agility will allow for shorter runs, enabling pharmaceutical companies to better respond to differing patient needs.

Why are partnerships such a fundamental aspect of the Medicines Manufacturing Innovation Centre?

Robertson: Partnerships are the building blocks that enable us to de-risk the adoption of innovative technologies into pharmaceutical manufacturing. For industry partners like GSK and AstraZeneca, incorporating new, advanced, and unproven technologies into medicines manufacturing often presents too much risk, outweighing potential benefits.

Berry: One of the most exciting parts of this collaboration is getting together with all of the partners in a pre-competitive environment. We are all able to collectively use our cross-sector expertise to advance the field. These partnerships have continued to evolve over the last few years. And we have now started introducing new partners that can contribute their expert technology, services, or know-how to the Grand Challenges. This includes companies who have expertise in fields seemingly "outside" of pharmaceutical manufacturing. Their knowledge and technology will enable us to accelerate advancements in our own industry.

What are the next steps for the Medicines Manufacturing Innovation Centre?

Robertson: Right now, we continue to work on the projects, but we are also thinking about new Grand Challenges, including Grand Challenge 3, which will focus on the development of oligonucleotides. Overall, the goal of the Grand Challenges is to improve medicines manufacturing, not just within the silo of the Medicines Manufacturing Innovation Centre or in the UK, but to help the entire global pharma sector.

Berry: My hope is that we can revolutionize medicine manufacturing as a whole. In the long run, the introduction of advanced technology into medicines manufacturing is going to have lasting positive effects that will change the way we make medicines for the better.

Blockchain Brainiac

Sitting Down With…
Jason Lacombe, CEO of Veratrak

How did you get involved with the WHO and the European Commission?

My work in Canada was focused on microsimulation modeling on the Canadian population as it related to improving costs and driving efficiency for the pharma industry in terms of the types of medicines patients receive. I noted that there was a lot of fragmentation and silos in the way that pharma organizations worked, particularly with different providers – and I found this very interesting to study.

I moved to the University of Oxford to take up a PhD scholarship. While there, I worked in a WHO collaborating center on population approaches for non-communicable disease prevention. I was very fortunate in that I had the opportunity to start influencing drugs supply chain policy at the global level early on in my career. I also had the opportunity to advise the European Commission in some policy changes in tackling chronic diseases.

What led to your interest in blockchain?

Through my professional background and studies, I became increasingly interested in the intersection between emerging technologies and the supply chain for the pharma industry. While at Oxford, I was one of the founding members of the Blockchain Society. Through the society and collaboration with some of the pioneers in this emerging field, it was clear that blockchain or distributor ledger technology could significantly drive efficiencies across the pharma supply chain whilst also ensuring trust, quality of data integrity and more data visibility.

And that interest led to Veratrak…

Correct. Veratrak is a company that grew out of the University of Oxford ecosystem – and a lot of our first employees came from that ecosystem. The university grew up a lot while I was there in terms of innovation and entrepreneurship. They created an Innovation Centre for Entrepreneurship called the Oxford Foundry – and Veratrak was one of the first companies to be incubated in their startup program. As you can imagine, there are a lot of challenges and growing pains when it comes to setting up a company, but we were fortunate in that Oxford provided mentorship and assistance with things like legal, accounting, business building, hiring, and all of the other elements you don't really think about when you're focused on building software!

At Veratrak, our aim is to bridge the gap between how pharma manufacturers share data and documentation with their contract server providers. From my past experiences, I learned that the majority of GxP documentation is being exchanged outside a company's four walls via email, which creates a number of bottlenecks and cybersecurity risks as well as data integrity risks. To alleviate these risks of insecure and inefficient document exchange we developed a web-based platform that allows for seamless review, exchange and electronic sign-off on GxP documentation through stepwise workflows between the pharma company and the service provider. All of this document exchange and communication/collaboration between businesses is captured in an audit log using our blockchain technology. There's been a lot of hype around blockchain. Some people think it can revolutionize supply chains – and it can – but blockchain only has the right effect when you also put in place the right stepping stones.

How has COVID-19 affected the uptake of digital technologies in pharma?

The pharma industry is adopting digital technology at a faster rate now than it has done in the past. With so many employees working remotely, companies have been forced to adapt. But I think companies need to be more proactive. Right now, companies are reactive – adopting digital technology only when they absolutely need specific solutions. For example, because of the pandemic, most companies halted or postponed auditing their suppliers and customers. It was only recently that the FDA, EMA, and MHRA published guidance on best practices for conducting assessments remotely, and they recommend using software to help the pre-planning, execution, and post-audit reporting. There are a lot of ways in which digital technology can add benefits and efficiencies to a company. Now that the industry is becoming more comfortable with new technology, I hope it will be more receptive to new solutions post-pandemic.

How did it feel to be named on the Forbes 30 Under 30 List?

Being named on the list was quite a surprise but it was also quite nice to receive an award! And it has opened up a number of networking opportunities for me, which have been great for the business as well.

At the same time, it's also quite humbling and makes you reassess where you've come from and how you've got to where you are now. Even though I've gotten some individual accolades along the way, they are still team accolades in my opinion. Our employees are the best! And we wouldn't be where we are without them.

There are some other achievements that I am really proud of. The UK has its All-Party Parliamentary Group on Blockchain, which advises the government on blockchain technology across multiple industries, and I was named as a blockchain influencer in Parliament.

Do you have any other goals in mind for your career?

I'm really interested in the next-generation therapies coming out, such as cell and gene therapies; in this space, there are a lot of important challenges around how the industry ensures that patients ultimately receive their treatment on time and to the highest quality. At the same time, there are concerns about affordability. In a perfect world, medicine as a whole should be accessible and affordable for all. These are challenges I'd love to get involved with.

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