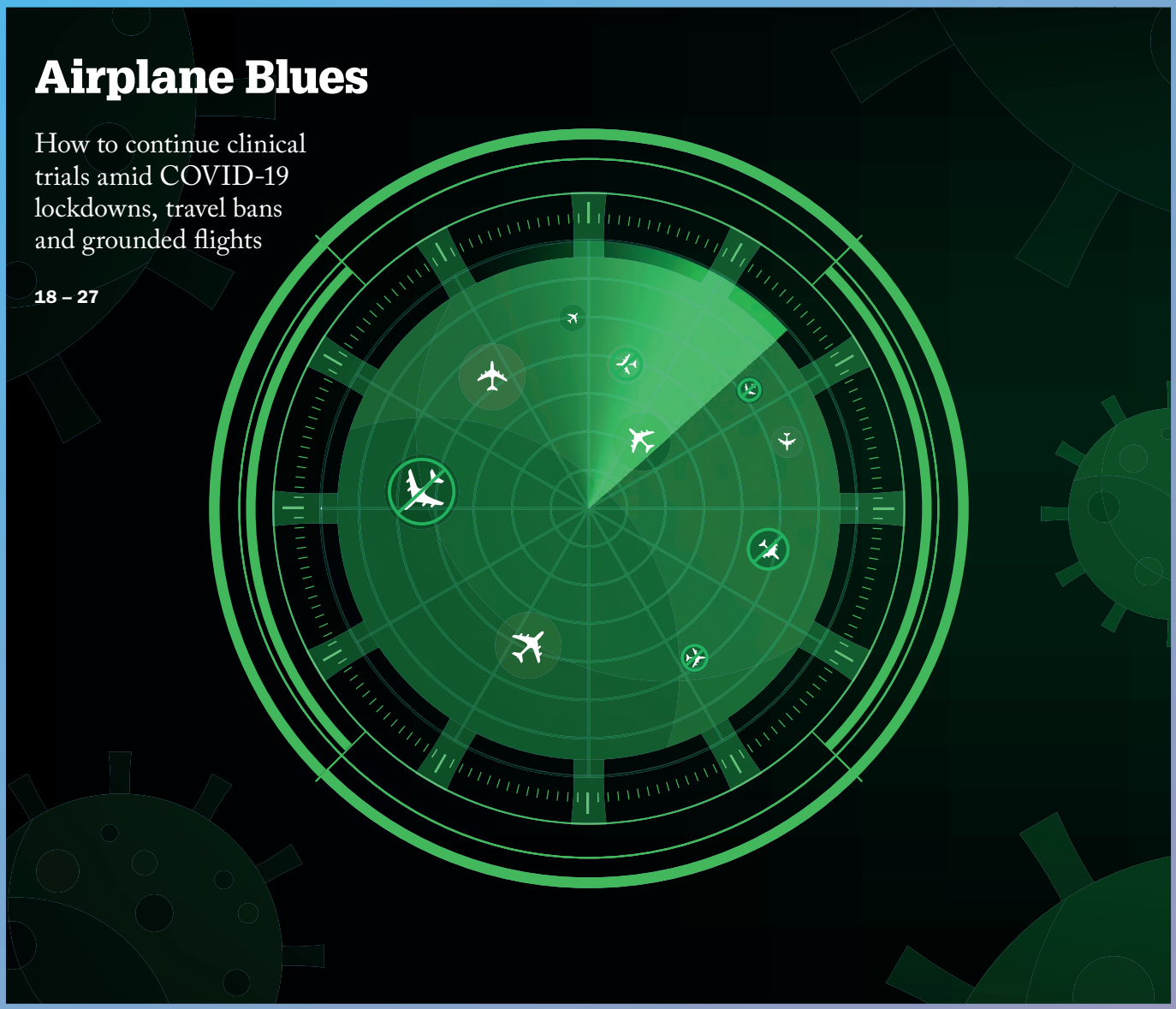
JUNE 2020 # 66

the Medicine Maker™



Airplane Blues

How to continue clinical trials amid COVID-19 lockdowns, travel bans and grounded flights

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Necessity Really Is the Mother of Invention

In under two months, the ISCT managed to pull together a gamified virtual conference platform, allowing attendees to "walk up" and chat with exhibitors

Last month, I attended my first virtual conference: the International Society for Cell and Gene Therapy's annual meeting, which was supposed to take place in Paris. I must admit that I was skeptical. Like many of the "virtual" activities that have popped up in recent weeks, such as gallery and museum tours, I figured sitting at home (with yet more screen time) could never compare with the experience of actually walking the halls of the Louvre – or indeed an exhibition center. But I was pleasantly surprised (about the latter).

The ISCT meeting had a series of presentations and panel discussions conducted via video chat. A particular highlight for me was the showcase on COVID-19, notably Diane Kadidlo and Heidi Elmoazzen's presentations on global supply chain issues – the topic of our cover feature on page 18. According to Kadidlo, the University of Minnesota's cell therapy trials for cancer were put on hold and could only be approved on a case-by-case basis. And as Director of stem cells at Canadian Blood Services, Elmoazzen faced a number of challenges – cord blood collections ceasing, registry donors becoming unwilling to donate, issues transporting stem cells across borders – echoing the experience of our feature contributors.

But presentations are only one of the reasons we attend conferences – and arguably the easiest to replicate virtually. Creating a means of networking is the tricky part but, in just two months, the ISCT managed to put together a virtual platform that allowed us to "walk up" and chat with exhibitors – in over 30 languages via a translator function. And the whole thing was gamified, with points and prizes for interacting.

I wouldn't say the experience was quite on a par with attending in person (it's hard to replicate that one important chance encounter, an introduction from a colleague, or a night on the town...), but it was certainly valuable – especially for those who wouldn't have been able to travel to Paris anyway.

Just as it seems the trend towards direct-to-patient clinical trials is unlikely to completely reverse when normality returns, I can't see virtual conferences going away either.

James Strachan
Deputy Editor

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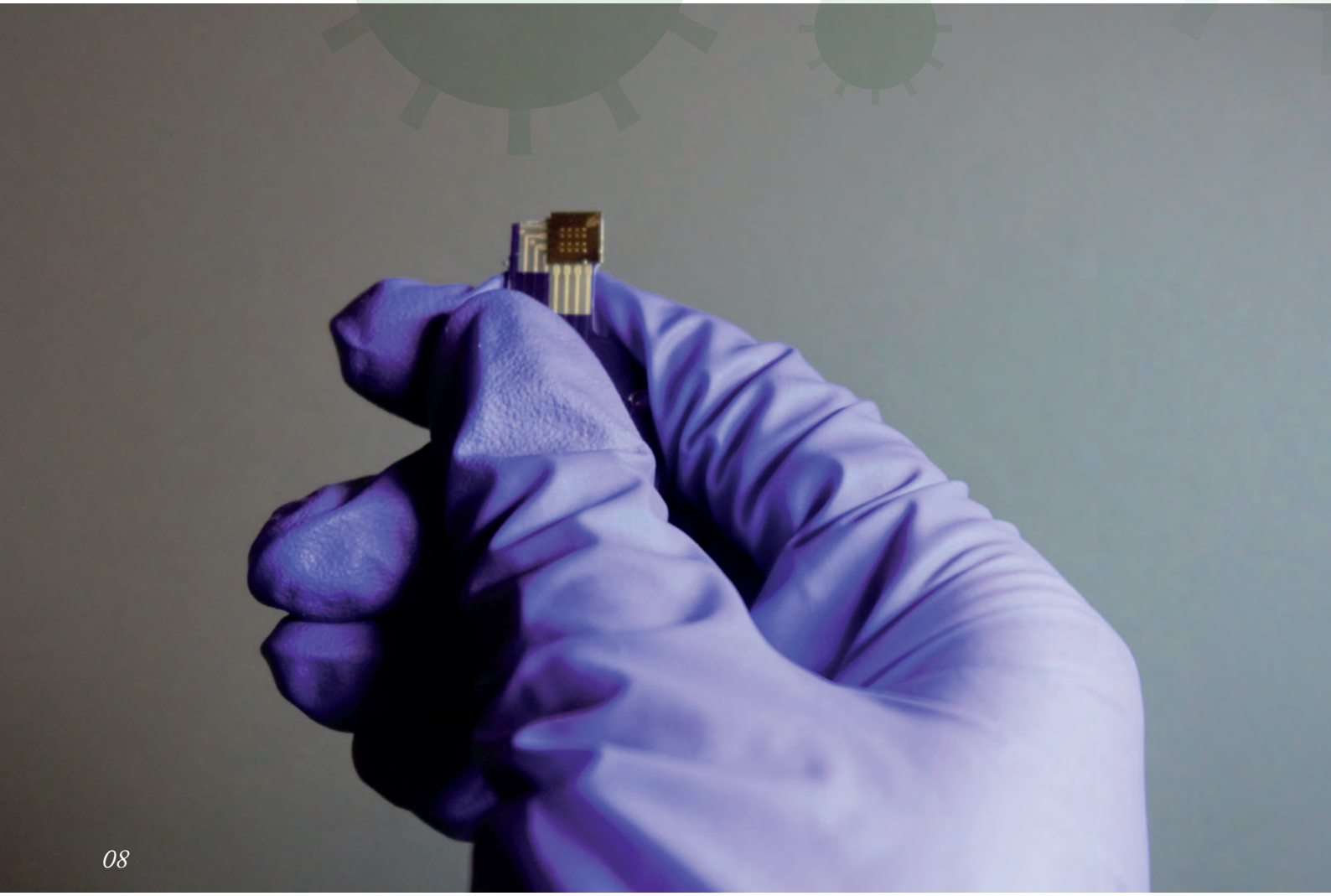

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Change of address info@themedicinemaker.com
Hayley Atiz, The Medicine Maker, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
+44 (0) 1565 745 200 | sales@texerepublishing.com

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Upfront

Research
Trends
Innovation

Calming the Cytokine Storm

How salivary compounds produced by blood-sucking parasites could be a good thing...

Evasins – proteins released by ticks to switch off inflammatory cytokines when they are sucking blood – are being investigated as a potential therapeutic avenue for COVID-19.

Biotech company ILC Therapeutics actually began collaborating with Shoumo Bhattacharya and his team at the University of Oxford, UK, in 2019, but the project took on a new direction – and increasing urgency – when the group realized how serious the COVID-19 pandemic was becoming. "My colleague, Alan Walker [CEO of ILC Therapeutics] likes to say that we didn't come looking for COVID-19, it came looking for us," says Bill Stimson, Chief Scientific Officer at ILC Therapeutics.

"Cytokine storms, which are associated with many respiratory diseases, are triggered by viral infection and cause the release of many inflammation-driving chemokines in the lungs," says Stimson. The overproduction of these pro-inflammatory cytokines results in lung damage and is associated with the onset of acute respiratory distress syndrome (ARDS) – a major cause of COVID-19-related death.

"We have combined three types of Evasins, and our early studies show that they can bind to the chemokines released during the cytokine storm, preventing the inflammatory response of all these chemical messengers, and thus treating ARDS," says Stimson. One potential advantage of the approach is that Evasins target the host's backfiring immune response rather than the viral trigger; "If Evasins do prove to be suitable treatments for COVID-19, it is highly likely they will be beneficial in other viruses in the future that cause ARDS too."

INFOGRAPHIC

ADCs on the Rise

After the successes of 2019, will the antibody-drug conjugate sector continue to progress?

3 FDA approvals in 2019

Enhertu
Polivy
Padcev

BUSINESS IN BRIEF

Scaling up manufacturing, new pricing models, and sold shares… What's new in business?

- GSK has signed an eight-year deal with Samsung Biologics to scale-up its biologics production. The deal, worth an estimated $231 million, commits the South Korean contract manufacturing company to provide additional capacity to GSK for the manufacture and supply of drug products, including blockbuster lupus medication Benlysta. The partners acknowledge that scale-up of Samsung's facilities will need to be flexible to meet GSK's future needs.
- President Trump has announced that insulin for senior citizens with Medicare Part D insurance will be capped at $35 per vial. In his remarks on the issue, he criticized Obamacare, claiming that older adults with diabetes would often pay as much as $1500 per year for the much-needed medicine. The new Senior Savings Model for insulin was launched as a result of government consultation with pharma, insurers, and other stakeholders, and, according to the President, will "save impacted Americans a minimum of $446" each year.

- Sanofi revealed its intention to sell some of its 23.2 million shares in Regeneron. The companies have a well-established partnership that has resulted in the development of five medicines. The move, worth an approximate $13 billion, is part of a restructuring plan announced last year, and will allow Sanofi to execute its "strategy for innovation and growth." Both companies claim that their commitment to the partnership remains as strong as ever.

Preventing the Viral Trigger Pull

A new vaccine protects against type 1 diabetes in animal models

Type 1 diabetes is caused when the body's own immune system attacks and destroys insulin-producing beta cells in the pancreas. But what triggers this autoimmune response in the first place? Although it's likely that both genetic and environmental factors are involved, infection by Coxsackievirus B (CVB) enteroviruses is believed to be an important trigger.

Now, researchers have collaborated on a vaccine to protect against the six known strains of CVB (1). They tested the vaccine in both mouse and rhesus monkey models with excellent safety results and evidence of a strong antibody response against CVB. What's more, the vaccine prevented CVB-induced diabetes in mice with a genetic predisposition to the disease.

The next step is to initiate a human clinical trial and – if the vaccine proves safe – administer the vaccine to children with a genetic predisposition to type 1 diabetes to see whether it lowers the number who go on to develop the disease.

Reference

1. *VM Stone et al., "A hexavalent Coxsackievirus B vaccine is highly immunogenic and has a strong protective capacity in mice and nonhuman primates," Sci Adv, 6, eaaz2433 (2020).*

Eight Drugs Have Reached Phase 2 or 3 Trials

Future forecast

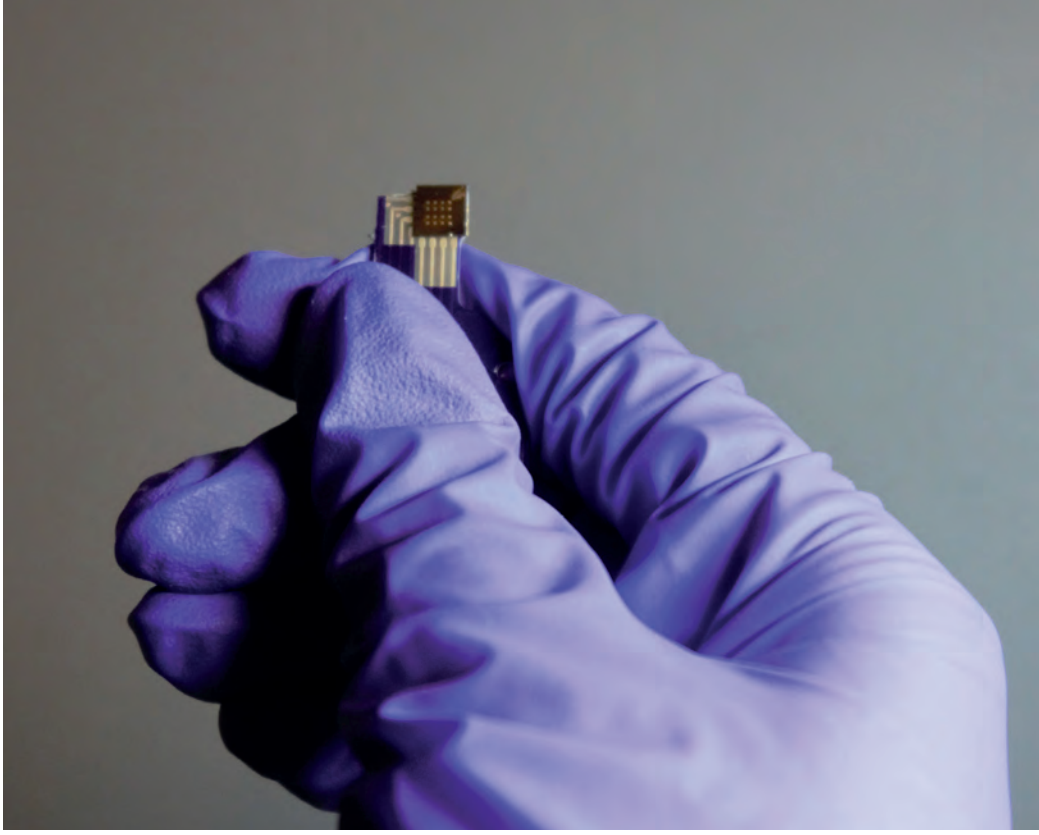
Market size expected to reach

$9.93 billion by 2025

Sector has projected CAGR of

25.9% by 2025

Sources:
Grand View Research, "Antibody Drug Conjugates Market Size, Industry Growth Report, 2025", (2020). Beacon Targeted Therapies, "ADC Landscape: Review H1 2020", (2020). Reuters, "Drug developers take fresh aim at 'guided-missile' cancer drugs", (2020).



Branching Out

Energy-saving hardware could reduce the carbon footprint of AI-driven drug development

From aiding in the development of new drugs to enhancing the efficiency of manufacturing practices, AI is changing the way pharma works. But AI's impact on the environment has not yet been fully addressed – it's estimated that the energy consumed by computers when training an AI platform results in a carbon footprint that is five times greater than the entire lifespan of a car (1).

Now, researchers at Purdue University have developed a hardware device made of quantum material that could inject extra intelligence, reducing reliance on energy-draining software platforms (2). According to Shriram Ramanathan, a professor at the university, the hardware's design was inspired by the way the human brain stores and recalls information.

"Human beings store elementary information in a hierarchical way in their brains. And this allows us to categorize complex information so that it can be recalled and reconstructed when needed," he explains. "Similarly our device relies on neural trees whose 'branches' hold information about different categories of data."

In brief, the researchers introduced a proton to neodymium nickel oxide – a quantum material – and applied an electric pulse to the proton, causing it to move through the material and create areas of electrical resistance that behave like data storage sites.

Ramanathan believes the device could eventually be of benefit to pharma, which will increasingly rely on AI. "Companies often deal with large and complex datasets. Using our hardware, patient, drug, and disease information could be sorted into various categories allowing patterns to be easily identified across datasets," he says. Understanding such patterns could help researchers extract the most meaningful information from their records and develop drugs best suited to specific disease areas.

References

1. *MIT, "Reducing the carbon footprint of artificial intelligence", (2020). Available at: https://bit.ly/2zNMz2k*
2. *H Zhang et al., "Perovskite neural trees", Nature Communications, 11, 2245 (2020).*

Blueprint for Supply Chain Success

A policy framework aims to boost the manufacture of critical drugs in the US

The Association of Accessible Medicines (AAM) has released the report "A Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain" that offers advice on how the Federal Government could create capacity to manufacture critical medicines in the USA and allied countries (1).

Suggestions include the government's direct engagement with pharma companies to identify opportunities for investment; the FDA's improved engagement with manufacturers, as well as the agency developing more efficient regulatory processes for the review and approval of pharmaceutical products; and the scale-up of the US Department of Health and Human Services to expand the nation's supply chain.

Reference

1. *AAM, "A Blueprint for Enhancing the Security of the US Pharmaceutical Supply Chain", (2020). Available at: https://bit.ly/3d5Rj1t*

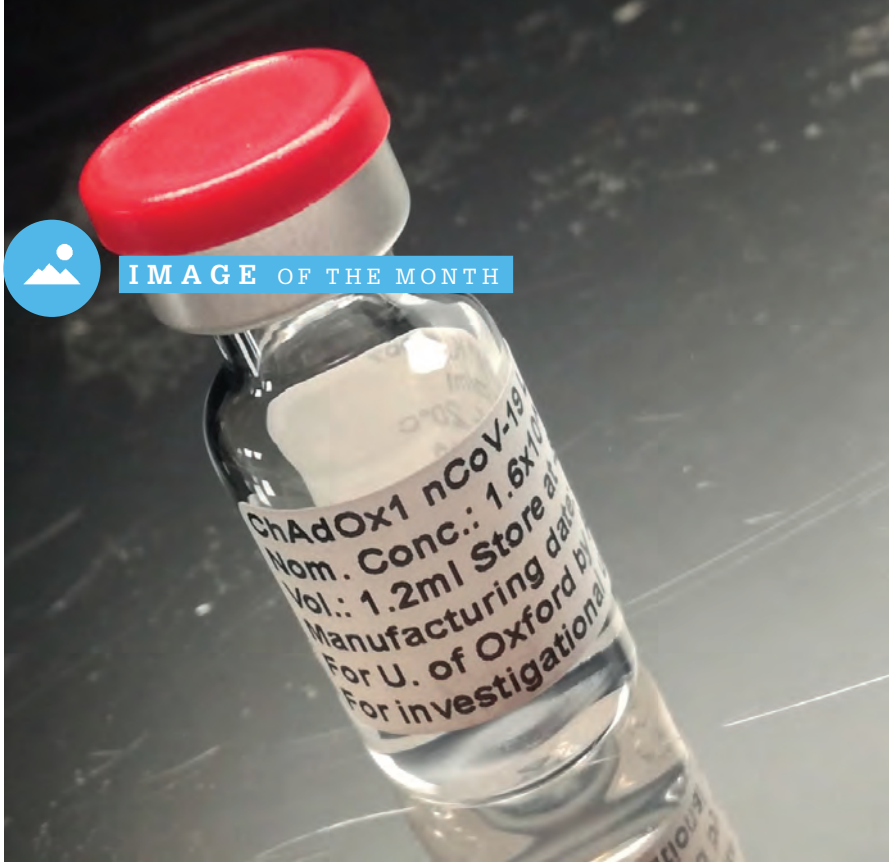


IMAGE OF THE MONTH

Trial Ready

Academics at the Jenner Institute at the University of Oxford, UK, have received 4000 doses of AZD1222 (formerly known as ChAdOx1 nCoV-19) for use in a Phase 2/3 trial from Italian contract manufacturer Advent, part of the IRBM Group.

Find out more at https://bit.ly/2AhceQD

Credit: Advent, IRBM

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

QUOTE of the month

"If a branded firm pays a generic firm to stay out of the market and they accept the deal, what stops the next generic drug maker knocking on the branded firm's door, looking for a similar payoff? And if they do, how much do they have to pay and how can the original deal be profitable?"

Farasat Bokhari, an Associate Professor at the University of East Anglia, on pay-for-delay deals. Read more at https://bit.ly/2TLXPmC

The COVID-19 Curator

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

The COVID-19 Curator – a weekly newsletter – curates the top scientific news from the pandemic and delivers it straight to your inbox every Friday. Sign up at: www.texerenewsletters.com/covid19newsletter

Using the Curator as a springboard, in this new section of The Medicine Maker magazine, we roundup the latest and greatest research studies and company announcements made over the course of the last month (May 8 to June 5).

Industry news

EMA. The EMA has raised concerns about the number of independent COVID-19 trials with few participants – and calls for resources to be pooled into larger multi-arm trials. Authors from the agency have written an article setting out "concrete actions" that stakeholders involved with COVID-19 clinical trials should take to generate the type of conclusive evidence needed to enable rapid development and approval of potential treatments and vaccines. *H-G Eichler et al., "Clinical trials for Covid-19: can we better use the short window of opportunity?" Clinical Pharmacology & Therapeutics (2020).*

Gilead. The FDA has granted emergency authorization to Gilead's remdesivir to treat COVID-19 patients – despite it not being approved yet for any indication. Remdesivir inhibits viral RNA synthesis, with Gilead's recent Phase III trial showing that five-day treatment of remdesivir results in greater clinical improvements compared with standard care alone. Various other studies are also emerging to highlight the potential of remdesivir. EMA has commenced a "rolling review" of data in Europe.

Moderna. Reporting positive interim Phase I data for its investigational mRNA vaccine (mRNA-1273) against COVID-19, the company aims to start a Phase III study in July. The study was led by the US National Institute of Allergy and Infectious Diseases (NIAID).

Eli Lilly. A Phase I study has commenced for LY-CoV555 – a neutralizing IgG1 monoclonal antibody designed to block COVID-19 viral attachment and entry into human cells. The antibody was developed in collaboration with AbCellera. AbCellera and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases identified the antibody in a blood sample taken from a patient who recovered from the virus.

AstraZeneca. AstraZeneca and the UK's University of Oxford are collaborating on an adenovirus-based vaccine (AZD1222) that entered trials in April. AstraZeneca has already signed a clinical and commercial supply agreement with Oxford Biomedica and committed to deliver millions of doses, including 100 million doses for Britain and 300 million for the US.

Sinovac Biotech. Preclinical results for CoronaVac show it is safe and efficacious in rhesus macaques. The company is also building a vaccine facility capable of manufacturing up to 100 million doses of the vaccine annually.

Catalent. Catalent will develop a powder-in-capsule formulation of Ennaid's ENU200, which is a repurposed oral antiviral drug. Ennaid selected ENU200 after an in silico bioinformatic search identified that the chemical compounds may block the spike-S glycoprotein and the key coronavirus enzyme, Mpro.

Early research

Of mice and mAbs. A fully human monoclonal antibody shows success in cell culture by targeting a communal epitope on SARS-CoV-2 that could prevent the virus from infecting human cells. The mAb was identified by researchers from Utrecht University, the Erasmus Medical Center, and Harbour BioMed, using Harbour BioMed's H2L2 transgenic mouse technology. The researchers have previously done work on antibodies targeting SARS-CoV.
C Wang et al., "A human monoclonal antibody blocking SARS-CoV-2 infection," 11 (2020).

A little help from llamas. An antibody present in llamas and other camelids is found to bind to the SARS-CoV-2 spike protein and interfere with receptor binding. Researchers from the University of Texas at Austin, the National Institutes of Health, and Ghent University linked two copies of an antibody produced by llamas. They hope to develop a treatment that could help soon after a person is infected.
D Wrapp et al., "Structural Basis for Potent Neutralization of Betacoronaviruses by Single-Domain Camelid Antibodies," Cell, 181, 1004–1015 (2020).

Blast from the past. Antibody first identified from recovered SARS patient in 2003 – S309 – is shown to neutralize SARS-CoV-2 and SARS-CoV pseudoviruses. The senior authors of the paper are David Veesler (assistant professor of biochemistry at the University of Washington School of Medicine) and Davide Corti Humabs (Chief Scientific Officer at Humabs Biomed SA, a subsidiary of Vir Biotechnology). Veesler's lab has been studying infectious diseases, including coronaviruses, for a number of years. The antibody has been fast tracked for development at VIR Biotechnology.
D Pinto et al., "Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody," Nature (2020).

Other avenues

Quitting chloroquine. A recent study and a systematic review have shown no benefit from the use of chloroquine or hydroxychloroquine as COVID-19 treatment or prophylaxis. Additionally, the WHO has halted trials of the drugs due to the risk of harm.
MR Mehra et al., "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis," The Lancet (2020); AV Hernandez et al., "Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review," Annals of Internal Medicine (2020).

Shortened shedding. Interferon-α2b has been shown to shorten duration of viral shedding by around seven days and to reduce levels of inflammatory proteins in COVID-19 patients.
Q Zhou et al., "Interferon-a2b Treatment for COVID-19," Frontiers in Immunology (2020).

Vitamin D consensus. High doses of vitamin D are not effective in preventing or treating COVID-19, but some evidence suggests low vitamin D levels are associated with other acute respiratory tract infections.
SA Lanham-New et al., "Vitamin D and SARS-CoV-2 virus/COVID-19 disease," BMJ Nutrition, Prevention & Health (2020).

Moonshot medicines. Computational screening has identified two approved anti-inflammatory drugs that inhibit replication of COVID-19 virus; the work has been validated in in vitro studies by COVID Moonshot.
A Gimeno et al., "Prediction of Novel Inhibitors of the Main Protease (M-pro) of SARS-CoV-2 through Consensus Docking and Drug Reposition," International Journal of Molecular Sciences, 20, 3793 (2020).

Taking stock. Researchers have created a database that tracks and categorizes off-label drug use worldwide for COVID-19. The database should help identify treatments for further clinical study – for both COVID-19 and other diseases.
DC Fajgenbaum et al., "Treatments Administered to the First 9152 Reported Cases of COVID-19: A Systematic Review," Infectious Diseases and Therapy (2020).

Invisible enemy. Aerosols exhaled by asymptomatic individuals may be responsible for a large proportion of COVID-19 spread, highlighting the importance of masks and social distancing.
KA Prather, CC Wang, RT Schooley, "Reducing transmission of SARS-CoV-2," Science (2020).

Understanding COVID-19

Starting early. Testing on a sample collected from a French ICU patient in December 2019 showed that SARS-CoV-2 was present in the country a month earlier than suspected, suggesting that pandemic outcome models may not be accurate.
A Deslandes et al., "SARS-CoV-2 was already spreading in France in late December 2019," International Journal of Antimicrobial Agents (2020).

Silent majority? A study of a group of isolated cruise ship passengers revealed that eight in 10 people testing positive exhibited no symptoms – a result with worrying implications for contact tracing and self-isolation approaches to infection control.
AJ Ing, C Cocks, JP Green, "COVID-19: in the footsteps of Ernest Shackleton," Thorax (2020).

Infection and immunity. A review summarizes what we know so far about coronavirus diseases, such as SARS and MERS, our current understanding of SARS-CoV-2, and where research is most urgently needed to address the current pandemic.
P Kellam, W Barclay, "The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection," Journal of General Virology (2020).

Double whammy. People carrying two faulty copies of the APOE gene (which is linked to increased risk of Alzheimer's and heart disease) face double the risk of severe COVID-19 – irrespective of pre-existing dementia or cardiovascular disease.
C-L Kuo et al., "APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort," The Journals of Gerontology: Series A (2020).

Mutational analysis. Human deaminase enzymes, which edit SARS-CoV-2 RNA, may play a role in both the evolution of the virus and the spread of infection.
S Di Giorgio et al., "Evidence for host-dependent RNA editing in the transcriptome of SARS-CoV-2," Science (2020).

Weakened defense. MicroRNAs that attack viruses diminish with old age and chronic health problems, which helps explain why those populations are especially vulnerable to COVID-19.
F Sadanand et al, "COVID-19 Virulence in Aged Patients Might Be Impacted by the Host Cellular MicroRNAs Abundance/Profile," Aging and Disease, 11, 509-522 (2020).

The Pandemic Diaries

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

Simon Tyler, Chief Operating Officer at CatSci

The pharma industry is very hands-on, so many people have been unable to work from home and must continue to go into the lab or manufacturing facility to carry out vital scientific research and development activities. Very early on, the industry had to get to grips with the types of issues now starting to be more widely considered across other industries as lockdown restrictions begin to ease in various countries. How do you maintain the same standards of operation within a laboratory environment in a safe manner? I've been humbled to observe, amongst the obvious heroism of front-line workers, the motivation of dedicated scientists who are continuing to undertake pharmaceutical R&D in the knowledge that it will one day contribute to the better treatment of, or help to defeat, the world's evolving healthcare challenges. Scientists have also had to work against a backdrop of huge uncertainty shaped largely by two factors: government action (would there be mandated closure of laboratories?) and customer decisions (will they proceed with projects or postpone?).

With regards to the former, scientific advice has (fortunately) been at the forefront of this decision-making process and many labs, including ourselves, have been able to carry on with important projects focusing on the development of small molecule therapeutics, provided, of course, that appropriate health and safety measures are implemented. With respect to the latter, we have found that there is a clear distinction in the market between two schools of thought: those companies that wish to continue as near as possible, undeterred, and those that have applied the brakes to see what happens (fortuitously, our customers have been predominantly in the first category). There is no right or wrong approach, and all pharma companies must figure out what is the best course for their individual business. However, these are all real issues that both sponsors and service providers are facing with regards to progressing pharmaceutical projects in the current environment.

At the time of writing, we are some three months into the COVID-19 crisis and the mixture of feelings and emotions is starting to settle down into the working practices of the "new normal." From an industry-wide perspective, there will no doubt be repercussions, but "business as usual" will continue to remain undefined for a while yet. We should all use this opportunity to focus on where we are truly adding value. We are certainly reflecting on that topic at CatSci. Perhaps COVID-19 will revolutionize our industry, ushering in a new era of doing business for good across the globe. Now that really would be something positive.

Nick Shackley, Global Vice President Innovator Products and Solutions, at Johnson Matthey

Our business has remained fully operational throughout the COVID crisis. Still, we have had to rethink the way we run our business to allow for social distancing, enhanced hygiene and increased security screening practices. It's also the right thing for businesses to get involved on the community level too, such as contributing to local measures to help minimize the spread of the pandemic and help out where we can.

Looking at the pharma industry as a whole, supply chain vulnerabilities have been exposed as demand surges. Globally, there is a shortage of medicines used in intensive care units. An example specific to our business is narcotic analgesics, given to patients on ventilators. We are seeing the demand spike and challenges arising from cross-border complexities and long supply chain lead-times, which are very

stressed. These vulnerabilities will need to be addressed in the future and will certainly raise questions around how the industry can be better prepared for future crises.

But there are also some very positive things that I'm seeing in the industry too. The broader life science and pharma industries have stepped up to develop solutions that can detect, treat and vaccinate against COVID-19. The pace at which the industry is introducing solutions, such as diagnostic tests, is largely enabled by purpose-led industry and good regulatory agency collaboration to reduce risk while enabling speed. We are excited to be partnered on several initiatives supporting development and manufacturing solutions related to COVID-19. As we learn to run faster, it will be interesting to see if we can more routinely apply these learnings to bring solutions to market quicker without the catalyst of a pandemic.

Chris Lowe, Head of Research Operations at Horizon Discovery

Our tools and services are used by those conducting COVID-19 research, so it has been vital that we continue to operate during these challenging and uncertain times! We've had to closely monitor our inventories and manufacturing capacity on a daily basis. And we've had to work closely with supply chain partners to maintain shipments around the globe. We've also looked at how else we can contribute to the crisis; for example, by introducing new licensing terms to facilitate rapid access to key platforms that can be used to develop or produce therapeutic proteins, diagnostic assay components and vaccines. And there are other things we can do outside of normal business. There has been a huge push from the scientific community to support medical workers on the front line. Our Cambridge site in the UK has responded to a local call for PPE by donating nitrile gloves to Addenbrooke's Hospital, and diverted fruit and milk to staff there too. Admittedly, it is only a small contribution, but if all businesses do something meaningful, the contributions add up.

Throughout all of this, the health and safety of our employees has been and continues to be a priority. We've adapted to the situation by ensuring that there is only a minimum number of people on site at any given time. Most of our team are working from home and only come in to perform essential scientific lab work – with social distancing in place. We've also set up COVID-19 response teams at both our UK and US sites and will continue to review government advice and business practices.

Andrew Bulpin, Head of Process Solutions at the Life Science business of Merck

The pandemic is putting the spotlight on the immense need for problem solving. Those working on solutions to this global challenge must balance priorities to protect public health, operate safely despite disruption, and plan for recovery. During the COVID-19 response effort, life science companies and others are focusing on the health and safety of employees while ensuring that their technologies, products and services reach the customers around the world who rely on them. Meeting existing needs is only one part of the equation — anticipating additional needs is another. Alongside the push for vaccines and treatments, the scientists and researchers at work in this response effort need the learnings, resources and technology to combat such a virus. Innovation comes from collaboration.

We are monitoring the situation closely and have established protocols and guidelines to minimize the impact, whenever possible, to our employees, to our sites, and to our supply. Employees who can work from home are doing so, and for those employees who continue to develop, manufacture, package, and ship products or provide services at our sites, we have implemented workplace distancing precautions and staggered shifts. For customers, we've set up a dedicated COVID-19 webpage to help ensure availability keeps up with demand.

One positive is that collaboration to accelerate our response has already begun in earnest. We have convened our Innovation Board – R&D leaders, biologists, chemists, data scientists, and engineers from across the organization – to suggest and discuss ideas to resolve the outbreak. The group is working to assemble an open session with scientific experts to share knowledge and build scenarios dedicated to fighting the virus. With collaboration such as this, the global scientific community can potentially find a treatment.

Though it will certainly look different, we are optimistic for the future. The silver lining in this pandemic is that life science companies are moving with unprecedented velocity to support the development of tests, treatments and vaccines, in collaboration with suppliers. There are so many opportunities to work together, to speed up processes, and to reduce unnecessary systems to name just a few areas ripe for improvement. Most importantly, organizations will likely have more of a willingness to collaborate in the future for the greater good across the different fields in which they operate.

The Digital Review

It's time to address the bottlenecks that lie in quality assurance review and release – and digital systems can help us

By Andrew Anderson, Vice President Innovation and Informatics Strategy at ACD/Labs

As the COVID-19 pandemic grips the world with fear and uncertainty, scientists are working long hours to develop novel testing, antiviral medicines, and vaccine technologies. And every day, incremental progress is being reported. However, there are some fundamental challenges being faced by pharmaceutical manufacturers; bottlenecks that have affected development for too long. In my view, it is time to address these challenges with tools that are already at our disposal.

Consider clinical trial material quality assurance. To ensure that clinical trial material is of sufficient quality, traditional release review and approval operations include the preparation of quality summaries. These summaries exist as human-readable documents (which is to say, document files presented to scientists on their computer screens and visually interpreted). Consequently, such summaries must be thoroughly examined and interpreted by expert quality assurance staff. The most fundamental decision quality assurance staff must make is, "Does this material conform to the quality specifications established for its intended use?" A comparative assessment is made, and quality test results are compared with acceptance criteria across all critical quality parameters. Moreover, QA staff must also confirm that the approved processes for generating materials were adhered to during manufacturing and downstream testing. The consequence of either a misinterpretation of a quality summary or an overlooked discrepancy is significant; releasing product batches that do not conform to quality specifications can have a significant impact on patient safety.

Digital systems (for example, LIMS, ELN, and LES) are used to capture all of the pertinent data used to prepare human readable reports to support the QA review and approval release step – and I believe these digital systems can be leveraged to provide better QA support overall. The documents used in materials release – upon generation, submission, and QA – are effectively decoupled from the systems used to generate them (electronic signature and document-traceability controls notwithstanding). Should these documents raise questions that require supplemental information to be prepared, additional human documentation efforts are conducted. The "forensic" investigations and further document preparation can create significant delays in batch release.

We can make the QA review and release step more efficient by reducing reliance on human-prepared document-driven decision making. First, by structuring specification and test data into machine-readable formats, software could then help augment QA decision making and approval. An example case is to prepare standardized, formatted chromatographic peak information from impurity profile tests. These machine-readable datasets can be presented to various business intelligence applications, which could programmatically compare peak information (for example, area percent values), and confirm whether these results conform to quality specifications – thus augmenting QA staff review oversight.

In addition, by storing and managing structured datasets (impurity profile chromatographic data, identity-confirming spectral data, material quality-confirming image data, and so on) in data management systems, the effort to prepare "portable" reports (document files that do not require specialization software applications) is greatly reduced; QA staff can simply perform queries themselves within specialized decision support applications in lieu of requiring colleagues to prepare and submit reports. The software also reduces the effort when the need to conduct forensic examinations arises. For example, when specific batch data does not conform to specification, any related batch information (for example, batch information for precursor materials) can be accessed – thus allowing for root cause assessment of non-conformance.

In addition to internal QA review innovation, machine-readable structured datasets could also accelerate external party review-and-approval steps – such as those to healthcare authorities. Machine-readable quality summaries could be submitted and reviewed by the recipients' own decision support software applications, greatly reducing the amount of effort required by external staff. The result is a new review-and-approval paradigm where internal and external review steps can be executed within a "human review by exception" model; in other words, business intelligence software can perform automated assessments of submissions, leaving more challenging assessments to review staff. In this new world, "availability notifications" to third parties could serve as an initial contact event – as opposed to a document submission.

Though scientists on the frontline are working to develop new treatments and vaccines against COVID-19, we need to remember that all of us in the pharma industry still have a role to play. Purveyors of digital transformation and innovators within quality assurance can support frontline colleagues by considering structural changes to how QA review and release approval is undertaken. Ultimately, we can make the entire process more efficient to bring new therapies to patients faster – whether for COVID-19 or any other disease area.

The Human Touch

In the midst of a global pandemic, ensuring the safety of employees is paramount

By Sunil Jha, Group Chief Human Resources Officer at ACG, Mumbai, India

The COVID-19 pandemic has changed the way the world conducts business. As borders close and restrictions are imposed, activities that would have been considered normal only a few months ago (such as importing raw materials or forming a new partnership) are now fraught with difficulty. But beyond the disruption to business functions, another significant challenge for pharma is that its workforce must adjust to a new professional environment. Some are, understandably, afraid to come into work and face the risk of contracting or spreading the virus. With no clear end in sight to the ongoing crisis, it is essential that companies implement measures to protect the welfare of employees.

There are many ways companies can support their staff during these uncertain times, and one of the most obvious is to simply allow staff to work from home if possible. Many pharma companies have adopted advanced IT solutions that make it possible for employees to carry out their roles from the comfort of their homes and maintain relationships with customers and stakeholders.

But this option is not available to a large section of the workforce, including those working on the manufacturing floor. Key workers will still have to commute to and from work, and companies will have to implement precautionary measures that demonstrate they care about the health and safety of their employees.

At the plant level, companies should consider daily sanitization of their facilities, screening employees with temperature checks before they enter company premises, and ensuring easy access to sanitizers across factories and company vehicles. Businesses can also work with local authorities to resolve some of the issues faced by supply chain and logistics staff. As an extension of support to the local authorities in remote villages in India, we distributed groceries, masks, medical kits and ambulance services along with educating their people on dos and don'ts to remain safe. As a result, the local village authorities backed our efforts to contain the spread of the virus and supported us in our operations outside our factories located in Shirwal, Dahanu and Pithampur in India.

To maintain hygienic standards, ACG has also divided work shifts into 12 hours slots. This has helped us manage workers and ensure that social distancing is maintained. In addition, we've made special arrangements at our guest houses so that workers can stay close to or within factory premises wherever possible.

When putting their plans in place, it is important for companies to appeal to their employees on a human level. In countries where lockdowns are in effect, some businesses are providing their key workers with ready-packed groceries and sanitation kits to be taken home, as well as special vehicles for their commutes and additional insurance cover. Most importantly, senior leaders are actively engaging with their teams. Our leadership, for example, is closely interacting with the workforce, especially at the factory sites, to manage their concerns. Maintaining open lines of communication with employees is crucial to overcoming problems as they arise. This pandemic has proven that actions as simple as sharing the latest government updates with staff or offering online activities for them and their families to socialize or learn can make a big difference by reducing stress and demonstrating that the company cares about their employees' welfare.

"The focus is on adapting to the evolving situation, and protecting ourselves and our colleagues to the best of our ability."

The situation we have found ourselves in is unprecedented and, for now, the focus is on adapting to the evolving situation and protecting ourselves and our colleagues to the best of our ability. Once the worst of the crisis is behind us and the dust has settled, it will be time for pharmaceutical companies to examine the outcomes and create case analyses based on their learnings. This will help them have a ready-to-go plan B that supports employees and helps maintain business operations in the event that we are faced with another global crisis of this proportion.

Keeping the Show on the Road

The COVID-19 pandemic has put additional supply pressures on cold-chain products, such as those encapsulated by LNPs – but delays can be avoided with sufficient safety stocks, additional suppliers, and good communication

By Kim Rice

Lipid nanoparticles (LNPs) are a great way to encapsulate and protect fragile molecules, such as nucleic acids, from degradation and deliver them to specific tissues and cells (1). A large number of RNA- and DNA-based therapies have made use of LNPs – perhaps most notably, gene therapies. As a contract manufacturer, it's incredibly rewarding to work with a number of clients to help deliver their potentially life-changing advanced medicines. But there are also challenges when working with LNPs, especially when it comes to supply chain management.

Many of the raw materials that go into these therapies and the final drug products themselves are transported via cold chain – at temperatures as low as -80 °C. Even during the manufacturing process, there are restrictions on how long a product can be outside the confines of the cold storage unit. Temperature monitors are needed in each cold storage unit and each is fitted with alarms to indicate if a unit is opened or if there is an excursion. Back-up cold storage capacity is also available in the unlikely event that something goes wrong with the main units. And, as a CDMO, we must rely on our logistics providers to use validated shipping lanes, trucks, and temperature monitors to transport the drug product to its final destination. Clearly, finding a reliable logistics provider is important.

One thing that often catches developers and sponsors off guard is underestimating the lead times associated with LNP-encapsulated products. Many of these therapies have specialized raw materials that are only manufactured by a limited number of companies, with set slots in their production schedules. When we begin working with a client, they may request a supplier we haven't worked with before – and that means we need to dispatch our quality team to audit and approve the supplier. These factors can extend lead times considerably compared with a product that uses more commonly used or off-the-shelf components and approved suppliers. In our experience, the sooner a company starts working with us, the better we can avoid potential delays from the beginning.

Dealing with COVID-19

The COVID-19 pandemic has caused numerous issues in supply chains. Some of our clients, for example, have struggled to secure flights for their products, forcing them to validate new shipping lanes. With cold chain products, such changes are more challenging, because companies must ensure there are no temperature or safety issues. Specialized temperature-controlled containers for cold chain transport have also been in short supply. And there have been delays in customs – a problem that also applies to raw materials. For us, flexibility has been key, as well as continuous communication with clients and their shipping partners. This has enabled us to avoid delays in most cases and minimize delays where they have occurred.

However, the pandemic has certainly revealed the importance of building redundancy into the supply chain where possible, and fully understanding the supply chain of all items you require for manufacturing. And that doesn't just apply to critical, expensive items, but also everyday consumables. For example, the industry is seeing shortages of basic items, such as face masks, beard covers, and other attire required for aseptic processing – items that companies have historically paid little attention to as they were always so easily sourced. At Exelead, we are fortunate to have set our safety stocks at a level that has enabled us to continue "business as normal" during the pandemic with no delays to our customers. We're also looking at adding backup sources for certain items, but we are confident that we have enough of everything we need to get us through the year.

Another crucial aspect for us right now is keeping clients up to date. Communication was important before COVID-19, but now – given the high uncertainty in the world – customers need to know that they can count on their partners more than ever before. As well as general updates on a customer's product and project, we also send updates regarding the status of where we are in the plant, what we're working on, and the safety of employees. If anyone tests positive for the virus, we will also notify customers (though, thankfully, we have not had to do this yet). But a conversation shouldn't be one-way, so we've also ensured that the communication path is open for clients to ask questions or raise concerns.

The safety of our own employees is paramount – and we've put a lot of thought into how we can keep as many employees away from the manufacturing site as possible through homeworking, but without disrupting the manufacture of products. Right now, only those

employees essential to the manufacture and testing of the products are on site. We are careful to monitor and follow all CDC guidelines to protect employees and the manufacturing environment.

The long-term impact

Supply chain robustness has been an important topic since well before COVID-19, with some companies and contract manufacturers taking the topic more seriously than others. Broadly speaking, the industry has coped well with the epidemic; companies have moved quickly to mitigate risks and gaps in the supply chains. But some businesses will have found serious chinks in their armor after taking ease of sourcing for granted. I don't think this will be the case going forward. The fragile nature of the supply chain has been exposed – and the industry can learn from this. Setting appropriate safety stocks for certain items – without going overboard or hoarding – will soon become the norm…

If you are a developer with needs in the LNP space, we encourage you to come to us as early as possible. LNPs are complex products with complex supply chains, so even before you have a manufacturing date it is good practice to engage with partners so that the project can run smoothly. As soon as you know the key materials you are going to need, we can give you an estimate on when we will be ready. Coming to us early also gives us the time to really look at our supply chain, contact suppliers, and qualify them, if required. An LNP product will likely require cold chain and may rely on difficult-to-source raw materials. The sooner we start the conversation, the easier it will be to meet your projected timelines and keep things on track – despite COVID-19.

It is imperative that the pharma industry keep the supply chain moving for the medicines it produces. We regularly encapsulate late-stage cancer drugs, treatments for neurological diseases, and other groundbreaking therapies. One mishap during transit could not only be extremely expensive, but also potentially devastating for a patient in a clinical trial. In short, all of our employees appreciate the importance of the products they are working with; we treat every medicine we work with as if it is extremely precious – because it is. After all, it may be a patient's last option.

Kim Rice is Director of Supply Chain and Project Management at Exelead

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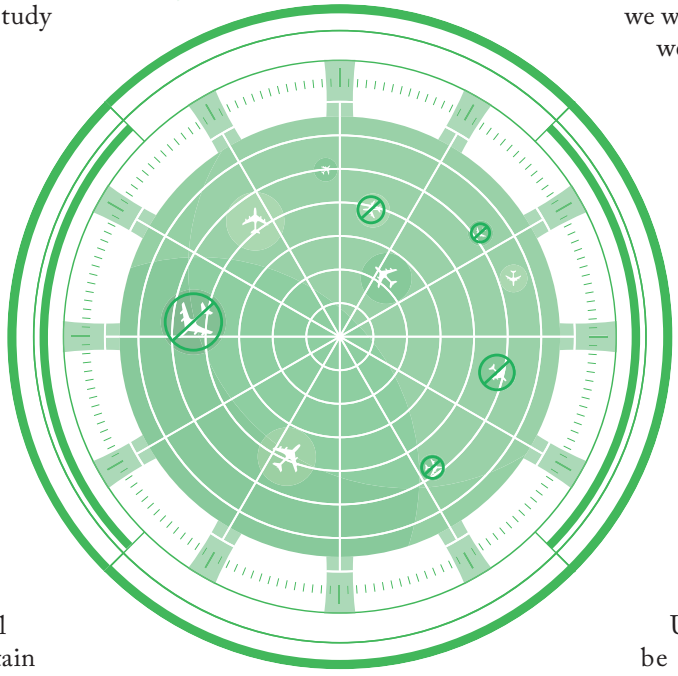
AIRPLANE BLUES

With planes grounded, strict travel bans, and stay at home orders enforced in many countries, how is the clinical trials industry recruiting patients, conducting studies, and distributing products in the thick of the COVID-19 pandemic?

By James Strachan

The COVID-19 pandemic has disrupted the lives of millions and shut down some industries. Pharma has felt the impact, but continues to work hard to ensure patients receive the medicines they need. When it comes to clinical trials, major disruptions will surely result in fewer therapies flowing through the trials pipeline – and fewer therapies mean more patient suffering. At the same time, we must not forget the patients participating in the trials who may benefit greatly – especially in fields such as oncology where an experimental treatment may be a patient's last option.

The pandemic poses serious questions to companies keen to continue their clinical trials. How can the industry ensure the supply of raw materials and delivery of clinical materials continues unabated? What can be done to get around the limitations on patient visits for scheduled study assessments and procedures?



TIME TO GET CREATIVE

According to Alex Guite, Vice President of Services and Alliances at World Courier, clinical trials are complex at the best of times. World Courier has handled the logistics for over 500 clinical trials in the last year, and Guite is responsible for products that fall out of the companies' immediate core – regular small molecules and biologics. "Certain products are sensitive to temperature, which means you need preconditioned packaging in the right place at the right time," he says. "But you might also need to deliver the product to the patient at a specific time for infusion in the case of cell therapies. When you're moving across international boundaries, we have to make sure our customers have the right documents to get through customs. The regulations are also constantly evolving and differ from country to country."

Unsurprisingly, the widespread lockdowns have compounded the challenges – in particular, as a result of the dramatic reduction in the number of commercial flights. "We've seen a massive contraction in air freight capacity," says Guite. "We use the bellies of these passenger planes but, for some airlines, over 80 percent have been grounded." Guite compares the situation to the 2010 volcanic events at Eyjafjallajökull in Iceland, which caused a similar contraction. "At that time, we had to look at alternative carriers to get products across the Atlantic – and we're doing the same now. But with COVID-19 it's like we've got volcanoes erupting across the globe simultaneously. Added to that is a public health emergency, like we saw with the Ebola outbreak in 2014 and 2016, which makes certain areas even more difficult to serve."

Fortunately, World Courier has not had to turn down a clinical shipment so far during the pandemic. How? "In a word: flexibility," Guite says. "We've always been carrier agnostic, which has helped us in our ability to pivot and use alternative carriers that we wouldn't typically use. However, we have found that there's a lot of extra work required to check flights and ensure they're running. This is especially so for the few remaining passenger flights we're using. Our teams have to be quick to respond and figure out a new route – potentially involving additional flight legs."

The company also had to respond quickly during the early stages of the outbreak when travel restrictions were being put in some places, but not others. "When the US announced that there would be restrictions on people and products coming from some European countries, excluding the UK, we quickly began routing things through London. When the UK was added to the list, we then looked at Canada. Of course, even Canada is now restricted," says Guite. "The situation has also been a real challenge for our teams on the ground. The amount of time it takes to process a shipment has increased; some teams are reporting that it is taking up to three times longer per shipment. This is a credit to our teams who have navigated these challenges and continue to connect life-saving therapies to patients."

According to Sascha Sonnenberg, Global Head of Business Development, Sharp Clinical Services, many companies have

been struggling to find accurate, up-to-date information on the extent of lockdowns and border shutdowns in different countries. "Some companies were receiving information from different sources and not all of it was accurate," Sonnenberg says. "For example, our contacts at one company believed that Serbia was completely shutting down its borders and that they wouldn't be able to import into the country. But in actual fact there were a number of freight flights available. Accurate information is crucial when it comes to making the right decisions on the ground."

Merck (Merck Group) has also had to respond quickly and creatively to reroute supplies, according to Chris Ross, Head of Life Science Integrated Supply Chain Operations. "A good example was when India went into lockdown. One of the critical raw materials that we use to manufacture a critical product in Switzerland for a customer comes from an Indian supplier. To provide this critical Active Pharmaceutical Ingredient to our customer, the Switzerland manufacturing site needed a shipment from the India supplier as soon as possible. We had to involve the Swiss and Indian embassies, government officials, compliance and supply chain leaders, as well as our site leaders in Switzerland. Fortunately, once the critical nature of the material was understood, the doors opened and we were able to move the product from the supplier to Mumbai Airport. Within a few days, it arrived at our site in Switzerland. Admittedly, we're not facing problems of that scale every day, but it does illustrate that this pandemic has forced us to think creatively and leverage our entire global supply chain network to make things happen."

Ross has also needed to deal with the lack of commercial flights. "We've had to secure far more cargo aircraft than we have in the past – which others are also doing of course," says Ross. "There does appear to be enough to go around because so many other industries have shut down – freeing up space – but there has been an increase in freight rates. Increased cost is a challenge we're having to deal with and it does tend to be

"WE'VE ALWAYS BEEN CARRIER AGNOSTIC, WHICH HAS HELPED US IN OUR ABILITY TO PIVOT AND USE ALTERNATIVE CARRIERS."

RESPONDING TO A CRISIS

By Chris Ross, Head of Life Science Integrated Supply Chain Operations at Merck Group

We realized quickly what was happening in China and then in Europe. Our first step was to create business practices that we could build on over time. As a global organization, it was critical that we empowered our distribution teams to take quick action. But we also needed a central yet flexible plan that individuals could follow – a plan that could evolve and incorporate learnings from across the global network. We have regular virtual meetings with leaders from across the network so that they can talk about their situation, including what they have put in place and what they learned from it.

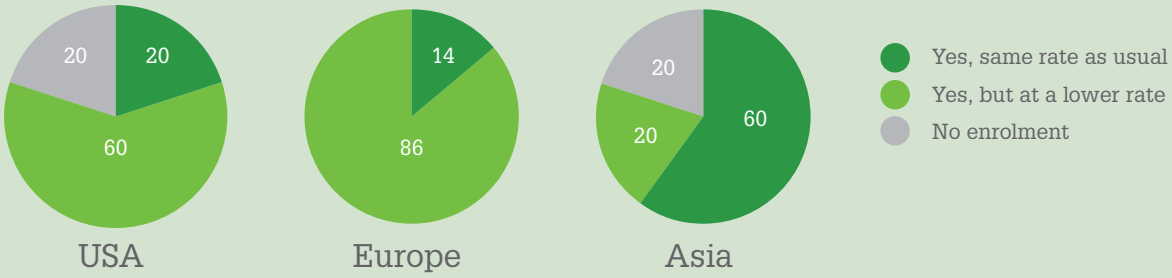
A central factor was ensuring the safety of our staff; for example, how to screen people entering facilities and ensure we have the right protective equipment, and testing. There have been shortages, but we have found ways to ensure people in the most critical areas are being tested for COVID-19.

We've been very happy with how we've managed the safety of our employees while maximizing output. But, as you can imagine, even with such measures in place, none of our sites are working at 100 percent of their usual capacity – and some sites are more active than others. We've also found that demand for certain products – particularly around the materials we provide for vaccines, antiviral therapies and testing – has been much higher than ever, which has had a big impact on some sites. Now, we must look at how we can grow to meet extra demand by adding resources and people to the plants in those critical locations. Normally, these kinds of expansion plans would be put out a year or two in advance, but we're having to move much faster, which adds another layer to the challenge.

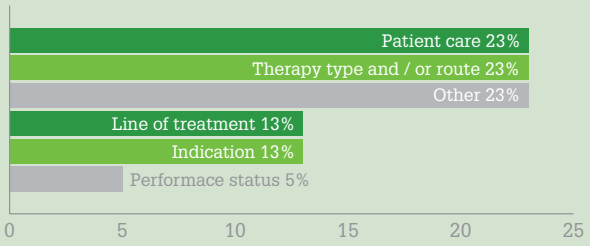
THE IMPACT IN ONCOLOGY

HOW IS COVID-19 AFFECTING CLINICAL TRIAL RECRUITMENT IN ONCOLOGY?

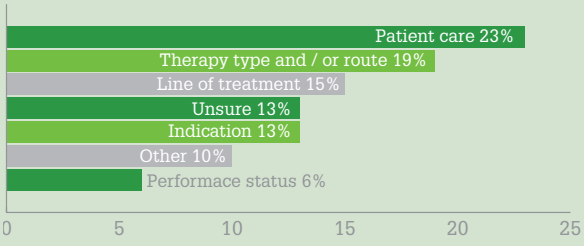
Proportion of survyed institutions continuing to enrol new patients into ongoing clinical cancer trials



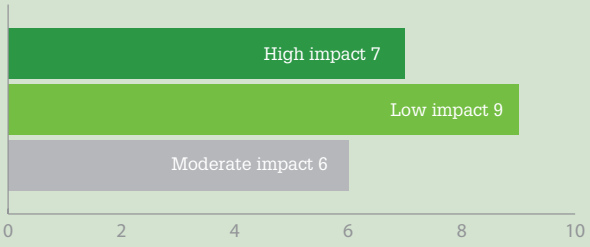
Trial considerations causing the most difficulty for enrolment in active trials



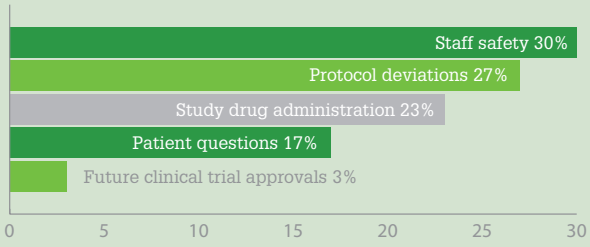
Key considerations for upcoming trials



Impact on delayed or cancelled visits for cancer patients in trials

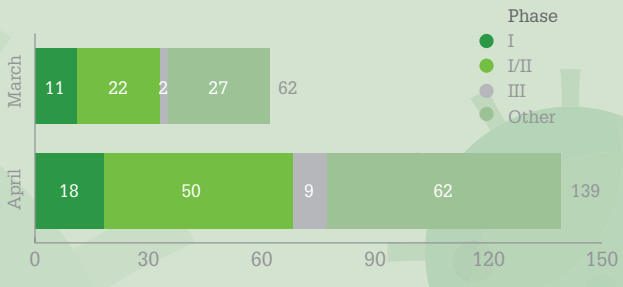


Focus of discussions with IRB/IEC



Risk type

Oncology trials suspended owing to COVID-19



Source
S Upadhaya et al., "Impact of COVID-19 on oncology clinical trials" (2020).

"WE'RE EVEN SEEING ADVANCED THERAPY TRIALS BEING CONDUCTED AT HOME, WHERE A NURSE WOULD VISIT A PATIENT'S HOME, ADMINISTER THE THERAPY BY INFUSION, AND CHECK FOR ADVERSE REACTIONS."

a little slower. The good news is that we are able to access the capacity that we need."

However, he is concerned about how capacities may be affected as more industries get back up and running. "We're going to start to see more and more people coming back to work and economic activity increasing, but we're not necessarily going to see much commercial air travel," he says. "We're going to keep a close eye on how this will impact the availability of cargo aircraft."

Merck has looked at sea freight as another option. "Speed and delivery times aside, there are challenges in terms of the quantity of containers – and the materials that are used for storage are not always up to scratch," he says."But it is absolutely an option that we are increasingly considering."

QUANTIFYING THE IMPACT

Companies may have been pulling out all the stops to maintain the flow of clinical materials for trials that are continuing to take place, but some trials have had to stop for other reasons, such as the lack of available patients for recruitment.

"Healthcare systems across the world have been put under enormous pressure," says Sonnenberg. "And, in some cases, they have had to shut down clinical sites to divert resources and people, especially nurses, towards fighting COVID-19. In addition, patients may be unable or unwilling to travel to sites that have remained open."

Medidata analyzed over 4,500 studies and 180,000 study sites to determine the impact of COVID-19. In their most recent analysis, they found a 74 percent decrease in the average number of new patients entering trials per study-site year-over-year during the first two weeks of May (1). In oncology specifically, a Cancer Research Institute survey found that, in the USA and Europe, patient enrolment in active oncology clinical trials was down (see infographic: The Impact in Oncology); only 20 and 14 percent of institutions were continuing to enrol patients at the usual rate in these two regions, respectively (2). For ongoing trials, respondents identified "patient care" as one of the top three factors causing the most difficulty for patient enrolment. In addition, nearly 60 percent of investigators reported a "moderate" or "high" impact on patient visits (delayed or cancelled), and the majority (~80 percent) of respondents anticipated that protocol deviations would cause unresolved queries, such as incomplete patient visit data.

Looking at individual companies, Pfizer, Merck & Co, Enanta, Bristol Myers Squibb, Eli Lilly, Provention Bio, Galapagos, and Novartis have all announced that they are pausing the launch of some new studies and enrollment in some ongoing studies (3, 4).

"There were a whole range of factors involved, including therapy indication (companies have done their best to keep potentially life saving treatments, or those for which there are no alternative treatments, going during the pandemic)," says Sonnenberg. "But a big determinate was whether or not they had built up the experience over the past few years to roll out decentralized and virtual trials."

THE DECENTRALIZED APPROACH

In simple terms, decentralized trials, sometimes executed by telemedicine, are conducted remotely; the participant remains at home, with clinical materials delivered directly.

World Courier was already seeing a trend towards direct-to-patient trials before the virus hit. "They were already growing in double figures," says Guite. "We're even seeing advanced therapy trials being conducted at home, where a nurse would visit a patient's home, administer the therapy by infusion, and check for adverse reactions."

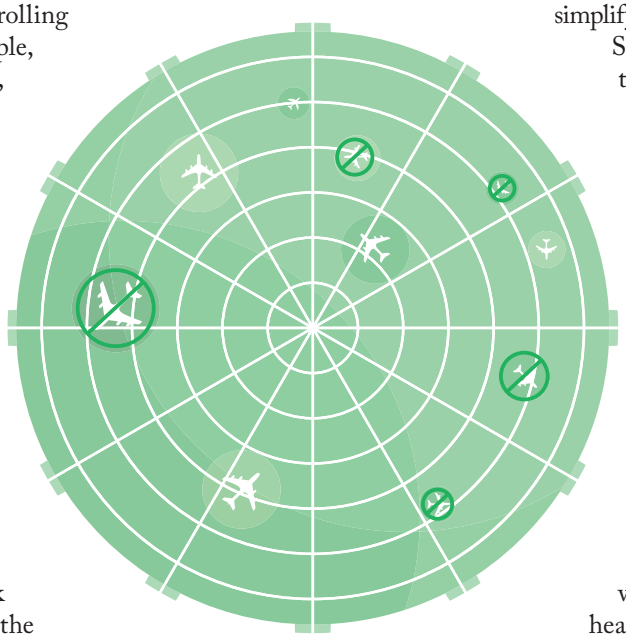
The main advantage for sponsors is that it can be much easier to recruit participants. "It's far more convenient and easier for a patient to fit around their work, kids or school life – we find

that the retention of patients tends to be higher," says Guite.

And from an economic perspective, a decentralized approach makes sense because faster recruitment and greater retention means reaching endpoints sooner. "If you can cut months, even years, from your development timeline, the economics stack up even if the logistical costs are higher," says Guite.

The advantages – especially during lockdown – are clear but, according to Sonnenberg, experience counts: "I've been watching the trend towards decentralization over the past six to seven years, and a number of larger sponsor companies have incorporated elements of virtual trials into their standard protocols. Those companies are performing extremely well in the current climate because they have the experience and the protocols in place – they've got a big head start on those starting from scratch."

Whatever the level of experience, there are a number of challenges when rolling out decentralized trials. For example, from a logistics perspective, Guite points out the difficulties of defining a delivery date. "When you're involving a nurse, whose time has to be paid for, it is critical that the timing of your delivery is perfect," says Guite. "Companies can benefit from a logistics partner who has a robust method of retrieving information, managing freight handlers, and so on."



Data privacy also requires extra consideration. "Companies really need to think about the integrity and security of the tools they're using for electronic records, as well as the accuracy and precision of any remote sensors used to take measurements," says Guite. Recent laws, such as California's Consumer Privacy Act and the European Union's GDPR, set a high bar for data to be considered "de-identified." According to Deven McGraw, General Counsel and Chief Regulatory Officer at Ciitizen Corporation, such legislation makes mobile consent more challenging because of the amount of information that must be provided to potential participants (5).

"GDPR in the EU is more strict than the US equivalent," says Sonnenberg. "I believe quite a few companies have decided to put trials in Europe on hold rather than adopting a decentralized approach because of regulatory hurdles. Another factor is the lack of harmonization throughout the EU," he says. "We found it quite challenging to deal with different regulations and restrictions; some said you should consider not conducting a trial; for example, the UK government stopped universities from engaging in clinical trials unrelated to COVID-19. Other countries have been clearer in how to continue."

The way clinical trials are conducted in the EU is set to change when the Clinical Trial Regulation (Regulation (EU) No 536/2014) comes into force later this year. The Regulation harmonises the assessment and supervision processes for clinical trials throughout the EU, via a Clinical Trials Information System (CTIS). "The new Clinical Trial Regulation in the EU would mean that companies could apply for a clinical trial in one country and conduct the trial in all EU countries, but that element is not yet active," says Sonnenberg. "I think this would have helped simplify things"

Sonnenberg also points out that there are ethical questions that companies have had to deal with; namely, should they employ a nurse to carry out clinical trial duties as part of a decentralized trial during a pandemic, when healthcare systems are already stretched to their limits? "Often you will need a nurse to perform measurements or administer a therapy," he says. "But we made a decision, despite the demand, not to hire any new nurses during the pandemic, as it would mean taking from the public healthcare system."

But in the future, increasing the number of decentralized trials may take pressure off healthcare systems and trial sites. "Even in normal times, healthcare systems can struggle to accommodate large numbers of clinical trial participants," says Guite. "Decentralized trials can help ease that burden."

NO GOING BACK

Overall, Guite has been impressed with the way companies new to

"PATIENTS, PHYSICIANS AND SPONSORS ARE NOW FAR MORE FAMILIAR WITH DECENTRALIZED, DIRECT-TO-PATIENT TRIALS, AND WILL BE MUCH MORE LIKELY TO CONSIDER THEM FOR FUTURE TRIALS."

the decentralized approach have coped during the pandemic. "Companies have had to shift very quickly and, in most cases, have dealt with the challenges effectively." And so, moving forward, both Guite and Sonnenberg believe that decentralized trials will become more commonplace. "The pandemic is accelerating an already established trend in this direction," says Sonnenberg. "Companies are learning a lot at the moment and will come out of the pandemic with the confidence that they can perform a decentralized trial." He raises the example of Boehringer Ingelheim. "Before the pandemic, they didn't have a great deal of experience with decentralized trials, but in recent months they were able to switch 15 trials over to a direct-to-patient model. And from what I've heard from the clinical operations team, this will remain part of their approach going forward."

Adds Guite, "Patients, physicians and sponsors are now far more familiar with decentralized, direct-to-patient trials, and will be much more likely to consider them for future trials. I can't see things going back to the way they were."

Guite also thinks that companies will do one of two things going forward. "Either they will consider decentralization as an integral part of the protocol from the beginning, or they will have plans to shift patients from a site to their home over time," he says. He also thinks hybrid trials will become increasingly popular, which would involve a mix of site visits and home elements. "It may be that it's different for each patient, depending on their needs."

Meanwhile, Sonnenberg thinks the trend towards decentralized, direct-to-patient trials will go hand-in-hand with just-in-time, on-demand trials. "Clinical trial materials would be held at a central site and could be labeled, packaged and dispatched immediately to patients – at their homes," he says. "This would optimize how companies use their inventories and lead to significant savings. However, it will probably result in a reduction in the volume of packaging manufacturing runs, but a higher number of packaging requests, which means Clinical Research Organizations will need to be far more flexible in the future."

In terms of other trends, Guite says that companies will give contingency planning a much stronger focus after the pandemic. "And when they select their partners – especially their logistics partners – companies will be looking at their track record during the crisis."

Ross agrees: "Business continuity plans have to be in place at all of your sites, and you need to know how to react and mobilize in a situation like his. Next time, it might not be a pandemic, but you need systems in place for how to keep employees safe, protect public health, and keep your operations running – in that order. This has always been of critical importance, but I think COVID-19 will serve as a pertinent reminder."

Beyond clinical trials, Ross wonders if and when commercial air travel will return to normal, and whether companies will go back to relying on the sector to be able to ship materials. "We'll have to see how that pans out, but it looks as though a permanent change may have taken place."

"The speed at which the industry was able to transition from passenger aircraft to freight aircraft, including some regulatory workarounds, has been incredible," says Guite. "To be able to do that and maintain capacity, while also shifting many trials over to a direct-to-patient model shows that the industry is far more nimble than anyone thought."

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HAVING A PLAN B... AND C

With Ricci Whitlow, President of Clinical Supply Services at Catalent

HOW IS THE COMPANY RESPONDING TO COVID-19?

To address the impact of the outbreak, we formed a multi-disciplinary Coronavirus Response Team, made up of senior leaders and reporting directly to John Chiminski, our CEO. While continuously monitoring the global situation, this group is charged with executing mitigation activities whenever and wherever required.

Given that the governments of many of the countries within which Catalent operates have deemed the company's work to be essential, we have sustained full employment, and taken action in line with national and local guidance to both ensure the safety of employees, business partners, and protect supply to patients. Recognizing that employees who were needed on-site faced additional challenges in coming to work, the company paid a "Thank You" bonus to laboratory, development and production employees at more than 40 global facilities.

WHAT KIND OF IMPACT IS THE PANDEMIC HAVING ON YOUR SUPPLY CHAIN AND BUSINESS OPERATIONS?

Early on in the outbreak, we looked at our operations and supply chains, even working with suppliers to consider their supply chains too – this remains an ongoing process and, to date, we have not identified any significant risk, delays, or concerns that may have a substantial effect on delivery of products or clinical trial supplies.

Safety measures implemented (in line with guidelines issued by the US Center for Disease Control and Prevention, the World Health Organization, and local authorities where our company operates) include re-emphasizing good hygiene practices to all, significantly restricting visitor access to sites, reorganizing workflows where permitted to maximize social distancing, limiting employees to only business-critical travel (where permitted by local government policy), facilitating safer alternatives for travel to and from work, and, wherever possible, employing remote-working strategies.

Globally, around a quarter of our workforce has been able to work from home, and we've put a COVID-19 response plan in place to manage any impact of the virus on employee health, site operations, and product supply too. This aspect includes immediate assessment of the health of employees reporting symptoms, comprehensive risk assessment of any impact to quality, additional cleaning protocols, and alternative shift patterns to compensate should fewer employees be available or able to work in a given area, while still respecting social distancing.

We've also adopted specific procedures to mitigate the risk of any potential disruption to ongoing operations – these include expanded safety stocks of raw materials and personal protective equipment (PPE) across networks, as well as ongoing monitoring of suppliers' stock levels to assure future deliveries.

WHAT ABOUT CLINICAL SUPPLY, SPECIFICALLY?

The pandemic has really highlighted the need to not only have a plan A, but also a plan B – and even a plan C – at the ready to respond to unforeseen challenges that could impact clinical studies. Before the outbreak, we were already supporting customers who needed help identifying, addressing and planning for variability in their supply chains with more flexible distribution services, including direct-to-patient clinical supply, to better meet the needs of their patients and the clinical trials of the future.

The pandemic has increased interest in the use of virtual clinical trials because sponsors have had to quickly react and adapt their logistics and trial operations to reduce or eliminate in-person clinical site visits. Even in some countries where previously direct-to-patient distribution was not allowed, such as China, governments are recognizing the critical need to keep studies running, and temporarily allowing patients to receive medications at home to support social distancing efforts.

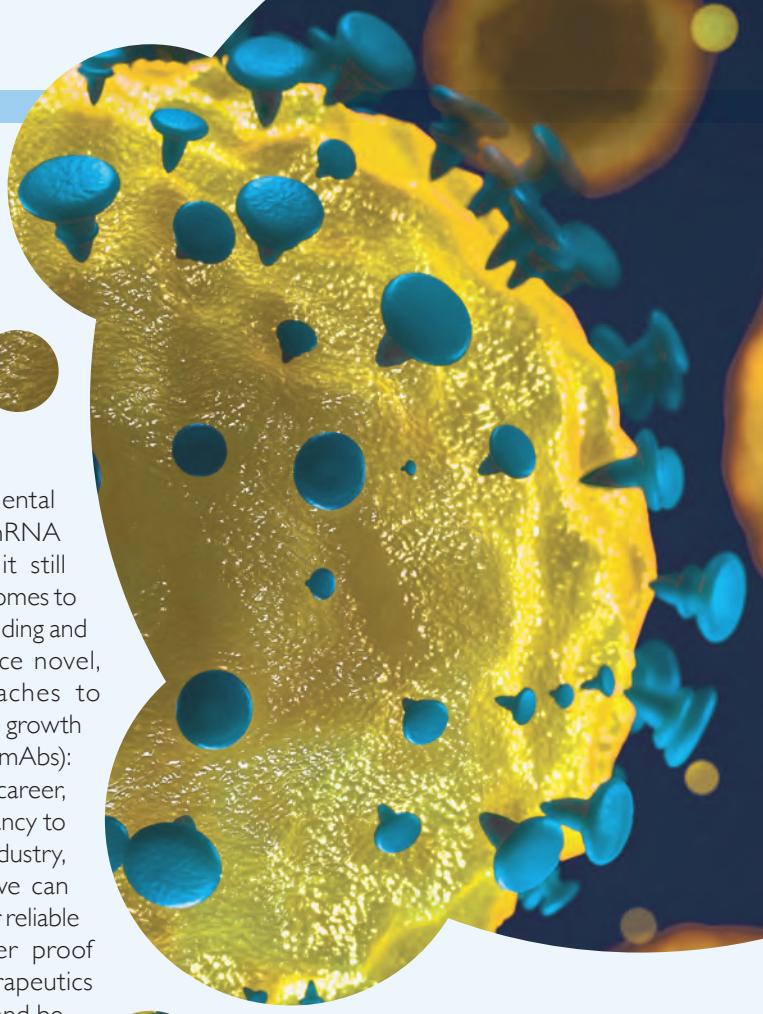
WHAT LESSONS HAVE YOU LEARNED FROM THE ONGOING IMPACT ON SUPPLY CHAIN OPERATIONS?

Several lessons have been learned from the impact of COVID-19 on clinical trials globally, but all ultimately boil down to three essential truths – always be prepared, stay vigilant, and be flexible. For example, business continuity planning to identify and qualify redundant suppliers, and model potential "what if" scenarios should always be a serious planning exercise versus a paperwork exercise. The ability to overcome logistical challenges means keeping distribution needs a priority so that workarounds to transportation challenges, such as country lockdowns, can keep supplies flowing to patients – the flexibility and courage to try new approaches can be invaluable in times of uncertainty.

Expediency is also absolutely necessary when managing a crisis in real-time, and trusted supply chain partners can and should become part of your early warning system to extend your own network of eyes and ears – for example, we were notifying customers in January of the trouble brewing in China and its potential impact on their studies well before most of the rest of the world was reacting. Learn from the successes and failures of those around you and weave those experiences into your framework as you evaluate potential courses of action and your own response to supply chain threats. And above all else, while the rest of the world may be shutting down, your business may be working harder than ever to keep the supply chain up and running – never lose sight of the importance of the human component of the supply chain: keeping your employees engaged and motivated is critical.

WHAT'S THE LIKELY LONG-TERM IMPACT ON CLINICAL TRIALS?

The continued loss of life is tragic, but I am hopeful that the worst of the COVID-19 pandemic will soon be behind us. As the world begins to regain its rhythm, the pandemic should continue to serve as a powerful reminder that future challenges with the potential to disrupt clinical trials will always be out there. It could be another global pandemic or a natural disaster, but there will always be something that threatens to disrupt the status quo. As an industry, we should always be innovating, looking for alternatives to do the work we do better, faster and smarter, and with an eye towards building a supply chain that is more flexible. For sponsors today, this could mean adding a provision for direct-to-patient clinical supply to study protocols – just in case it is ever needed – even for just one patient. Proactive contingency planning should be a given in every clinical supply plan too. As for the longer term impact of COVID-19, it has accelerated the use of remote or virtual studies at a faster pace and more broadly than would have occurred without the present day challenges. For patients and the future of clinical trials, this may be a good thing as it will help us collectively move towards new improved ways of conducting life-changing research.



Biopharma Banding Together

How has the COVID-19 pandemic changed the industry? And how can we respond faster next time?

By Bill Jarvis

In some ways, it is still business as usual in the pharma industry. After all, the pharma industry was already working on vaccines and therapeutics long before COVID-19. However, the focus has certainly shifted, with many companies now concentrating on how they can adapt their research and technologies to address COVID-19, and get viable therapies (either new or repurposed) and vaccines to market as quickly as possible. The good news is that companies can develop a new therapeutic or novel vaccine far more quickly than they could 10 or 15 years ago – progress can be rapid, as evidenced by the large number of clinical trials that have already commenced.

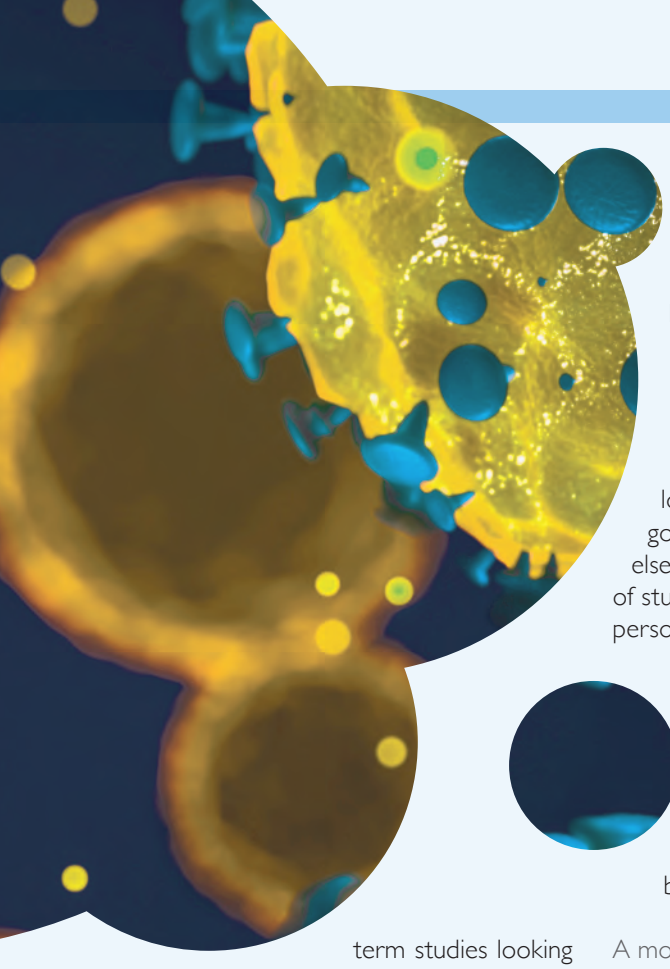
We are also seeing increased collaboration throughout the industry in various areas. We have been helping immunoglobulin companies refocus their efforts on COVID-19 as quickly as possible. And many of these companies are getting involved in partnerships of unprecedented scale; for example, Takeda, CSL Behring, Biotest, BPL, LFB and Octapharma are all working together on a plasma-derived therapy for COVID-19. To see so many competitors banding together so quickly and freely to address a common issue is unique and inspiring.

Over time, we may also see changes on the regulatory side. As the crisis goes on, we may start to see regulators becoming keener to examine novel or repurposed vaccine platforms, such as mRNA. At a fundamental level, we know that mRNA technology is safe, but it still needs to mature when it comes to regulatory body understanding and the willingness to embrace novel, platform-based approaches to therapeutics. Consider the growth of monoclonal antibodies (mAbs): during the course of my career, mAbs have gone from infancy to maturity; we now, as an industry, really understand how we can modify mammalian cells for reliable manufacture. MAbs offer proof that new, disruptive therapeutics can become mainstream and be readily accepted by regulators.

Preparing for the next crisis

The pandemic has also made companies consider how they can prepare to deliver therapies and vaccines to patients more quickly in the future, when new infectious diseases inevitably occur – whether that be a coronavirus or another novel influenza strain. Overall, the situation has highlighted the industry's lack of flexible aseptic manufacturing capacity. On a modern fill line, equipment is expensive and lead times are long; that means it is not practical or simply a sound business decision to hold spare filling capacity just waiting for the next crisis. Ideally, manufacturers need flexible equipment that can be repurposed quickly depending on the need – without disrupting supply for other, still critical products that use that same equipment to produce drugs ready for distribution to the population quicker. In addition, for the production of immunoglobulin, as a specific example, there were no appropriate, validated, small-scale production trains available to process the first small volumes of donated plasma that became available from recovered COVID-19 patents. That means a group of the plasma processing companies have pooled plasma donations from COVID-19 patients to collect sufficient raw material for processing in large-scale production equipment. Going forward, responsible companies who produce immunoglobulins will likely look to install small- to intermediate-scale production equipment so that specialty production lines can respond more quickly to a similar need in the future.

As a company, we've also had to play our part in the COVID-19 pandemic by ramping up our support for all clients. We've been involved in many short-



products and sterile materials all the time, we have useful knowledge and perspectives on the various techniques that can be used to sterilize equipment. By proactively reaching out to local medical service providers and government bodies, we see where else we can help, such as the facilitation of studies on short-term sterilization of personal protection equipment.

It may feel like the modern world has stopped because of the pandemic, but human disease has not. We still have many clients working in other therapeutic areas – and we must ensure their needs are also being addressed.

term studies looking at rapid response and the specific manufacturing needs of a variety of platform technologies. We've been examining how we can design and outfit facilities so that the fundamental technology can receive a degree of regulatory approval immediately, resulting in smaller hurdles to address later on when that technology is adapted to treat a specific indication.

We've also been advising companies on the rapid sterilization and reuse of medical equipment. As we deal with production facilities for pharmaceutical

A more flexible future?

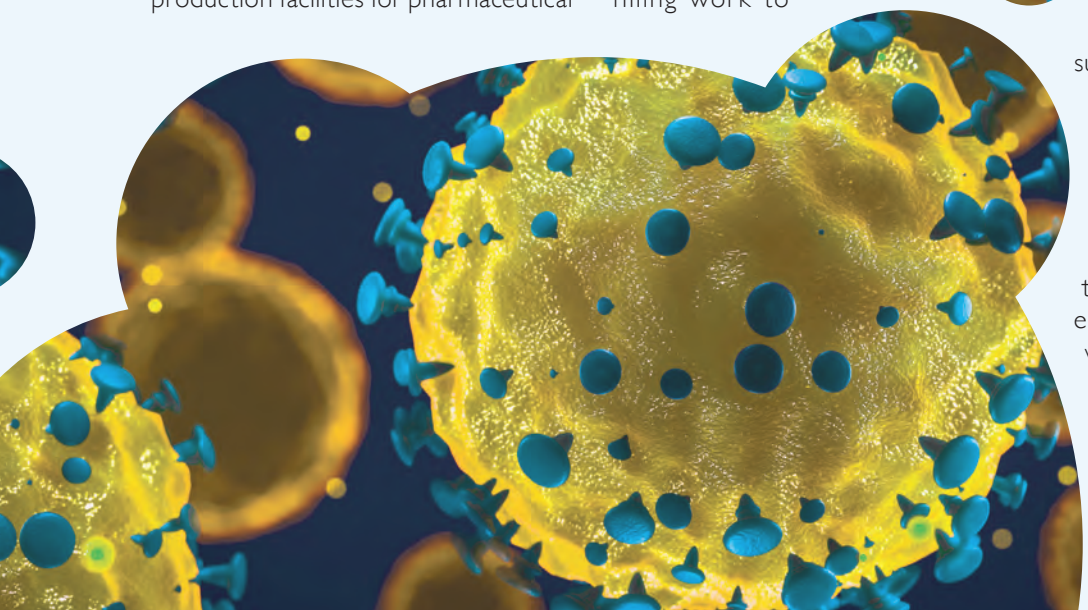
The ideal facility of the future should not focus on just one production capability for existing products on a large scale; more now than ever, manufacturers need flexible small-scale production that is able to quickly respond and swap between products. We also need to consider spare capacity. Right now, for example, strategic government agencies are approaching contract manufacturing organizations to ask them specifically, to displace ongoing formulation and filling work to address capacity for incoming vaccines. Perhaps unsurprisingly, there is rarely free production space in the industry; all companies aim for around 85 percent or higher occupancy, as it is simply not profitable to have installed capacity sitting idle for too long. But building in the flexibility to have spare capacity – specifically in the area of formulation and filling – is something we will need to address as an industry. When pandemics occur, it is the pharma industry's responsibility to deliver treatments and vaccines. It's true that creating a flexible facility is expensive – the equipment and the facilities themselves are expensive – so we should consider pooling common resources and accessing government funding to help companies install emergency capacity.

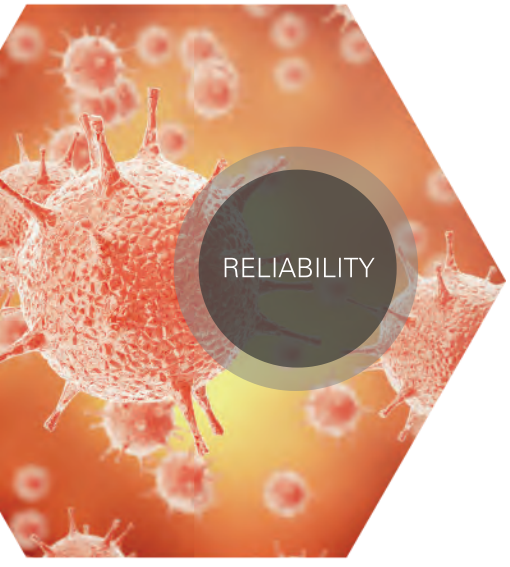
I consider myself fortunate to be involved with clients who are working with cutting edge technologies that will undoubtedly create waves in the future – not only for COVID-19 but also other therapeutic areas. And I'm energized by the sense that we are all in this together. As a chemical engineer, I have spent much of my career struggling to explain to family and friends exactly what I do (I'm sure many of you will relate!).

Now, the wider public is starting to realize how important this industry is – not just the pharma manufacturers themselves, but all the other companies who play a role, such as CRB.

As we fight against this pandemic, the whole industry is learning valuable lessons about its production facilities and processes. And though I hope we do not see another pandemic for a very long time, we must ensure that the facilities of the future are flexible enough to support patients, whatever we may face.

Bill Jarvis is Chief Chemical Engineer at CRB





LIFE SCIENCES

LIFE INSPIRED, QUALITY DRIVEN

SGS Life Sciences' integrated network of laboratories offers extensive experience in novel vaccines, providing biosafety, biologics characterization and bioanalytical testing solutions to support the fight against COVID-19.

Our biosafety testing laboratory provides testing support for the biosafety and characterization of raw materials, cell bank and virus seeds for vaccines, cell and gene therapies, monoclonal antibodies and other recombinant protein based biological medicines, including a vaccine testing solution for coronavirus.

We provide established expertise and resources for all aspects of biopharmaceuticals characterization – from physico-chemical properties, to primary, secondary, and tertiary structures, as well as aggregation. Our characterization services include antibody testing and batch release testing for large number of doses.

Our GLP/GCP compliant laboratories offer the expertise to both develop assays from scratch (including LC-MS/MS, immunoassays and cell-based assays). We support large-scale routine sample analyses, from regulatory pre-clinical (toxicology) to early and late clinical studies (Phase I to IV).

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WHEN YOU NEED TO BE SURE

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Access Not Denied

Any diagnostics, treatments and vaccines developed to combat COVID-19 must be suitable for use in all countries, including resource-poor settings

By Stephanie Sutton

COVID-19's devastating impact on wealthy countries, such as Italy, Spain, the UK, and the US, has been well publicized. These countries have modern healthcare systems and significant resources, and yet have still struggled to contain the virus and protect their populations. But what about low-to-middle-income countries, where access to even essential medicines can be difficult? Latin America has recently emerged as the new COVID-19 epicenter – and has far less resources than western Europe to deal with the situation. In Africa, up to 190,000 people could die of COVID-19 in the first year of the pandemic if containment measures fail, according to the World Health Organization (1). Other low-to-middle-income regions are also facing the oncoming wave.

Companies and academic institutions are making significant efforts towards finding and developing treatments and vaccines for COVID-19, but there is a question mark over whether the resulting medical countermeasures will be accessible – or relevant – for low-to-middle-income countries. If the needs and priorities of the most vulnerable populations are not taken into account by global initiatives working to evaluate the safety and effectiveness of new diagnostic tools, drugs, vaccines, and non-medical interventions against COVID-19, there is a risk that millions will be denied access to life-saving interventions.

Nathalie Strub-Wourgaft, Director of Neglected Tropical Diseases from the Drugs for Neglected Diseases initiative (DNDi) reminds us that COVID-19 is a global pandemic. Research efforts must not be confined to wealthy countries. We must find solutions that can be rolled out in resource-poor settings so that patients the world over can benefit. To help, DNDi and 150 partners – half of them based in low- and middle-income countries – have recently launched the COVID-19 Clinical Research Coalition to coordinate international research collaborations to support African, Latin American, Eastern European and certain Asian countries.

Tell us about the COVID-19 Clinical Research Coalition…

The COVID-19 Clinical Research Coalition was launched through a comment in The Lancet at the beginning of April 2020 (2), and involves scientists, physicians, funders, and policymakers from over 70 institutions and over 30 countries.

The idea for the coalition came about in a meeting between DNDi and two of our partners: Mahidol Oxford Research Unit in Thailand and Oxford University's Infectious Diseases Data Observatory (IDDO). We were concerned that the specific needs and expertise of scientists and communities from Africa, Asia, Latin America, and the Middle East might be overlooked without a concerted effort to include them. We believed that COVID-19 clinical research should also be conducted in resource-limited settings to ensure that the end results are relevant to all countries. A one-size-fits-all approach would probably not work in different settings: different co-morbidities, different socio-economic conditions and different cultures have an impact on the efficacy and safety of treatments. Clinical research should reflect those differences.

The coalition, therefore, aims to ensure that research institutes based in resource-limited countries have what they need to quickly launch high-quality clinical research, and identify workable solutions for COVID-19 prevention, diagnosis, and case management as quickly as possible. An important element of the coalition is the sharing of research and protocols. Sharing also helps to avoid the duplication of research efforts and to promote synergies among projects.

"A treatment that requires constant refrigeration will be of little use in a region with unreliable access to electricity."

For example, a professor in Thailand preparing a clinical trial to test a promising prophylactic solution could use the coalition as a platform to share a protocol with other researchers, enrol other institutes that are willing to carry out the same study at their clinical sites, and find partners who can provide funding, materials, and technical expertise. Essentially, through the coalition, researchers in any part of the world developing a clinical study are able to gain access to a protocol that has already been developed by colleagues elsewhere. They do not need to start from the beginning: they can benefit from a validated protocol, adjusting it to their specific needs. Precious time can thus be saved because the coalition – and its web-based platform to facilitate peer-to-peer collaboration – will help avoid research duplication.

The coalition will cover a number of areas relevant to COVID-19 management, including therapeutics, preventative medicine and vaccines, diagnostics, social science, epidemiology and modeling, and clinical pharmacology. And we may also add more study areas as time goes on.

Why are there concerns about the current COVID-19 clinical research climate?

There has been an unprecedented research response to COVID-19, with impressive collaboration going on at the international level. More than one hundred countries, for example, have joined the WHO-led Solidarity trial. The COVID-19 therapeutics accelerator, initiated by the Gates Foundation, Wellcome, and Mastercard to share research, pool resources, and invite pharmaceutical companies to collaborate is another example of a highly promising initiative.

However, the vast majority of clinical trials are being conducted in Europe, the US, and northeast Asia. Out of the 1500 – and counting – COVID-19 clinical trials registered to date, very few are planned in resource-poor settings and most of the existing ones will assume that doctors will have considerable access to materials, tests, staff, medical equipment, and infrastructure. But a treatment that requires constant refrigeration will be of little use in a region with unreliable access to electricity, as will a treatment that requires frequent blood tests, which are difficult to administer in regions suffering from an acute shortage of healthcare workers and laboratory capacity.

Much of the research being conducted in high-income countries also focuses on the evaluation of treatment for severe, hospitalized cases. There is a growing interest in low- and middle-income countries to evaluate treatment for mild – and even asymptomatic disease – to halt onward disease transmission and prevent cases from becoming more severe. Such an approach would reduce demand for overburdened health systems with limited intensive care capacity. In addition, it is imperative that further research is conducted looking at the effect of co-morbidities on COVID-19 mortality rates. In Africa, there is a high prevalence of underlying parasitic infections and diseases, such as HIV, which weaken the immune system and could fuel higher COVID-19 death rates. Clinical research must be designed to reflect this situation.

Another issue of concern is the administrative/bureaucratic context. In many countries, review by ethics committees and regulatory clearance for importation and production of drugs, vaccines, and trial material takes some time. Participants in the coalition will

identify and promote processes that can facilitate rapid reviews by ethics committees and national regulatory agencies – as the African Vaccine Regulatory Forum (AVAREF) did for Ebola vaccine trials. Approvals for the importation of study material will also be accelerated through fast-track mechanisms and agreements.

How is data from the coalition shared?

Data will be shared using a data-sharing platform. Each signatory of the coalition commits to share their protocols and results in a transparent manner, according to the principles of open science. Research knowledge and data will be credited appropriately, and will be made easily accessible to facilitate the work of other researchers and to inform decision-makers.

These open science and data sharing principles need to be applied at all stages of COVID-19 research to accelerate progress. Furthermore, standardization of protocols and key measures in terms of research results and data collection will be facilitated, making sharing and analysis even faster and easier. When clinical trials are designed separately, they measure different key indicators that do not allow for easy comparison. We want to avoid this in the coalition.

For the past 15 years, there has been an increasing number of models emerging that favor a more open innovation approach to drug development – and DNDi relies on these open innovation models to develop effective treatments for some of the world's most neglected diseases. For malaria, leishmaniasis, and Chagas diseases, IDDO is pooling all research data from participating organizations, such as DNDi, so that it can be accessed by a larger community of scientists (3). Such an approach allows us to derive crucial conclusions that would have been beyond the scope of a single, isolated, clinical study.

This type of collaboration is essential for the COVID-19 response, as it will feed faster responses to inform national and international guidelines.

"Pharmaceutical companies are not incentivized to focus on long-term research that does not bring short-term benefits."

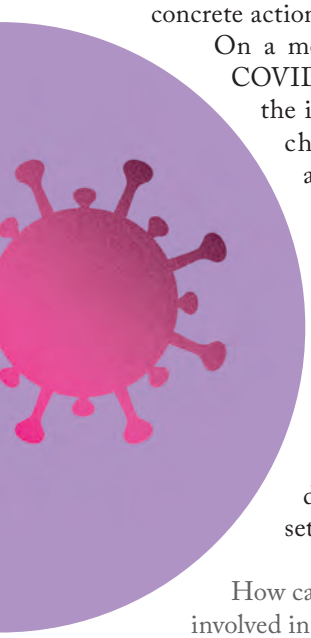
In a post-COVID world, what key lessons will have been learned?

The COVID-19 crisis has really put the "global" back into "global public health." It has taught us that public health concerns us all – and that the best way forward is through collaboration. The pandemic also reminds us that preparation is key. The emergence of a novel coronavirus with pandemic potential was not a surprise – and research on coronaviruses should have started much earlier. But the way in which R&D is funded, prioritized, and steered means we were not ready. In that sense, the crisis also highlights the systemic limitations of the current system where R&D priorities are not yet set by a public health agenda. Initiatives such as the Coalition for Epidemic Preparedness Innovations (CEPI) in the field of research for vaccines against infectious diseases, or the WHO R&D blueprint for action to prevent epidemics are, however, important steps in the right direction.

Pharmaceutical companies are not incentivized to focus on long-term research that does not bring short-term benefits. For the last few decades, we've seen large pharma companies actively withdrawing from infectious diseases, antibiotic resistance, and pathogens with pandemic potential – while these issues are increasingly threatening humanity. Governments have a responsibility here in that they set the frame under which the industry operates. We must set up a new economic and research model to fight infectious diseases, with stronger involvement of governments, public interest research institutions, NGOs, and civil society groups.

In that regard, the recently launched WHO-led Access to COVID-19 Tools Accelerator was highly encouraging (4). Leaders worldwide came together for the virtual launch of the Accelerator,

calling for multilateral responses, scientific collaboration, and equitable access to all tools. German chancellor Angela Merkel and French president Emmanuel Macron described vaccines as a "global public good." World leaders espoused a bold vision based on public and private collaboration in scientific research. These are values long cherished by DNDi. But the challenge now is to move from vision to specific concrete actions!



On a more granular level, the COVID-19 crisis also highlights the issue of the drug supply chain. Many countries are unable to access and produce the drugs they desperately need. The issue is often not only technological, but also regulatory; intellectual property barriers and administrative hurdles are hindering access to affordable life-saving drugs in resource-limited settings.

How can organizations get involved in the coalition?

Please contact us. All organizations and research institutions ready to contribute existing capacity to facilitate clinical trials in resource-limited settings are invited to join. Coalition signatories must share our values of open science, transparency, and collaboration.

Organizations willing to get involved can fill in our short questionnaire available at http://tiny.cc/2104oz to map the capacity and interests of coalition members. It takes three minutes to complete. More information can be found at www.covid19crc.org.

The coalition was launched on April 3, 2020, with 77 initial members from 31 countries. It has since increased to nearly 120 members from some 40 countries, most of which are low- and middle-income countries. Many coalition members are public research institutes from low-to-middle-income countries. They also include health ministries, universities, non-profit organizations, private sector health facilities, regional research coalitions, and funders from across Africa, Latin America, South, and South-East Asia. In addition, the majority of the coalition's steering committee are representatives of organizations from low-to-middle-income countries, and are leading the governance of the coalition.

On a concluding note, it is necessary to remind everyone that global health crises and pandemics will keep arising in the future. It is urgent that we reconsider the whole public health system globally, and build a new research model that ensures everyone, without exception, has access to life-saving drugs.

The impressive and unprecedented effort on a global scale by the scientific community to fight COVID-19 must also be applied to neglected diseases, which, for decades, have been plaguing the life of millions of vulnerable people.

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Dimensions of Progress

How far have we traveled along the road to 3D cell culture technologies?

By Maryam Mahdi

With the ability to promote levels of cell differentiation and tissue organization not achievable in 2D cell models, a new generation of 3D disease models and assay technologies are changing the industry's approach to the study of human pathophysiology. These organotypic 3D human tissue models enable drug developers to simulate conditions of complex diseases in a well, a feat that could potentially help shorten development cycles and produce better lead and compound identification. But despite the clear benefits of 3D assay technology, some reluctance to move away from 2D models lingers – and not without reason. Pharma has an established history with 2D culture and a plethora of comparative literature cites their use. Even though simplistic 2D cell cultures don't mimic human biology or allow cells to interact the way they would in vivo, 3D technologies and disease models have perceived challenges. At first glance, 3D assays seem more expensive than comparable 2D assays and high-volume spheroid model production for industrial scale testing isn't easy. Moreover, 2D fans will cite another valid concern: 3D cell cultures don't lend themselves to maintaining quality readouts over time and thus have the potential to introduce variability into experiments.

Here we speak to Jan Lichtenberg, CEO and Co-founder, and Frank Junker, CBO, both at InSphero, a biotechnology company based in Switzerland that provides scalable 3D in vitro cell culture platforms for drug discovery and safety testing, about the benefits 3D cell culture and disease models are bringing to the industry, the current challenges associated with adoption of new technology, and what it will take to encourage hesitant companies to explore 3D solutions further.

What's the story behind InSphero?

Lichtenberg: Along with Jens Kelm and Wolfgang Moritz, two friends from university, I co-founded InSphero, a company that offers cell culture assays for predictive compound classification. While my co-founders were both biologists, my background was very different – and I an engineer with experience in microfluidics, the technology behind emerging organ-on-a-chip solutions. But our differences allowed us to work collaboratively, exploiting our knowledge to develop fresh perspectives on 3D cell culture assays.

Jens and I had actually worked on a cell-related project together years before. He was interested in cell architecture, the possibilities that scaffold-free 3D cell culture techniques could offer, and how tissues could be rebuilt and their building blocks manipulated. We put these tissues onto microchips that I had been working on to see if we could get some meaningful readouts… and the results were interesting.

Although we hadn't imagined setting up a company together at that point in time, we later realized that it was a path worth pursuing. The pharma industry was looking for new ways to perform in vitro testing and there was certainly a lack of predictive assay systems available for drug discovery and drug safety. We were still at the academic level in terms of pitching our ideas to the pharmaceutical industry, but we could see how the lack of cell culture systems represented a growing problem.

We wanted to create a platform that could address the issues of productivity and predictability and replace conventional cell culture techniques without compromising on scalability. In time, we decided to quit our jobs and built InSphero from the ground up!

What are some of the major benefits of 3D cell culture technologies?

Lichtenberg: Being able to discern whether specific compounds help to reduce disease states in tissues is essential when trying to develop clinically relevant medicines – mediums that lack specificity are unable to bring value to companies interested in developing therapeutics for complex conditions. The development of novel therapeutics for non-alcoholic steatohepatitis (NASH), for example, has been hindered by a lack of biologically relevant in vitro models that mirror the complex mechanisms underpinning the development and progression of the disease. NASH is a form of non-alcoholic fatty liver disease characterized by liver inflammation, hepatic cell damage, and the buildup of fat in the liver. The condition affects somewhere between 3 and 12 percent of the US adult population and can lead to the development of cirrhosis and liver cancer. Screening using animal models can be a lengthy process and fails to determine, with certainty, if compounds will work in humans.

Using 3D-based culture platforms, we can rapidly drive tissues into disease specific states (as well as out the disease state with the right medicines). Importantly, these platforms allow for automated screening of drugs or drug combinations, helping to determine clinically relevant endpoints. A significant problem experienced by industry was the huge number of compounds failing late-stage testing due to liver toxicity and the lack of availability of long-term assays, but long-term 3D liver tissues are now available on the market and helping new drugs to be developed.

What concerns are industry players expressing about 3D cell culture technologies?

Junker: Some companies have simply never had a negative experience in using 2D cell culture. When you're comfortable with using a technology

and haven't had any crucial mishaps with it, what would be the motivation to move away from it? 3D technologies are superior as proven by many publications, but come with a greater level of complexity – and compared directly to 2D models, are initially more expensive. A greater amount of effort has to be put into creating the microtissues, a process which isn't as straightforward for companies inexperienced in doing so. However, there is a general realization that the benefits of 3D outweigh the challenges associated with its use.

Another concern is reproducibility. Because this approach relies on the use of primary human cells from donors, the risk of variability is a valid concern. But there are experienced players in the 3D cell culture arena able to provide customers with consistent products across lots. Establishing strong and trusting relationships with these types of companies is important for any researcher considering the transition from 2D to 3D cell culture technologies.

How will education play a role in helping adoption?

Junker: The shift toward 3D technologies that we're now starting to see can be contributed in part to the conference landscape that has developed over the last couple of years. The pharmaceutical industry is notoriously conservative, but as more results are published and presented at conferences, companies that have relied on 2D models for 20 to 30 years are now reevaluating the potential of 3D because of data, training, and other resources now at their disposal.

Lichtenberg: 3D technologies were initially considered disruptive, and because of this they occupied a very niche area of industry in its infancy. Now, we're seeing people beyond the enthusiastic early-adopters embrace what it has to offer. With time, applications of microfluidic systems will naturally broaden, and companies holding on to traditional 2D models will have to ask themselves why they have yet to embrace the change.

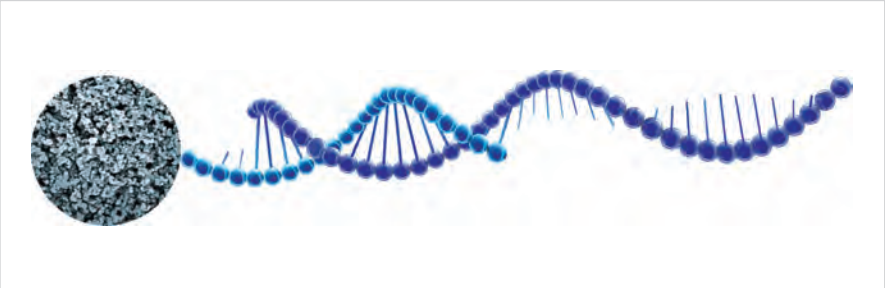
What does the future look like for 3D models?

Lichtenberg: There is a growing interest in the development of 3D models for quality control in the production of biologicals, and combining microengineering with cell biology to replicate organ- and systemic-level functionality in microphysiological systems suitable for organ-on-a-chip applications. This field has a great deal of opportunity and room for growth. These technologies are still in their infancy, but this incents us all to explore potential applications and with time we should see more complex technologies which can create the benefits that customers are looking for begin to reach the market.

However, more relevant is the near future, which will see a widespread adoption of robust, industry-grade 3D cell-based assays. As with every new technology, it takes time after the initial hype to reach a level of productive use – and we are closing in on it. Once we are there, 3D cell-based assays will be a keystone of predictive, patient-centric development of drugs, helping to accelerate discovery in all therapeutic areas.

A Shot in the Arm for mRNA Vaccines

Standard methods of preparing mRNA require multiple purification steps, sometimes-costly single-use resins, and various chemicals. At the commercial scale, such methodology is impractical; at the vaccine scale (hundreds of millions of doses per annum), it is impossible.



Large pore bead with increased binding capacity for the efficient capture of mRNA.

The concept of mRNA therapy has gone from concept to realistic prospect with remarkable speed, but not everyone was taken by surprise. Scott Zobbi (Senior Business Development Manager, Thermo Fisher Scientific) first saw a significant increase in research into RNA therapeutics several years ago, particularly with regard to using mRNA as an alternative to recombinant proteins. But the really exciting development, according to Zobbi, is the application of mRNA to vaccination – not only in cancer immunotherapy, but also for infectious diseases.

In fact, mRNA vaccination constitutes an entirely new immunization modality. Administration of mRNA rather than protein antigens induces the body to produce antigenic proteins internally, eliminating some of the more expensive and time-consuming components of traditional vaccine manufacture. Similarly, the mRNA approach permits more rapid and responsive vaccine development: a simple RNA sequence change will quickly accommodate viral strains that have mutated away from the original vaccine, and entirely new vaccines can be promptly developed when dealing with a novel virus pandemic, such as COVID-19.

Broad commercial application of mRNA vaccines, however, assumes availability of appropriate supporting technology; for example, cost-effective, scalable mRNA purification methods. As Kelly Flook (Senior Product Manager, Purification Products, Thermo Fisher Scientific) puts it: "The move towards mRNA therapeutics and vaccines demands methods to achieve high purity mRNA in as few steps as possible, at the lowest cost possible."

Cleaner capture at lower cost

Flook explains that there are a number of deficiencies with existing methods. "Usually, mRNA is purified with ion pair reversed-phase chromatography, or similar techniques, which rely on ion-pairing reagents," she says. Reagent disposal and elimination of toxins from the drug product comes at a cost – a cost that becomes significant during scale up. "Manufacture of mRNA for COVID-19 mass vaccination would involve the production of millions of doses – hundreds of grams of mRNA – and purification steps requiring hundreds of liters of resin," says Flook. "Costs would be higher still if it turned out that each vaccine course required multiple shots, or if annual vaccinations were necessary. The industry needs a scalable product that can efficiently accommodate such demand."

How did Thermo Fisher Scientific address the need? "It wasn't always straightforward," says Zobbi, who notes that a critical part of the process was screening the different base beads that Thermo Fisher Scientific uses for its affinity capture products. "We found the best performance was provided by our POROS polystyrene divinylbenzene bead at the largest pore size, which wasn't the obvious answer when we started out," he says.

Similarly, the length of the poly-T capture ligand required optimization to ensure efficient capture of the mRNAs of interest. "Eventually, we found a 25-mer poly-T to be ideal, but this took a lot of work. For example, we had to test various coupling chemistries to ensure the poly-T behaved appropriately in the resin," says Zobbi. "Similarly, a balance had to be found between maximum mRNA capture and the quantity of poly-T ligand on the resin. We want to capture as much mRNA as possible, but increasing the poly-T concentration beyond a certain point does not provide an economically defensible increase in yield."

Flook notes how each aspect of the development process was driven by demand: "We optimized raw materials characteristics to ensure the resulting product fitted the market need – efficient, scalable mRNA purification." The outcome of the development process is the latest addition to the Thermo Scientific POROS family of products, Oligo(dT) 25 Affinity Resin. Comprising base beads with a

hydrophilic coating, formed from a highly robust, structurally rigid backbone, the Oligo(dT) resin permits sample loading in high salt solution – to favor mRNA-polyT annealing – and elution with reduced salt buffer or water. Key advantages of the system include:

- Efficient use of space and material – the polymer's structural attributes enable dense column packing
- Ligand stability at extremes of temperature (70 oC) and pH permit column clean-up and re-use over multiple cycles, thereby saving material costs
- Hydrophilic bead coating resists non-specific binding, thereby reducing purification cost and complexity
- Elimination of toxic reagents reduces operating risk, as well as cost and complexity of waste disposal
- Universal approach (applicable to all mRNAs) enables manufacturers to apply a single platform to all mRNA products in their portfolios, thereby saving development time
- Easy to use, simple to scale-up; cost savings become highly significant at commercial scale

And Thermo Fisher Scientific's clients back up these claims (see The Customer View). Flook adds, "Customers have reported plasmid DNA removal to below detectable limits, and binding capacities of 5 mg RNA per mL of resin for a 4000 base pair mRNA, which is excellent!"

Opportunity knocks

Manufacturers have a unique opportunity to take advantage of the cost and time advantages associated with Oligo(dT) – and the adoption process is simple. "We are always happy to have conversations with clients regarding optimization and scale-up," says Zobbi. Those who wish to evaluate the product can benefit from the technical expertise of Thermo Fisher Scientific's field sales force, which routinely provides clients with detailed support during process development and scale-up. "Our field-based application support team has global reach and can assist with the complete range of Thermo products for mRNA preparation," says Flook.

In conclusion, Zobbi adds, "We welcome new collaboration partners, and are very familiar with the variety of needs they may have."

Pharmaceutical Grade Reagent. For Manufacturing and Laboratory Use Only.

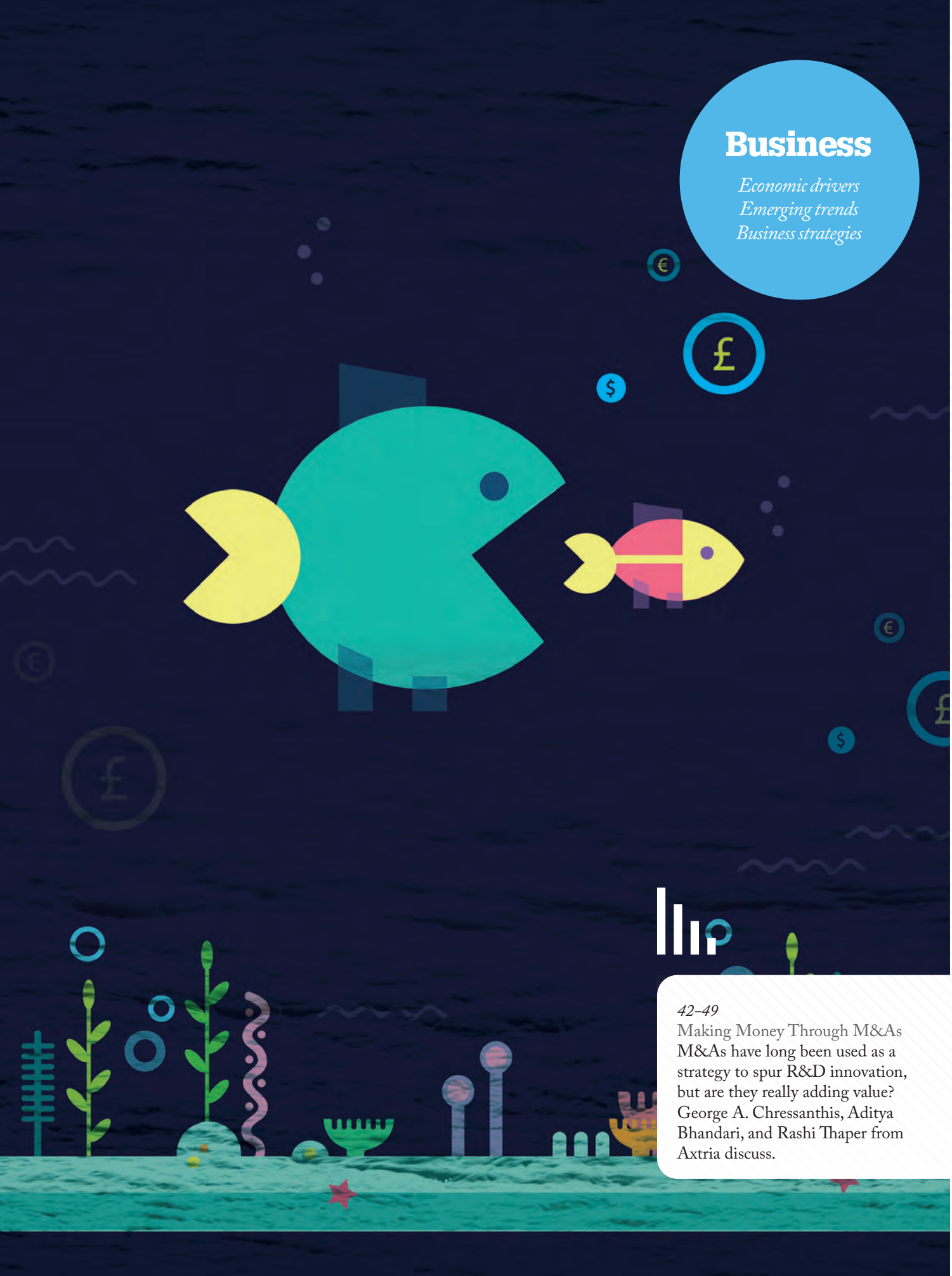
The Customer View

AmpTec manufactures pharmaceutical grade nucleic acids for diagnostic and therapeutic applications. We asked CEO, Peter Scheinert, for his views on the evolution of mRNA manufacture.

AmpTec has been manufacturing nucleic acids for fifteen years; today, the growth in mRNA applications – such as cancer immunotherapy and genome editing – is one of our strongest drivers. But we are particularly excited about the field of mRNA vaccines.

Standard vaccine production involves time-consuming steps, such as virus propagation and antibody generation. By contrast, the mRNA approach – injecting viral antigen mRNA – gets the body to produce the vaccine. It's much more flexible than standard vaccine approaches in that we can rapidly and easily modulate mRNA to reflect new mutations or to respond to new viral threats. But this speed and flexibility demands equivalently rapid and robust purification methods. Routine HPLC methods are associated with toxic reagents – requiring specialized ventilation and waste disposal systems – and scale-up difficulties. Our search for better upscaling solutions led us to a partnership with Thermo Fisher and the opportunity to work with them on the development of the Oligo(dT) resin, an easy-to-handle product that gives excellent mRNA yield. And it works equally well with all mRNAs; efficiency is unaffected by sequence or length. Furthermore, it binds the poly-A tail, and so returns full-length mRNAs, not truncated RNAs, which simplifies purification. Finally, it uses toxin-free reagents, thereby reducing method costs and complexity.

In brief, there is a dramatic and continuing increase in large-scale mRNA production, with mRNA vaccines being a key driver. We believe Oligo(dT) will be a critical manufacturing tool, not least for COVID-19 vaccine trials. Furthermore, the ease of use of this product, and the absence of toxic reagents, means that it can be used in any lab without any special safety or clean-up requirements. AmpTec is now assessing Oligo(dT) in large-scale processes, and I am confident that it will become our standard large-scale purification option. I think it's a fantastic tool!



Business

Economic drivers
Emerging trends
Business strategies

Making Money Through M&As

Do pharma mergers and acquisitions improve R&D productivity and increase shareholder value?

By George A. Chressanthis, Aditya Bhandari, and Rashi Thaper

Mergers & acquisitions (M&As) have long been used as a critical strategic instrument in the pharma industry to spur R&D innovation, sustain financial growth, and generate cost efficiencies (1). Huge mergers in the 1990s and 2000s dramatically altered the landscape of the pharma industry, such as those between Ciba-Geigy and Sandoz (Novartis) in 1996, Astra AB and Zeneca (AstraZeneca) in 1998, and Glaxo Wellcome and SmithKline Beecham (GlaxoSmithKline (GSK)) in 2000. Likewise, large acquisitions by pharma companies of other organizations also pre-date today's recent activity, again changing the face of the industry, such as those by Pfizer (Warner-Lambert, 1999; Pharmacia, 2002; Wyeth, 2009), Sanofi (Aventis, 2004), Merck (Schering-Plough, 2009), Roche (Genentech, 2009), and more recently Actavis (Allergan, 2015).

But are M&As successful in achieving their strategic objectives? The practitioner business literature gives mixed signals on this question when looking at M&As across industries. Numerous studies cite a commonly held belief in a 70-90 percent failure rate for M&As; for example, as noted in 2011 and 2016 Harvard Business Review (HBR) articles (2, 3). An earlier published article in HBR noted a series of errors and challenges companies make and face when trying to accurately estimate the value of mergers (4). However, a more recent 2018 HBR article explained why the 75 percent failure rate for mergers is a myth, where companies that gain experience in doing M&As over time (noted as programmatic M&A) are more likely to achieve "real wins" (5). This study also noted that smaller M&A deals work out better, which would be intuitively consistent with the potential for greater errors and challenges in estimating the value of larger M&A deals.

Why do companies engage in M&As? A McKinsey study concluded that there are three fundamental motivations that drive M&As: 1) as a source of innovation, 2) to unlock synergies, and 3) to realign portfolios (1).

Recent changes in corporate tax law in the US (i.e., the 2017 Tax Cuts and Jobs Act) were expected to have a stimulative effect on the number and type of M&As in the pharma sector, with a Boston Consulting Group study noting some provisions of the tax law that would affect corporate strategy and M&A activity (6):

- A reduction in the corporate tax rate from 35 percent to 21 percent
- Mandatory repatriation of offshore cash, with a one-time tax of 15.5 percent
- Immediate expensing of investment in tangible business property
- New limits on interest deductibility

These corporate tax law changes make M&As more attractive to sellers, and provide greater incentives for companies to take their liquidity and invest in deals that allow them to achieve strategic objectives. The new tax law also encourages the repatriation of offshore cash held by pharma companies – among the largest held overseas by any industry – by reducing the tax charge on that money, thus allowing the net balance to be used for productive investments, such as M&As.

In addition, certain types of deals, such as Pfizer's 2014 attempt to acquire AstraZeneca to significantly lower taxes through an "inversion" strategy by shifting the company's location from a high-tax country (like the US) to a low-tax country (like the UK) are expected to eventually disappear (6), as the substantial lowering of the US corporate income tax rate places it in sync with other developed countries. Further restrictions placed by the US Treasury rules on implementing an "inversion" approach also now make such deals far less profitable and attractive.

While tax law changes have certainly had some effect on the number of recent M&As, and the type of deals, other pharma trends and market forces are also at play. M&As represent an opportunity for pharma companies to achieve strategic objectives. Maintaining a robust and productive R&D pipeline

"While tax law changes have certainly had some effect on the number of recent M&As and the type of deals, other pharma trends and market forces are also at play."

Male new cases			*Female new cases*		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	7%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	5%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	870,970		All sites	891,480	

Table 1. Leading areas of new cancer cases (2019). Estimates by gender.
Source: See reference 10. Percentages represent a fraction of all new cancer cases.

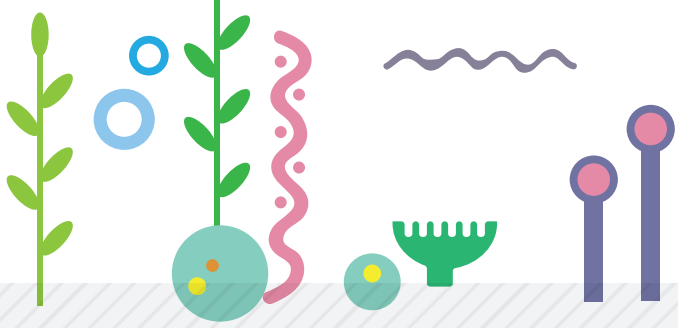
is the lifeblood for a pharma company. M&As may also be used to address a relative short-term issue such as a "patent-cliff problem", which is not about buying R&D productivity, but rather purchasing an immediate acquisition of top-line growth to stabilize a worsening profit and loss statement.

The oncology field deserves special attention when discussing M&As. Numerous companies recognize the oncology therapy area as a critical source of future growth and are expanding their market presence in this field. For example, companies like Pfizer, which was heavily involved in chronic disease areas like cardiovascular disease, or GSK, which previously dissolved its oncology presence, are now shifting a significant portion of their portfolios to oncology as a major driver of business growth (8). The market opportunity is huge for oncology. US spending on oncology comprised $58.4 billion (12.1 percent) in 2018 on a base of total non-discounted spending of $482.0 billion (9). Only the antidiabetics therapy class was greater in non-discounted spending for 2018 at $60.6 billion (12.6 percent). There are also substantial unmet medical needs in oncology (see Table 1 and 2). However, the oncology area also has its challenges, such as high inherent clinical trial failure rates (see Table 3 on page 48) – expressed here as Phase Likelihood of Approval (LOA), according to the referenced research article (11). LOA denotes the probability of reaching FDA approval from the current phase, and is also expressed as a percentage. LOA is calculated as the product of each phase success probability leading to FDA approval. The n value associated with LOA is the sum of the n values for each phase success included in the

Recent Deals

Examples of significant deal-making activity seen in the pharma industry:

1. Amgen agrees to buy Otezla from Celgene in a $13.4 billion deal (August 2019)
2. Gilead Sciences signs 10-year $5.1 billion partnership with Galapagos NV (July 2019)
3. AbbVie Inc. agrees to buy Allergan plc for about $63.0 billion (June 2019)
4. Pfizer spends $11.4 billion to acquire Array Biopharma (June 2019)
5. Novartis spends about $1.6 billion for a group of drugs by acquiring a subsidiary of Boston-based IFM Therapeutics (April 2019)
6. Merck partners with Eisai Co. Ltd. to develop and market the cancer drug Lenvima in a deal potentially worth up to $5.76 billion (March 2019)
7. Bristol-Myers Squibb agrees to buy Celgene for $74.0 billion (January 2019)
8. Takeda completes $62.0 billion acquisition of Shire (January 2019)
9. GSK enters an agreement with Boston-based TESARO, Inc. to bolster its oncology pipeline for an acquisition cost of $5.1 billion (December 2018)



Strategic Reasons for M&As

Drive Productivity and Synergies

a) Increase R&D pipeline productivity and opportunities to expand existing drug indications, especially in the oncology therapeutic area. Oncology has seen the greatest focus when it comes to new drug launches because of both the challenges and opportunities these medicines represent for development (1).
b) Need to find cost efficiencies through synergies derived from M&As and quickly expand and/or develop a company's market presence (either within a therapy class or by geography).

Fund Portfolio Shifts

c) Shift to specialty medicines, especially in the areas of large molecules, biosimilars, genomic-based therapies (often targeted personalized medicines), and/or orphan drugs treating rare disease populations; traditional small molecule target opportunities have become heavily genericized and lack economic viability for continued development (1). The shift to specialty medicines coupled with advances in medical technology also fuels the need for continued innovation and the launch of new active substances to address continuing significant unmet medical needs.
d) Drive to find more value-based drugs (showing improvements in health and economic outcomes) as payers, providers, employers, and patients express greater concerns over affordability and access of new medicines (1).

Build Capabilities

e) Pressure to counter the trend of the increasing cost and risk of pharma R&D (2), as clinical and economic endpoints needed for commercial success become more challenging to attain (3, 4), and requires the building of internal capabilities through M&A activity to affect economies of scale (size) and scope (diversity of a firm's development efforts) that can improve R&D productivity (5). Recent analysis of clinical development success rates for investigational drugs clearly show significant increases in inherent challenges in bringing new drugs across all therapy classes, and especially in oncology (4).

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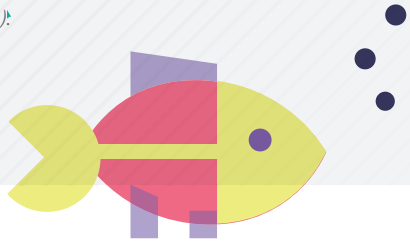

LOA calculation. Their research also calculated success rates from phase to phase. An overall key finding of their research is that clinical development success rates are lower than previously thought. This would provide a strong reason for M&A activity in oncology to bolster clinical success rates to try and overcome greater inherent risks of clinical trial failure.

Outcomes from previous research

There has been a good deal of empirical research in the academic business, economics, and scientific literature on the effects of M&A activity on pharma R&D productivity and shareholder value. Here, is an indication of general conclusions from a sample of prior research:

a) 2001 study (12): There is no relationship between economics of scale (size) and increasing the success probability of individual R&D projects among a sample of large pharmaceutical firms. However, there is a strong positive effect caused by economies of scope (diversity of a firm's development efforts). As noted by the authors, "Scope is confounded with firm fixed effects, however, suggesting an important role for inter-firm

Male			*Female*		
Lung & bronchus	76,550	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	321,670		All sites	285,210	

Table 2. Leading sites of new cancer deaths (2019). Estimates by gender.
Source: See reference 10. Percentages represent a fraction of all new cancer cases.

differences in the organization and management of the development function." Economies of scope is likely to play a greater role in the success of M&As driven to improve oncology R&D productivity – given the nature of cancer research and cross-fertilization of ideas across sites.

b) 2005 study (13): There is a strong positive effect of a firm's overall experience for larger and more complex late-stage trials. Products developed through an alliance have a higher probability of success in phase II and III trials – and if the licensee is a large firm.

c) 2007 study (14): Acquisitions create shareholder value but not mergers (though mergers do not diminish value). The effect of acquisitions varies depending on whether the target is based in the US, or elsewhere.

d) 2007 study (15): In general, no value creation (using three performance measures – research productivity, return on investment, and profit margin) was found from M&A activity on a sample of large pharmaceutical M&As and independent non-M&A rival firms.

e) 2007 study (16): Controlling for merger propensity, large firms that merged experienced a similar change in enterprise value, sales, employees, and R&D, and had slower growth in operating profit, compared with similar firms that did not merge.

"Relying solely on a company's internal R&D portfolio without M&As will likely not be sufficient to achieve strategic objectives over the long run."

f) 2010 study (17): Reducing late-stage (phase II and III) attrition rates and cycle times during drug development are among the key requirements for improving R&D productivity. Investments in drug discovery and early clinical development, from target selection to clinical proof-of-concept, are essential to increase R&D productivity. Transforming biopharmaceutical organizations into a fully integrated pharmaceutical network will allow for funding the number and quality of pipeline assets.

g) 2016 study (18): This academic-style and extensively-research working paper analyzing pharma mergers affecting European product markets found negative effects post-merger of patenting and R&D expenditures for the merged entity but also among non-rivals. This result is consistent with the majority of prior empirical studies they reviewed that found negative effects of mergers on

Industry Perspectives

With Aditya Bhandari, Axtria Principal, and his team member, Rashi Thaper

What is – and will be – driving current and future M&A deals?

R&D is diverse and requires heavy investment. Organizations look for mergers that can save time and money, ultimately leading to a better return on investments. It takes approximately $2.6 billion to develop a new drug and most of this cost is incurred due to a very high failure rate, with 90 percent of drug development costs attributed to clinical trials that do not reach the market (1).

Most large pharma companies manage their product portfolio by organically working on a pipeline of drugs and/or engaging in M&A activities. Since a significant portion of drug development is done by emerging specialty pharma and biotech companies, these are lucrative targets for large pharma companies. For example, AbbVie's acquisition of Allergan for $67 billion allowed it to bypass the risky process of R&D as it faced the loss of patent protection for Humira (2).

Also, research-patenting adds to the crowded R&D M&A space. If the research methods that are required are patent-protected by another organization or institute, this will necessitate an M&A.

Do M&As improve R&D productivity?

M&As allow large pharma companies to acquire small, innovative, specialty pharmaceutical and biotech companies to enrich/complement their product pipeline and solve the classic patent-cliff problem. M&A drivers include the constant need for innovation and enhancing the value (knowledge/technology) base of the organization to stay ahead of the competition.

On the other hand, there are theories suggesting that innovation intensity goes down after M&As due to a reduction in an entrepreneurial, innovative, and agile environment. Bain & Co. research shows that pharma companies spent an average of $1.1 billion to develop and launch a new drug in the late 1990s (3). A decade later, that investment doubled to $2.2 billion. At the same time, R&D productivity, measured by the number of new molecular entities and biologic license applications per R&D dollar spent, declined by 21 percent a year. Also, analysis suggests that the likelihood of R&D success when large pharma companies are involved is comparatively higher.

Thus, to say that M&A by itself ensures R&D productivity may not be entirely true. The road to a successful M&A is paved with many factors, which, if orchestrated well, shall boost R&D productivity. However, if this equation is not balanced well then it may transfuse risk to the broader portfolio and prove to be detrimental.

Do M&As increase shareholder value?

At first, an M&A usually decreases the shareholder value as skepticism takes over for the short-term – usually until 2-3 years from completion of the deal. One example from 2018 is Takeda's sinking valuation after it disclosed its interest in acquiring Shire, with a market cap of $40.79 billion on March 27, 2018, just before the interest announcement to $26.33 billion on December 28, 2018, prior to the announcement of the deal closure (4, 5). However, the trend prior to this announcement event was already downward, so how much the Shire interest announcement and subsequent deal negotiations contributed to further declines in Takeda's market cap over time is up for debate and empirical analysis (6).

However, other M&A examples reflect significant growth in shareholder value, such as Roche & Genentech, Merck & Schering Plough, and Sanofi & Aventis (7). However, this question is hard to answer without looking at the deal value, asset portfolio, management ability to synergize different teams, optimally planning portfolio launch, loss of exclusivity, etc.

What kinds of analyses should companies conduct when considering M&As to increase the probability of such deals improving R&D productivity and increasing shareholder value?

The correct valuation of the assets being acquired and its impact on stock prices holds high importance. Large pharma companies have dedicated teams that continuously evaluate various targets and synergies between assets. Detailed analysis needs to be done on the following aspects:

1. Identification of the best deals that blend well with the current resources of the acquiring company and align with strategic goals.
2. In-depth analysis of both portfolios and a compatibility check.
3. Evaluation of the value that can be unlocked from the combined resources of both companies and calculation of metrics defining the rate of return of the deal.

A deep-dive into all of the above parameters will help with improving the predictive accuracy of the success of the deal and the final go/no-go decision.

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innovation in the merged entity.

h) 2017 study (19): This study noted that the prior literature on the relationship between mergers and R&D productivity is mixed. Their study of more recent large pharmaceutical mergers found a statistically significant increase from mergers on R&D productivity. They point to two factors as critical in driving R&D productivity: depth of scientific information and objectivity of decision-making based on that information, both of which could be expected to increase because of a merger.

Scale versus scope

Economies of scale says the average total cost to produce a drug decreases as more volume is produced. Traditionally, the pharmaceutical average total cost curve (total fixed cost + total variable cost)/volume starts off high because of the high total fixed costs relative to low volume. However, this then quickly drops as volume increases until it flattens over a large, relevant production range of output. It is possible the average total cost curve increases at very high levels of output due to diseconomies of scale (e.g., higher total average costs caused by logistical and administrative problems when running an extremely large organization – and other costs – due to size). However, generally in pharmaceutical production and cost theory and practice, we do not see the effect due to diseconomies of scale.

Economies of scope, on the other hand, say that the average total cost of a drug decreases with a greater variety of drugs produced from the same inputs. This is where "diversity" of the R&D portfolio enters and becomes critical – where resources under scope

"Overall, the research literature is very mixed on the effect of M&As on R&D productivity and shareholder value."

	Phase 1 LOA	Phase 2 LOA	Phase 3 LOA
Oncology – All indications	6.7%	10.5%	37.0%
Oncology – Lead indications	13.2%	19.1%	45.3%
Oncology – All indications by FDA classification	10.4%	16.2%	50.0%
Breast cancer	5.7%	8.4%	39.2%
Non-small cell lung cancer (NSCLC)	5.7%	6.5%	21.7%
Prostate cancer	5.6%	7.8%	37.5%
Colorectal cancer (CRC)	5.1%	8.2%	38.5%
SPA or orphan drug oncology	23.0%	27.1%	44.4%

Table 3. Selected clinical development phase LOA for oncology investigational drugs
Notes: See the source article for the methodology to derive each of the selected clinical development Phase LOA. LOA means "Likelihood of Approval" and SPA means "Special Protocol Assessment" (11).

"The challenges for pharma companies are making the right targeting decisions for M&As and tactically ensuring such deals achieve strategic goals."

can be complementary to each other that are then used to generate novel medicines. There are numerous famous drug development examples; consider the discovery of Viagra for erectile dysfunction, which was the result of a cardiovascular study for the treatment of hypertension and angina pectoris; the creation of Viagra was an unintended effect. This type of discovery has been repeated many times in the history of pharma R&D discovery.

Further, the nature of oncology development and the building of new indications is likely more consistent with scope than scale (mere size). We see this in firms trying to create highly diversified oncology portfolios to gain economies of scope rather than economies of scale. This effect is also consistent with the fact that many drug discoveries are the result of serendipitous events. So, building R&D portfolios where the resources and clinical trials are more complementary to each other will more likely increase R&D productivity than simply having more (size) of the same resources.

Overall, the research literature is very mixed on the effect of M&As on R&D productivity and shareholder value. However, two effects do continually stand out in the literature: the role of economies of scope (developing a diversity of R&D expertise), and fixed-firm effects, meaning that M&A effects can be dependent on firm-specific attributes. The remarks from the 2017 study mentioned above echo these key findings and would explain, for example, the depth by which recent pharma mergers have taken to delve into the oncology therapy area to build scientific expertise and expand product franchises through additional clinical indications. This effect is also consistent with prior research that noted economies of scope as a more important driver of R&D productivity than economies of scale (size). Lastly, this study affirms the effect of firm-specific decision-making, which can be affected by an array of attributes, such as organizational network design and the role of analytics in helping to improve objectivity in decision-making, on the relationship of mergers and R&D productivity and shareholder value.

The importance of M&As

The preceding analysis highlights the importance that M&As will have on the future performance of pharma companies. M&As will be required to achieve strategic objectives by augmenting and/or complementing existing company R&D pipelines as the risks and costs of developing new innovative medicines increase over time. The challenges for pharma companies are making the right targeting decisions for M&As and tactically ensuring such deals achieve strategic goals.

As closing remarks, pharma executives should consider the following when contemplating M&As:

a) Taking into consideration all the instrumental factors for an M&A, a well-evaluated and orchestrated M&A is an essential instrument for pharma companies to increase R&D productivity and shareholder value over time. Having said that, a poorly planned M&A has equal probability to increase disruptions and prove counterproductive. Thus, detailed examination of the M&A

will help shift the scales in the right direction.

b) Relying solely on a company's internal R&D portfolio without M&As will likely not be sufficient to achieve strategic objectives over the long run.
c) Companies must improve on their therapy class target selection as a starting point for further development, and then seek out the right company targets to satisfy R&D objectives. This means building strength and expertise in selected therapy areas, and realigning your portfolio to the winning agents you find – which are generally found outside the company.
d) Companies are increasing their focus on oncology and rare diseases for further development for a variety of reasons; companies should use M&A to seek out areas of competitive advantage in an increasingly crowded field. However, M&As must not be seen as building "brands" but rather "franchises" based on increasing the indications from a single drug approved for multiple uses. This will increase the return on R&D, while allowing companies to differentiate better their franchises in the market.
e) Point d) also means that companies must decide whether to use M&As to continue with the traditional approach to R&D portfolio development; for example in oncology, by focusing on late-stage cancers and extending the life of patients; or to instead target early-stage cancers in the hopes of finding a cure. AstraZeneca recently announced a change in their cancer R&D portfolio strategy to focus on early-stage cancers as a way to differentiate themselves from the competition (20).
f) The execution of M&As to achieve strategic objectives carries with it many risks and uncertainties, given the nature of limited information at the time of assessing an M&A deal. Analytics need to be employed to assess accurately future costs, revenue, and synergies expected.
g) One key conclusion from prior pharma empirical research is that economies of scope (advantages gained through building research diversity) are far more important on the ability of an M&A to increase R&D productivity compared to increasing economies of scale (size).
h) Finally, another key conclusion from prior pharma empirical research is the effect of firm-specific attributes in realizing gains or generating losses through M&As. As noted by one previous article, achieving success through M&As is acquired through experience gained and learned over time (5). A useful research project would be to review all pharma M&As for the purpose of detecting whether some companies do it better than others and why.

For the full references list, visit the online version of this article at www.themedicinemaker.com.

George A. Chressanthis is Principal Scientist at Axtria, Aditya Bhandari is Axtria Principal, and Rashi Thaper is a member of Aditya's team.

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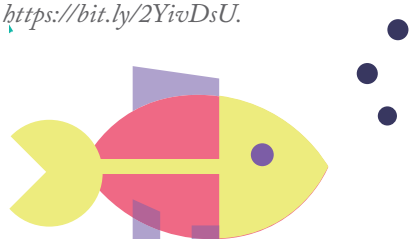

Signs of Success

By George A. Chressanthis, Aditya Bhandari, and Rashi Thaper

A recent article in The Wall Street Journal caught our attention, noting that the megadeals involving the Bristol-Myers Squibb acquisition of Celgene in November 2019 and the AbbVie acquisition of Allergan in June 2019 appear to have achieved their initial checkup toward eventual success (1). This is evidenced by the rebounding of share prices from their immediate post-deal declines, increasing pipeline success and new drug approvals from the FDA, strengthening and diversifying their existing portfolios, and building confidence with investors by moves made to pass regulatory hurdles (1-3).

But both deals are still in their early phases of execution. The companies involved must overcome several future elements of risk and uncertainty – both internal to each deal but also due to changing external environmental forces – to achieve long-term success. We look forward to hearing more about what executives and their operational teams did at both pairs of companies to achieve initial milestones of success, and how it affirms or rejects prior notions of the key drivers for M&A success.

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Going With Your Gut Instinct

Sitting Down With… Paul Peter Tak,
President and CEO at Kintai Therapeutics

What inspired your interest in the microbiome?

I've been interested in this field since before the term "microbiome" was coined. In the 1990s, I conducted research at Leiden University Medical Center on the role of microorganisms in the pathogenesis of rheumatoid arthritis (RA). We were the first to take biopsies from the target tissues of inflamed joints of patients with RA and other forms of inflammatory joint disease, and analyze them using 16s PCR. We detected microbial DNA in different forms of arthritis and predicted that it would be derived from the gut.

There were a few other things that I did after that, including working as a visiting scientist on sabbatical at the University of California, San Diego, being a Professor of Medicine and Head of a large academic department at the Academic Medical Center of the University of Amsterdam, and serving as Chief Immunology Officer and a Senior Vice President at GlaxoSmithKline. My move to industry was actually sparked when someone asked me about my impact on patients. Did I think I could have a bigger impact by treating hundreds or thousands of patients as a physician, or by developing medicines that may affect the lives of millions of patients?

I didn't work on the microbiome at GSK, but I've always remained interested in the field.

In your early career, did you have ambitions to become the CEO?

Absolutely not! Throughout my career, I was very much focused on the patients and the science. Even before joining the pharma industry, I had a reputation as a good physician – I received an award from the Minister of Health in the Netherlands for being the best rheumatologist, based on clinical work elected by my peers. But as well as being a professor and a physician-scientist, I also started my first biotech and enjoyed consulting for pharma companies.

How did you come to join Kintai Therapeutics?

During my seven years at GSK, I learned a lot about leadership and drug discovery and development. It was a very positive experience, but I liked the idea of joining a smaller, more entrepreneurial company and learning more about the business. I was particularly drawn to Boston, Massachusetts, which is currently the capital of the biotech world. I researched many companies and found Kintai Therapeutics. Kintai is applying gut microbiota knowledge to design small molecule-based therapeutics for various disease areas, including obesity, chronic kidney disease, oncology, and neurology.

How has research into the microbiome accelerated in recent years?

Each of us have about three pounds of microorganisms living in our gut. It can almost be considered as an organ but it has largely been ignored as a source of drug discovery. Moreover, when developing drugs, we don't just need to look at how the drug is cleared or metabolized by the kidneys and liver, but also how it may be altered by the gut microbiome. In recent years, the scientific community has realized that the microorganisms inside of us are important for many conditions and diseases, and can also affect how we respond to medicines; there have been a number of high impact publications in this field. However, translating microbiome science into therapies is a complex challenge because we harbor so many different microorganisms with variation in different parts of the gut.

Kintai has a lead candidate that focuses on obesity – why?

Obesity is an area of enormous unmet need. Research published in the New England Journal of Medicine estimated that by the year 2030, 50 percent of the US population will be obese. Obesity leads to other health issues, such as type 2 diabetes and cardiovascular disease, and is also a strong risk factor for cancer and unfavorable outcomes in COVID-19. However, it has proven highly difficult to develop safe anti-obesity medicines that induce distinct weight loss and have beneficial effects on other aspects of metabolic syndrome, such as glucose tolerance, hyperlipidemia, inflammation and liver health. Safety is also crucial – if a medicine is approved for treating obesity, it has the potential to be used in very large patient numbers. Many anti-obesity drugs fail because of safety.

KTX-0200 is a small molecule anti-obesity treatment. We can't reveal the mechanism of action here, but I am pleased to say that preclinical results have been consistently promising, showing that it can drive weight with improvement of all other features of metabolic syndrome.

Why focus on small molecules, as opposed to live biotherapeutics?

The growing research on the microbiome has opened up a new world of drug discovery, but ultimately it's important to turn this research into something that can be developed in a straightforward, safe and consistent way. The microbiome can almost be seen as a black box. There is still a lot that we don't know, and if we want to use actual microorganisms as treatments then there are many different complexities to consider, ranging from manufacturing, to CMC, to regulations.

At Kintai, we are inspired by the human microbiome. The microorganisms that dwell in our guts produce many small molecules that are critical to maintain health and fight disease. By studying the microbiome in relationship to the gut immune system and the enteric nervous system throughout the gut, we have developed a new class of medicines, called precision enteric medicines (PEM compounds), that are activated in a specific region of the body, under the influence of enzymes that are produced by microorganisms. Effectively, we are developing small molecules that can replicate the positive effects that microorganisms have on human biology. Small molecules, after all, are well understood by the industry and its regulators, and are more straightforward to develop.

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