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Meet The Small Molecule Manufacturer!

It might seem that large molecules and advanced therapies are all the rage, but the vast majority of pharmaceutical products on the market are small molecule drugs, as are many of the drugs on the WHO's list of essential medicines. We believe small molecules should get the recognition they deserve. And that's why we have launched a new publication called The Small Molecule Manufacturer.
You can find out more about The Small Molecule Manufacturer at: http://tmm.txp.to/0519/MeetTSMM

Follow our Brexit coverage online...

On page 38, we feature an interview with Frithjof Holtz, head of Merck Life Science's Brexit mitigation project, who discusses how Merck has been preparing for a no-deal Brexit – a subject also covered in this month's editorial. The Medicine Maker has also been developing exclusive online Brexit content.
For a bite-sized version of our latest article, check out Deputy Editor James Strachan's Twitter thread: twitter.com/j_strachan_edit
And you can find a narrated animation of our last Brexit article on the challenges faced by drug developers here: tmm.txp.to/brexitanimation

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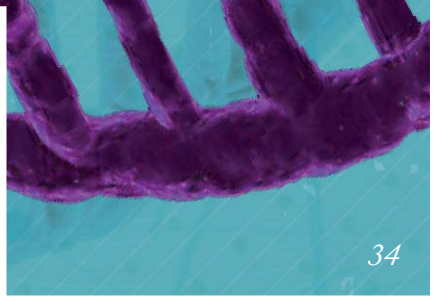

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ISSUE 55 - JULY 2019

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Distribution:
The Medicine Maker (ISSN 2055-8201), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK.
Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com)
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Are You Suffering from Brexit Fatigue?

The uncertainty surrounding the UK's future with Europe is having a measurable effect on the pharma industry (and many others). But I'm afraid to say the end is nowhere in sight.

Last month marked three years since the UK voted to leave the European Union. A great deal has happened in British politics in those three years and yet, the more things change, the more they stay the same. We still do not know how the Brexit process will end – but it's not looking great.

As Steve Bates, CEO of the UK BioIndustry Organisation, said in June, the risk of "no deal" has risen in recent weeks (1). Parliament has rejected the Withdrawal Agreement (WA) on three occasions; EU leaders have made it clear that there will be no renegotiation of the WA, nor will they consider another Article 50 extension for the purpose of reopening negotiations on the WA. Meanwhile, both candidates for Prime Minister have promised to renegotiate the WA and, if the EU isn't forthcoming, to leave the EU on October 31 without a deal.

Given these facts, no deal looks more likely than ever. And you would be forgiven for adopting a "let's just get it over with" mindset, when faced with the negative impact that uncertainty is having on pharma. A stark example: the Department for International Trade's inward investment results show a 41 percent drop in new Forein Direct Investment projects and a 45 percent drop in new jobs created in the UK biotechnology and pharmaceutical sectors over the past three years (2).

But I'm afraid to say that no deal wouldn't be the end of it. After the fallout, both sides would be back at the negotiating table, except this time a deal would need to be unanimously ratified by the entire EU27 – including all regional parliaments. And even if the WA is signed before the new October 31 deadline, it says little about what the UK's final relationship with the EU might look like. A reasonably hard brexit is still a possibility after the two-year, standstill "transition" period.

On page 38, Frithjof Holtz discusses how Merck has been preparing for no deal. He says that "everything remains constant" following the extension – and, even if the deal is signed, they will still be preparing for big changes. I think that is the right attitude. Brexit is a process, not an event; though the coming months will be the most important so far, vigilance is a must. The industry must be ready for the long haul.

James Strachan
Deputy Editor

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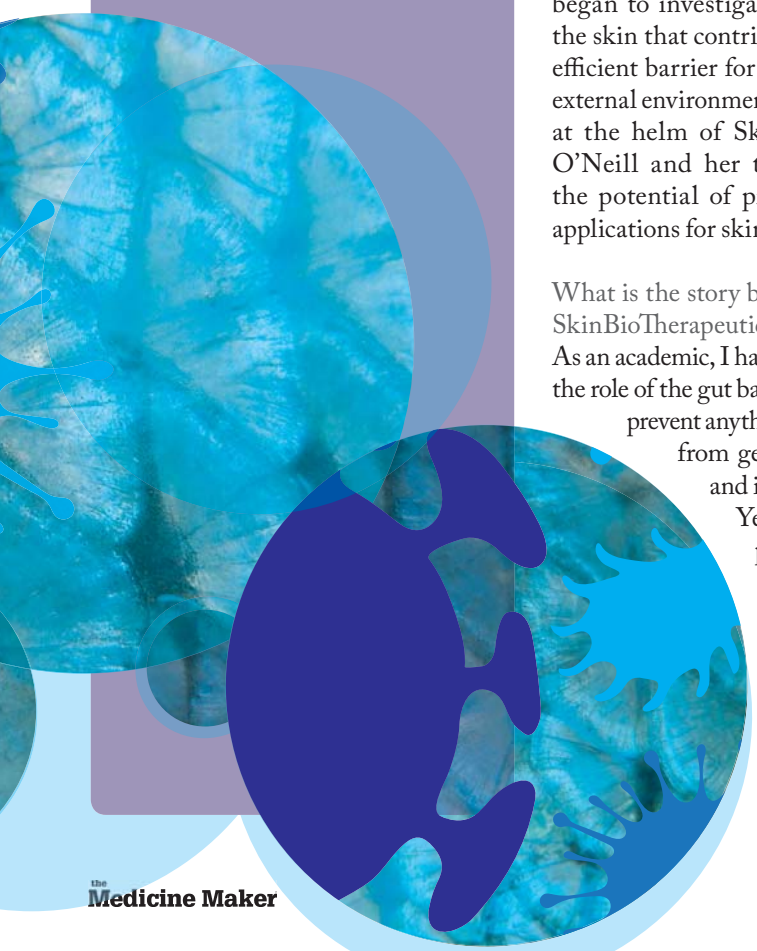
Upfront

Reporting on research, personalities, policies and partnerships that are shaping pharmaceutical development and manufacture.

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com



Solutions In… the Skin-Biome

Harnessing the power of the microbiome – and the skin-biome – could lead to new therapeutics, particularly for skin deep problems…

We have all heard of probiotics. These defenders of the gut environment have been shown to assist in wound healing, preventing infection and strengthening our gut barrier. But the role of these "good" bacteria doesn't begin and end in our bowels as these microbes carry out equally applicable activities on the surface of the skin. Catherine O'Neill, CEO of SkinBioTherapeutics and professor of Translational Dermatology at the University of Manchester, UK, began to investigate the structures in the skin that contribute to making it an efficient barrier for the body against its external environment 15 years ago. Now, at the helm of SkinBioTherapeutics, O'Neill and her team are exploring the potential of probiotic bacteria in applications for skin health and disease.

What is the story behind SkinBioTherapeutics?

As an academic, I had a historic interest in the role of the gut barrier and its ability to prevent anything toxic or infectious from getting across the gut and into the bloodstream. Years of research has proven the integral role of bacteria in strengthening the barrier function in the gut and, given this link, it wasn't a huge leap to question whether the skin microbiome might also participate in the skin's barrier function!

My team and I were able to identify a particular bacterium that had positive effects in skin models at my lab at the University of Manchester. SkinBioTherapeutics was then set up to develop this bacterium, Skinbiotix, as a therapeutic for skin in health and disease.

When we began we could only make a tiny amount of Skinbiotix in a test tube in my lab. We've now shown that we can scale it up and manufacture it with a third party and we've formulated it into a cream.

What applications does Skinbiotix have?

Skinbiotix is a lysate (extract) of a probiotic, which improves the barrier function, accelerates wound healing and also prevents infection from Staphylococcus aureus, the most prevalent pathogen that affects skin. Our Skinbiotix technology does not use live bacteria due to potential safety concerns and it is easier to formulate an extract.

Our therapeutic is being developed for the treatment and prevention of eczema, which affects 20 percent of the pediatric population in the West. Due to its weak barrier, eczematous skin can be frequently infected with S.aureus, so our technology could be very effective in the treatment of this condition.

Earlier this year, we were able to demonstrate Skinbiotix's safety and tolerance in a large patient group. The results of this human study will allow us to begin to optimize our technology and develop formulations better suited to different patient demographics. There are also other skin conditions that our technology could potentially be used for, such as cosmetic applications and as an anti-infective.

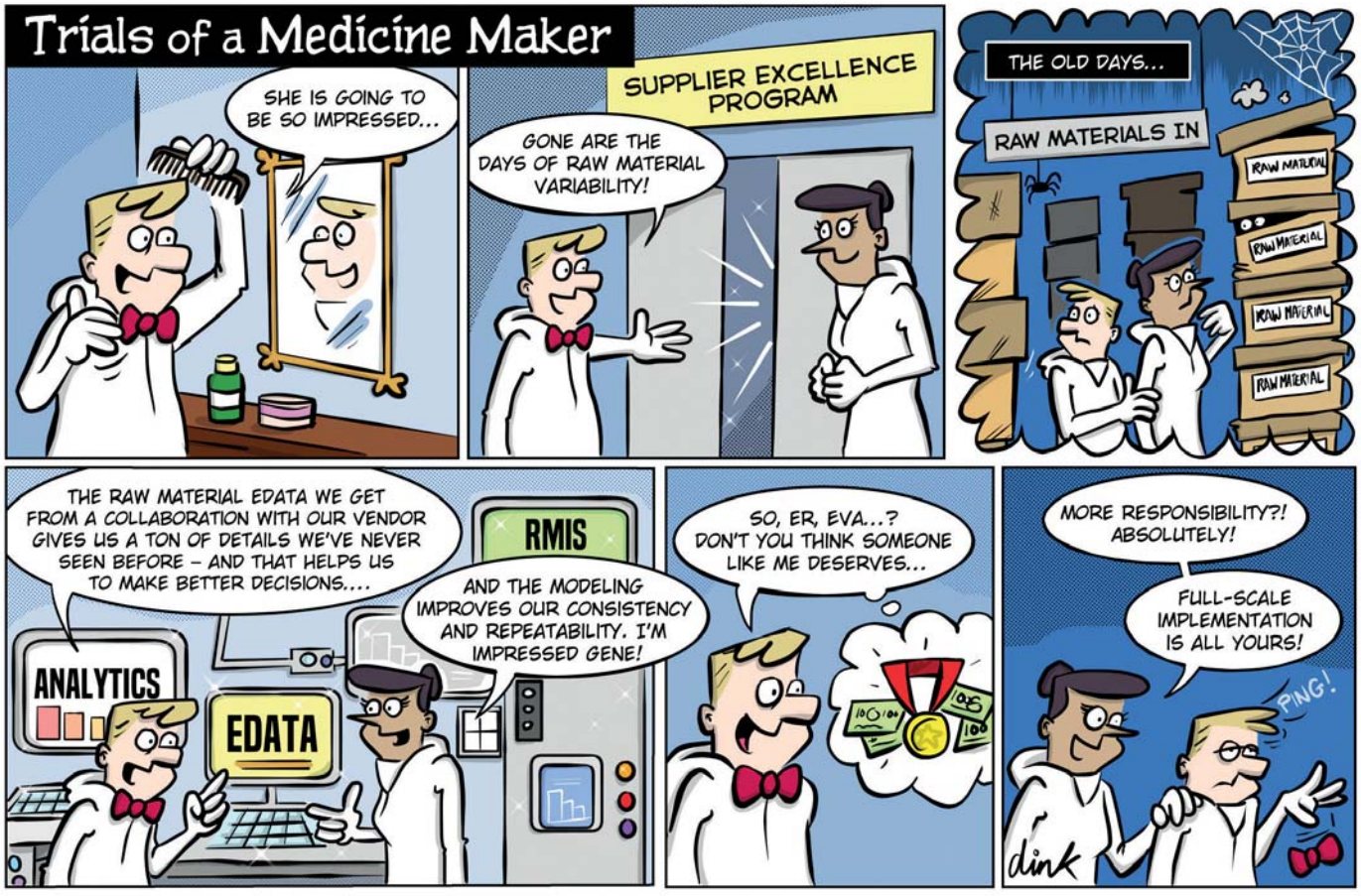
The pharma industry is now beginning to exploit the gut microbiome for novel therapeutics. Can the same be said when it comes to the skin-biome?

Our current understanding of the skin-biome is about 30 years behind that of the gut, but the work in this area is definitely growing. We're only at the beginning of our journey with commensal communities of the skin and the opportunities to help patients living with a variety of skin conditions are waiting to be discovered!

What are your aspirations for the company?

The human microbiome is a factory that constantly makes many interesting chemicals, some of which could be beneficial for the skin or other areas of health and disease. My aspirations are to continue to develop microbiome-based technologies that have the potential to bring new therapeutics to patients.

For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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A Smarter – and Synthetic – Workflow for Bioengineering

Can artificial approaches trump the conventions of traditional organic synthesis for the production of raw pharmaceutical products within cells?

Researchers at Japan's Kobe University have developed an integrated synthetic biology system that supports a more environmentally friendly approach to the synthesis of raw pharmaceutical products within microbes. Using a Design, Build, Test, Learn (DBTL) workflow (a pipeline for the discovery and optimization of biosynthetic pathways), the team constructed novel metabolic pathways and enzymes within cells that could be systematically optimized for the production of larger volumes of pharmaceutically relevant compounds (1).

The project was carried out in collaboration with NEDO, a Japanese organization that funds many green research projects focusing on energy and industrial development. The Kobe group is leading NEDO's Smart Cell Project, with a goal of developing adaptable cell factories for the production of diverse industrial materials. Using biological systems to produce industrial chemicals is more sustainable when compared to traditional chemical processes, but the current range of possible bioproduction targets is limited by known enzyme functions. Their recent report shows that it is possible to engineer new enzyme functions that can expand production capabilities towards new types of valuable chemicals.

"In this particular study we produced reticuline, a plant alkaloid and a key intermediate in the production of pain medications," explains Christopher Vavricka, Assistant Professor in the laboratory of Tomohisa Hasunuma, a professor at Kobe University. "Previously, alkaloid intermediates like reticuline, and its precursor tetrahydropapaveroline (THP), have been produced using microbes and were unable to be produced at commercially viable levels."

One barrier to large scale THP production is the relaxed specificity of monoamine oxidase (MAO) to the substrate dopamine. Using the predictive software, M-path, the Kobe team was able to identify an enzyme found in insects, which could bypass the issues associated with MAO. The researchers then used structure-based enzyme engineering methods to identify key amino acids in the silkworm enzyme, called 3,4-dihydoxyphenylacetaldehyde synthase (DHPAAS), and produce their own artificial DHPAAS, which could be used to improve production of the key alkaloid intermediate THP.

"We want to reach the point where we are able to produce reticuline at industrial levels; however, our current titers are still at the milligram per liter level. Therefore, we need to carry out more DBTL cycles with the goal of increasing production titers to the gram per liter level," says Vavricka. The research team also wants to accelerate the entire process by increasing throughput and automation, but it may take some time to reach such a milestone. "Many experimental skills are an art that cannot be taught to machines any time soon," adds Vavricka. "However, the handcrafted art of an experienced scientist is often slow and unpredictable. I hope the systematic and high-throughput approach of synthetic biology will speed up the development of applied biotechnology and help push science closer to its full potential."

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Playing for Change

The game "Tumor Quest" seeks to improve people's understanding of cancer

What?
Tumor Quest is a free game where players match three or more mutations associated with a tumor type to make them disappear. The aim is to help engage players in how tumor-specific and tumor-agnostic targets are helping to tackle cancer. The game was launched in time for the American Society of Clinical Oncology (ASCO) conference and allows its users to select from three different paths: nonspecific, tumor-specific or tumor-agnostic. To help build its users' understanding of the various tumor types implicated in cancer, the game is accompanied by a short, yet informative, animation.

Why?
Getting people to talk about tumors and biomarking isn't the easiest task in the world – and so, public awareness around personalized treatment types is low. Advances in science and technology are helping to uncover the underlying genetic causes of cancer, and the gaming platform aims to keep a wider audience informed.

Who?
The game was developed by Roche's Genentech. It isn't the first time the Roche Group has used creative approaches to reach out to the public to help boost awareness. Roche has also created animations, comic strips and podcasts to investigate new ways of engaging with the public and patients on science and medicine.

Where?
You can check out the game at https://bit.ly/2xazv21.

Business in Brief

Scouting for new leadership, prices hikes and successful acquisitions. What's new for pharma in business?

Appointments

- Despite abolishing a rule that prevented CEOs running the company past the age of 65, Merck Sharp & Dohme is now seeking a replacement for longstanding leader Ken Frazier, who is set to leave the company ahead of his 65th birthday in December. Frazier, who joined the company over 25 years ago, served as its CEO for 11 years. He oversaw a period of massive growth, with drugs, such as Keytruda, gaining regulatory approval and pushing sales past the $7 billion mark. Though there has been speculation as to who will fill Frazier's shoes, no official statement has been issued by MSD.
- Sanofi has hired Paul Hudson to be the company's new CEO. Hudson will replace Olivier Brandicourt, who left the company for early retirement. Hudson, a British pharma executive, was a former executive at Novartis and will take the reigns at Sanofi from September 1.

Pricing

- As US Congress calls for caps on the price of insulin, Eli Lilly has launched Lispro, a generic version of Humalog with a list price of $137.35 per vial. The drug is 50 percent cheaper than its counterpart.
- The UK's Competition and Market Authority (CMA) has cast blame on four UK pharmaceutical companies (Alliance Pharma, Focus, Lexon and Medreich) for pushing up the cost of prochlorperazine, an anti-nausea drug often used for the treatment of patients undergoing chemotherapy. The price paid by the UK's National Health Service for the anti-sickness drug shot up by 700 percent (from £6.49 to £51.68 per pack) when the companies allegedly made an agreement against competition. The annual costs incurred by the NHS increased from around £2.7 million to £7.5 million during 2013-2018. According to the CMA, the agreement prevented rivals to Alliance Pharma from entering the market, driving up the cost of the drug. If the CMA investigation unveils unlawful conduct, each company could face a 10 percent financial penalty on their worldwide turnovers.
- Novartis has set the price tag for Zolgensma (a gene therapy for the treatment of pediatric spinal muscular atrophy) at a record-breaking $2.1 million. As a result, some industry watchdogs and patients, have questioned whether companies are out of control in their attitudes toward drug pricing. Novartis claims that it used "value based pricing frameworks to price Zolgensma at around 50 percent less than multiple established benchmarks including the 10-year current cost of chronic SMA therapy."

Regulation & Approvals

- The FDA has selected four industry partners to participate in its latest Drug Supply Chain Security Act (DSCSA) pilot program. IBM, Merck, KPMG and Walmart have been invited by the regulatory agency to help create a blockchain network for the US market. The collaborative project will see the industry develop a system capable of identifying and tracking prescription medicines and vaccines in real-time.
- Five months after receiving approval from US regulators, Lynparza, a PARP inhibitor for the treatment of ovarian cancer, has received approval in Europe. The EU approval was based on a study in which Lynparza showed a 70 percent reduction in the risk of disease progression or death in patients with BRCA-mutated ovarian cancer.

Facilities

- Catalent is set to acquire Bristol-Myers Squibb's manufacturing and packaging facility in Anagni, Italy. The facility is used for the manufacture of oral solid dose forms, biologics and sterile products. Upon the acquisition of the facility, Catalent will continue to produce the products in Bristol-Myer Squibb's current portfolio. The handover is anticipated to be completed by the end of the year, provided that regulatory approval is gained and other closing conditions are met.
- LSNE has purchased its first European site for the manufacture of sterile drug products. The CDMO currently owns four stateside facilities, but chose to buy the Spanish facility to help manage its growing client base in Europe. The site, based in León, Spain, has been inspected by both the FDA and Spanish authorities and can serve both the US and EU markets. The newly acquired site will add prefilled syringe, ophthalmic and sterile bulk lyophilization capabilities to LSNE's repertoire and help support commercial-scale lyophilization.

The Road to Interoperability

The FDA has accepted TraceLink's blockchain and digital recall project into its DSCSA Pilot Program

TraceLink has been approved to join the FDA's Pilot Project Program, which aims to support drug supply stakeholders, including the FDA, in developing interoperable electronic systems capable of tracing Rx drugs through their distribution. Projects will begin in August 2019, and the FDA plans to publish a report based on the findings to help solve challenges associated with the current pharmaceutical supply chain and protect consumers against counterfeit medications.

TraceLink entered a submission focused on two workstreams: an interoperable blockchain network solution called Trace Histories, and digital recalls. Both are intended to bring together companies from across the pharmaceutical supply chain.

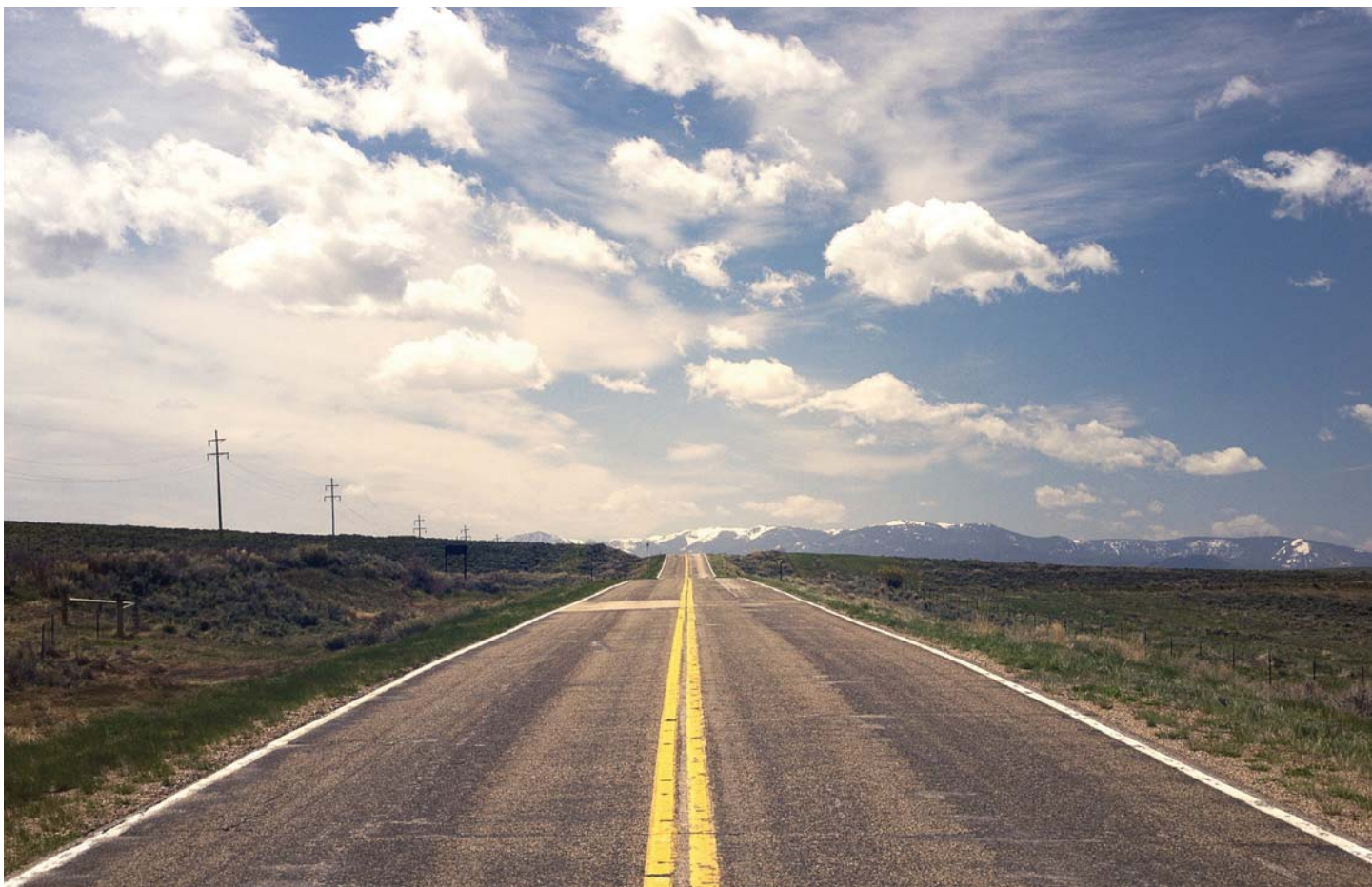
"We are interested in the power of blockchain because of its ability to provide secure, immutable methods of information sharing across the industry. The Trace Histories workstream will explore the validity of using blockchain technology in a revolutionary way, which enables participants to post and share necessary compliance information on the blockchain while simultaneously safeguarding confidential business information." explains Paul Cianciolo, Senior Vice President, Business Management at Tracelink.

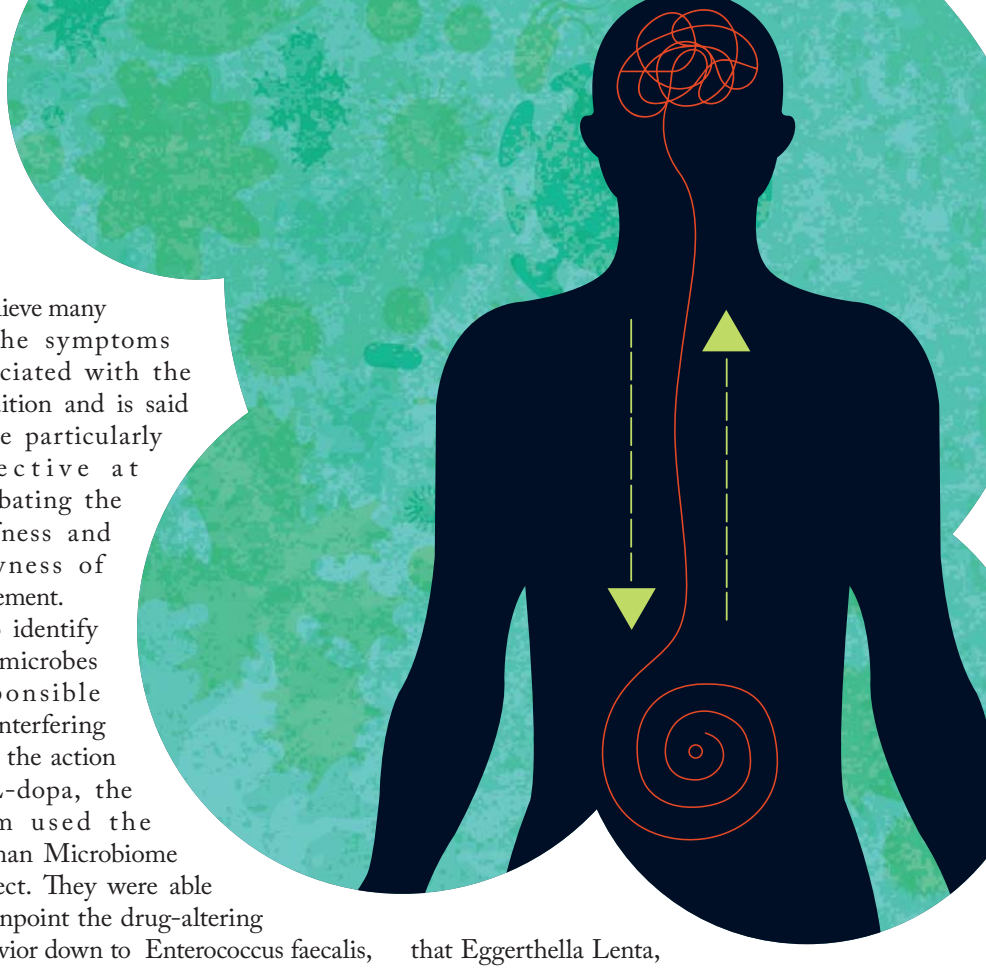
The second workstream focuses on digital recalls."Recall verification and notification is a notoriously challenging issue across the pharma and healthcare industries," says Cianciolo. "The lack of granularity (scale of detail in a dataset) associated with the products in a supply chain, the existence of information silos and the absence of a dedicated network to distribute recall events all contribute to the inefficiency of the recall process."

In other words, a recall from a pharmaceutical manufacturer may currently have difficulty reaching the hospitals, pharmacies and patients in possession of affected products.

The digital recalls workstream will evaluate effective methods of data exchange and coordinate with industry stakeholders to prevent recalled product from reaching patients.

"Combining insights from these leading companies with TraceLink's digital supply network and solutions will garner compelling information that will contribute to the innovation, security, and interoperability of the supply chain."





Attack of the Drug Eaters

How do we battle the bacteria in our gut that may stop medicines from working as well as they should?

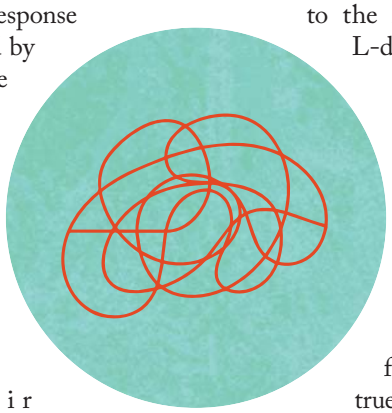
Research at Harvard University has shown that the commensal communities of bacteria in our gut are able to interfere with levodopa (L-dopa) – a commonly-used drug in the treatment of Parkinson's disease (PD). The work highlights the role of the microbiome in the efficacy of drug metabolism (1).

PD attacks neurons responsible for the production of the neurotransmitter, dopamine. As this crucial chemical is lost, patients with the condition can suffer from symptoms such as tremors, speech changes and the rigidity of muscles.

"Previous findings had indicated that the gut microbiota was capable of metabolizing and changing the chemical structure of the PD medication, L-dopa. This led to the introduction of carbidopa, a drug to block L-dopa metabolism, to the market," says Emily Balskus, Professor of Chemistry and Chemical Biology at Harvard University. "We have identified a specific microbe in the gut that chemically alters L-dopa, preventing it from having the intended effect in some of the PD patient population."

L-dopa is used to replace the dopamine lost in PD and can be used as a treatment option at all stages of disease progression. It is relied upon by patients for its ability to relieve many of the symptoms associated with the condition and is said to be particularly effective at combating the stiffness and slowness of movement.

To identify the microbes responsible for interfering with the action of L-dopa, the team used the Human Microbiome Project. They were able to pinpoint the drug-altering behavior down to Enterococcus faecalis, a Gram-positive inhabitant of the GI tract and its enzyme, PLP-dependent tyrosine decarboxylase. "Between 1 and 5 percent of L-dopa actually reaches the brain, so the variability in response to the drug caused by the gut microbiome is a huge issue which greatly impacts patients' quality of life and the relief they experience from taking the drug," explains Balskus.



While their discovery was exciting, the team were more intrigued by the fact that L-dopa's action was not completely blocked by carbidopa. Maini Rekdal, the lead researcher and first author of the paper outlining their results, speculates that carbidopa may be unable to penetrate E.faecalis cells. The team have, however, identified a molecule that exhibits inhibitory effects against PLP tyrosine decarboxylase. Futhermore, they found that Eggerthella Lenta, a gut acintobacterium, consumes dopamine produced by L-dopa decarboxylation to generate a product called meta-tyramine that could contribute to the fluctuations in efficacy of L-dopa seen in patients.

Though their work solely focused on the role of the gut microbiome on the metabolism of L-dopa, the scope to explore additional facets of the gut microbiota is immense. The bacterial communities of our guts represent a new frontier to be explored as the true impact of them on our health has yet to be discovered.

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Cutting Out the Middleman

Proposed legislation could offer patients in China the opportunity to purchase cell and gene therapies directly from hospitals, but it could also leave regulators out of the equation...

With China's capacity for cell and gene therapy (CGT) research expanding at a rapid rate, the country is keen to expand access as much as possible. A draft proposal from the Chinese health minister aims to allow elite hospitals to sell CGTs without the seal of approval typically required from regulators. 1400 Chinese hospitals that provide specialist care and conduct medical research will have the chance to apply for a specialist licence enabling them to sell CGTs to patients after proving their competence in processing these therapies and conducting clinical trials. Hospitals and companies who fail to obtain the licence would still have to receive approval from the China Food and Drug Administration (1).

The proposed legislation represents a u-turn from previous thinking. After the death of a student in 2016, the country took heavy measures to ensure that unapproved CGT products could not be sold. The student, who suffered from a rare form of cancer, paid over $30,000 for an immunotherapy, which ultimately resulted in their death. Prior to this, the sale of CGTs went unregulated, giving many hospitals across the country the opportunity to sell them despite ongoing safety and efficacy testing. The restriction imposed by the government sought to protect patients from adverse, and even fatal, outcomes but as also led to a decrease in the number of patients participating in clinical trials.

The new draft policy has been met with mixed reviews. Though some within the Chinese scientific community support the proposal, citing its potential to put patients in control of their own health and bolster the clinical trial process, others are more skeptical about the inadvertent sale of dangerous therapies.

In early June, the International Society for Stem Cell Research (ISSCR) released a statement requesting that China abandon its plans (2). A three page letter was sent to Jiao Hong, Diretor at the National Medicinal Products Administration outlining the group's concerns. The letter cites safety, efficacy, the lack of preclinical studies and regulatory scrutiny as points of contention for ISSCR, which has over 4000 international members. The organization also expressed it concerns about the Chinese healthcare system being exposed to undue harm upon the implementation of the proposed guidelines.

Internationally, regulators are taking a more active stance on the regulation around unproven CGTs. The group has encouraged China to take a similar position in an effort to harmonize standards on the issue and has made it plainly clear that they oppose China's plans unless "significant revisions to the draft guidelines" are made.

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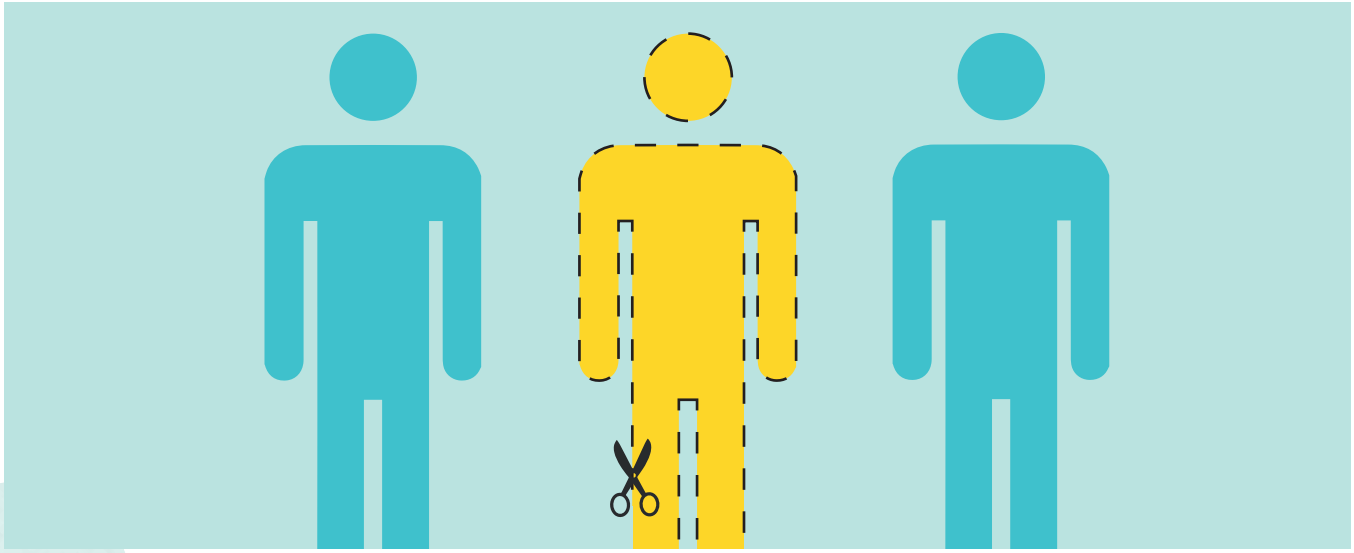

In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Expect the Unexpected

Jobs for life are a thing of the past – make sure you develop the tools to survive and thrive, wherever your career takes you.

By Yong Guo, Fairleigh Dickinson University, School of Pharmacy and Health Sciences, Florham Park, New Jersey, USA.

Before Forrest Gump's mother died, she told him: "Life is like a box of chocolates. You never know what you're gonna get."

Life certainly is unpredictable, and so are careers. As young professionals eagerly embark on their first forays into the job market, they naturally tend to take an optimistic view of the future, without being fully aware of the unpredictable nature of their chosen path. A case in point – when I started my first job in the pharmaceutical industry, I would never have guessed that 22 years later I would be starting a whole new career as a teacher.

Young scientists starting out today should expect to have not just multiple jobs but multiple careers throughout their professional life. To live under the illusion that you will maintain one job indefinitely would be naïve, but that's not to say you can't find success and fulfillment – perhaps even more so than if you had stayed on a single trajectory. Some of these changes will be by choice to pursue better pay or prospects, but others may be forced by unforeseen circumstances, such as closures or layoffs. I've experienced my fair share of "reorganizations" during my own career in the pharmaceutical industry, and a question I am often asked is whether there is a way to prepare for this unpredictability. While certain situations are beyond our control, I strongly believe that there are steps we can take to be ready for change. My comments will particularly focus on the pharmaceutical sector, but I hope that young scientists in all industries can find something that fits their situation.

First, you need to establish yourself. Young graduates may be surprised to find that work in industry is quite different from their training, even at the PhD level. Whether you are starting your first job or taking up a new position elsewhere, you should aim to establish yourself as a valuable contributor as soon as possible. For example, the pharmaceutical industry is notorious for its use of jargons and abbreviations – take the initiative and learn them. You will not be provided with a course on such things, and this is a very small part of the learning curve ahead.

You will almost certainly be working in a team. Enthusiasm for the work and a "can do" attitude will help greatly with your success. Another step towards establishing yourself is to find a niche area in which you are recognized as the "go to" person. This is especially important for PhD scientists. A "jack of all trades" is useful, but also dispensable. Recognized expertise in a specific area leads to more opportunities.

Second, work continuously on your communications skills. I find that the young scientists often have excellent training in the technical aspects, but

"Young scientists starting out today should expect to have not just multiple jobs but multiple careers throughout their professional life."

lack sufficient training in communicating information; for example, writing reports and giving presentations. The corporate world is more complicated than the ivory tower. You must communicate well with a range of culturally diverse colleagues, and do so from various functional perspectives and with different agendas in mind. You must communicate effectively across all barriers. Unfortunately, there is no shortcut to acquiring these skills. The only way is to pay attention and practice, practice, practice.

Third, explore new areas and passions. When you are happy in your role, there is a danger of becoming complacent as the everyday becomes routine. It is important to remember that employer requirements often change over time, potentially making your expertise (and maybe even your role) redundant. Many pharma companies offer job rotation programs – a great opportunity to broaden your skills. Another option is to pursue an MBA or business certificates; additional training in business may be an asset when new opportunities knock on your door.

Fourth, build your network. Scientists tend to exist in small social circles within their discipline. While that may be ideal for a certain level of discussion, you may find your address book is rather thin when it comes to pursuing new opportunities. Step outside your comfort zone and expand your network – not randomly, but with your long-term goals in mind. Joining and volunteering your time to scientific and professional organizations is a great start.

Your network should include a mentor and preferably also a sponsor. What's the difference? A mentor advises you, but a sponsor (a senior staff member at your current employer) actively advocates for you and helps you to advance. Sponsors are hard to find but tremendously valuable.

Finally, keep an open mind regarding future opportunities. Unexpected opportunities may come your way, but you should focus on those that are aligned with your long-term goals. When such an opportunity presents itself, you need to be ready; sometimes the perfect opportunity only comes along once and you must be ready to seize it when it does.

Quality, Not Quantity

Qualitative risk assessments are a great way to approach quality management – and train your operators at the same time.

By Iain Moore, Head of Global QA at Croda; President of EXCiPACT asbl.

What is the best way to define your GMP implantation strategy? Many will be familiar with a traditional gap analysis starting with a GMP Guideline. You take the list of requirements and compare them line-by-line with your activities to see whether you comply and then implement action to close any gaps. This approach is moderately effective but limited in terms of flexibility and how much you can actually learn about your activities.

My preference is to use a risk-based approach, where you systematically examine your activities, process by process to identify, analyze, evaluate, treat, monitor and communicate the risks in their proper context. However, many risk-based approaches are compromised by failing to understand the understand the difference between risks and hazards.

Let's say you're swimming in the sea off the coast of Australia. A shark is a hazard – and I'm sure you can guess what the consequences of meeting in the water are! If you are also in the sea, then you can't eliminate the hazard completely and reduce the risk of a shark attack to zero. But you can greatly reduce the probability of a shark attack by taking steps to reduce the likelihood, such as by only swimming at designated beaches protected by shark nets. By reducing the probability of realizing the consequences of the hazard we can reduce the risk to a tolerable level.

So which risk assessment tool can we use to help us with our GMP gap analysis? There are a number of out there. ICH HQ9 discusses a large number, including failure mode and effects analysis (FMEA): this is a qualitative method, which can be great if you've got information concerning the rates of failure in various activities. But the

"A central benefit of this approach is that it places all of your activities in context. It is also simple and logical."

problem with numbers is understanding what they mean and what to do about them… What's the difference between a reading of 586 and 738? A qualitative judgement where you categorize risk in terms of high, and low is simple and effective. If it's low, you don't have to do anything; but for high, definitely take some actions.

My preference is to analyze your process or activity step by step. At each step identify the hazards, an assign a number (say one to five) to the consequences of the hazard, and then consider the probability of realizing the consequences on a similar scale (one to five). Multiply the two to define the risk on a 1-25 scale. Then identify what mitigations you already have in place to address the risk. Set a criticality level, so any step with a risk over 18 is a critical step.

Then determine what mitigations you need to apply at this point. Here the GMP Guidelines have many tested and proven approaches to reducing risk. Once applied recalculate the risk with the reduced probability score.

With the entire process analyzed in this manner you can then set some boundaries on whether the residual risk is low, medium or high. If the risk is low, then no further action is needed. Remember the risk can never be zero if the hazard is present. If the risk is high, then you must go back to the GMPs and see what else you can do to reduce the risk.

With the risk analysis completed then the analysis also provides you with a means of identifying the critical points in you process. Any controls that reduce the risk by a large number, say from 25 to 10, would be critical steps so any deviations at this point must trigger a thorough investigation.

Who do you want in your risk assessment team? You should include the people who actually perform the tasks. They are doing the job and they know what's happening on a day-to-day basis.

A central benefit of this approach is that it places all of your activities in context. It is also simple and logical. It uses the flow of the activity in question as the basis of the risk assessment, and then matches the GMP controls required to manage and reduce those risks. Like all risk assessments, it has to be reviewed and revised when there are changes, and more importantly when deviations are realized.

For me this risk assessment is also the best GMP training your operational people can receive – they know the activity and the analysis will make them much more aware of the hazards, risks and the GMP controls that they need to apply.

A New Purpose

Drug repurposing is in vogue, but it's not always as easy as you think.

By Gerallt Williams, Director Scientific Affairs at Aptar Pharma.

It is often said there is no such thing as an original idea – inspiration is always derived from something or someone else. And this is by no means a bad thing. As one example, consider drug repurposing for nasal delivery. This strategy became popular around the mid-nineties with companies wanting to leverage existing drug products through new routes of administration to give them a new lease of life. Nasal delivery was a popular option as its convenience was seen to improve patient compliance and allowed anyone – even a casual bystander – to administer drugs effectively in the event of an emergency. But existing drugs can be repurposed in many other ways as well.

"Repurposing presents a complex network of challenges that need to be addressed for the whole project to succeed."

Drug repurposing has recently seen a resurgence in the industry – mainly because of economic drivers. The

development and commercialization of new drug therapies requires up to 15 years of development work, and can represent around a $2.6 billion investment. Repurposing is cheaper and less complicated, although, as I will discuss later, it remains a complex exercise – and in my view, that complexity is often underestimated. But it is certainly an effective option to avoid extensive development work, and 54 percent of biologics launched or approved in the US in 2017 were for existing drugs repurposed for new disease indications, reformulations or combinations (1). For industry-newcomers and disruptors alike, there is space within the sector for them to make their mark. And with the recent approval of Spravato, an FDA-approved antidepressant adjunct, and Nazolam, a short-acting sedative drug, both repurposed for nasal drug delivery, the playing field is seemingly wide-open.

Repurposing presents a complex network of challenges that need to be addressed for the whole project to succeed. The correct choice of device is key – is it intuitive for the patient? Can it support adherence to the regimen? Consider the site of deposition – droplet and particle size, droplet velocity and the anatomy of the nasal cavity are all key considerations when repurposing a drug for nasal delivery. The impact of the epithelial membrane and mucus layer should also be clearly understood. Bottom line is that developers must understand three core objectives: deposition in the desired location; retention within the nasal cavity; and therapeutic effect. The strategy to achieve these objectives will depend on local versus systemic indications.

There can also be confusion about the regulatory process. First introduced in 1999, the FDA's 505(b)(2) pathway offers companies the opportunity to develop new formulations from existing products – so long as they will have a meaningful impact for patients. This registration pathway gives companies up to three years to develop and protect a repurposed product, as opposed to the 180 days available through other regulatory pathways, and the chance to pursue "innovation without duplicating existing work". While the benefits of this pathway are undeniably significant, the challenges that it presents are equally important. Some of the information required for approval through this pathway doesn't come from the company developing the drug; rather, it is derived from previous studies not conducted by or for the applicant. This can often leave companies in a dilemma as they search for relevant studies to support their application. Most FDA guidance documents referring to New Drug Applications do, however, outline the steps required for a drug to be approved. With that being said, there is no specific guidance on 505(b)(2) drug development programs from the FDA, which may overwhelm those unaccustomed to it.

And for a repurposed drug product for nasal delivery to be successful, it must employ an effective delivery system. We are witnessing a move to unit dose or bi-dose delivery devices for a number of reasons. For example, they can deliver powder or liquid drug formulations, are primeless, can be delivered 360°, are intuitive to use, and the protective chamber decreases the risk of misuse. They can also be administered by a third party in an emergency mode, are cost effective with minimal dead volume and, critically, have multiple market drug references already available in multiple regions, which means they are a proven technology.

For years, repurposing to nasal delivery seems has been a forgotten application, but I'm delighted by its resurgence. Many of us have short memories and there is a natural temptation to view it as new. This also leads us to assume that a new innovation is for trailblazers and that the risk can be as great as the reward. But nasal delivery is truly well established in the industry and, in my view, should be more widespread.

"The complexity of the development process is significantly underestimated and people often do not take into account all of the key challenges involved."

Let me restate: it is often said there is no such thing as an original idea, every idea is inspired by something or someone else. Repurposing isn't an original idea – it is decades old and the expertise is already well founded in the market. The challenge is that the complexity of the development process is significantly underestimated and people often do not take into account all of the key challenges involved.

Reference

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Logistics Will Prevail

Early collaboration between couriers and manufacturers will be key to overcoming the logistical challenges presented by advanced therapies. Fortunately, history is on our side.

By Sam Herbert, President, World Courier.

It might be hard to imagine a world where cell and gene therapy manufacturing and logistics is fully standardized with little human intervention – all at a reasonable cost. But prior to the 1980s, who could have imagined that it would be possible to ship biological samples across the globe to carry out clinical trials? I think the story of World Courier nicely illustrates how logistics evolves to meet the demands of industry – especially pharma.

Let me take you back to 1969, when James R. Berger, a grain broker from Downtown Manhattan, founded World Courier. He knew that his industry needed a means of rapidly shipping documents to various international points to arrange overseas shipments of grain. The US postal service would take three weeks, even with a first-class stamp. So Jim decided to ship documents on commercial airline flights – and hence World Courier was born.

Over time, the company built a global network. And by the 1980s, the pharma industry had started large infectious disease trials, involving central labs where samples had to be shipped to and from, globally. World Courier entered the biopharma industry to facilitate these trials, eventually moving into the commercial space. This required innovation in cold-chain technologies to ensure that products could be maintained at the right temperature.

Later, as an increasing number of trials were being carried out at academic hospitals, it became apparent that product was being wasted due to the large variations in patient recruitment – couriers were always oversupplying. In response, World Courier created in-country clinical storage depots so that we could respond to variations in patient recruitment quickly, which then evolved to store commercial product – so that changes in demand could be met.

Today, we're seeing another huge change with cell and gene therapies. We now have autologous therapies, where patient material is shipped to a manufacturing site and then returned to the patient – all within a day or two. A central challenge is that you can't be too early or too late. With traditional therapies being delivered to a hospital, you have quite a large window, but when you're delivering a CAR-T, for example, nurses (who will receive the therapy to ensure the integrity of the product: making sure the temperature stays within range) will only have specific time-slots. The same goes for the manufacturer, who will have all of their slots planned out in advance. Miss, and you lose a very expensive therapy and, potentially, a patient's chance of life.

In the past, therapies would be developed and the logistics would be sorted out later – there would be a hand-off to a completely separate infrastructure. Cell and gene therapies are different because the logistics is built into the manufacturing process – the patient is part of the process.

There's plenty of room for improvement. Greater standardization of procedures is sorely needed, for example, as different companies have developed their own ways of delivering these therapies during the development process. In my view, we also need new capabilities in cryogenic storage and technologies to track chain of identity and custody – and new solutions in this area are starting to emerge.

How can we make this vision a reality? The key is for manufacturers and couriers to collaborate much earlier in the development process. Just as quality by design has become a key feature of pharmaceutical manufacturing, so too must logistics by design. There's great value in making an early decision on the manufacturing and logistics process, such as how many sites are you going to have? What sort of packaging are you going to use? And where are you going to charge your packaging? Couriers can advise on these things and, at the very least, supply some data on the implications of decisions on future costs. For example, if you have dry shippers that can only be charged at set points around the world, then you're automatically adding a leg to your logistics process. And more legs means greater costs and potential quality problems, especially when manual hand-offs are involved. Alternatively, you might choose to leverage technologies where you can charge at a courier's office. There's no right or wrong answer; it's about understanding the implications of your decision early, so that you don't face any unexpected challenges later on.

It's incredibly exciting to see new therapies coming through, but there's a lot that we, in collaboration with manufacturers, can do to improve safety and efficiency – and ultimately bring down costs. But if history has taught us anything, it's that innovations in logistical technologies and processes will evolve to facilitate the delivery of new therapies.

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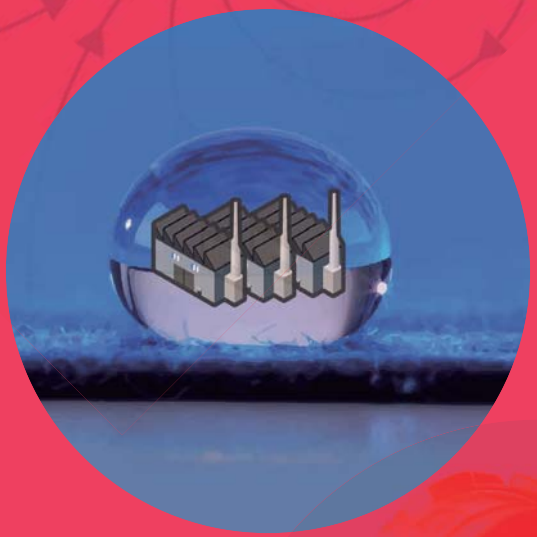

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The Perfect Cover Up

With many APIs exhibiting a strong, bitter taste, taste-masking is essential, particularly for pediatric patients. Dr Krizia M Karry, Global Technical Marketing Manager for Pharma Solutions at BASF, discusses how taste-masking tactics have changed over the years and how to overcome some of the common challenges in the area.

The molecular revolution

In a 2003 survey conducted by the American Association of Pediatrics, unpleasant taste was identified as the biggest barrier for completing treatment in pediatrics. Later in 2007, it was published that the average rate for compliance with treatment was only 58 percent in children, with major deterring factors attributed to formulation and palatability. These facts have helped to fuel advances in taste-masking technologies.

Initially, taste-masking relied mostly on the addition of sweeteners and flavors. The problem with this approach is that for very bitter compounds, such as ibuprofen, the bitterness will dominate because you can only include so much sweetener in a tablet without making it too large, or further masking the metallic taste of the sweetener. Another problem is in formulating APIs that are highly soluble and need to be administered in high doses (e.g., acetaminophen), because both the sweetener and drug will start to dissolve in the mouth, and the sweet and bitter taste receptors in the tongue will activate to trigger an unpleasant reaction in the patient.

Coating is an increasingly used technology that overcomes most of these challenges for aggressively bitter APIs, but coating does have its own caveats, such as ensuring minimal (or none) coating imperfections and adequate in-vivo drug release. Water soluble (e.g., polyvinylpyrrolidone and hydroxypropyl methylcellulose) and insoluble polymers (e.g., polyvinyl acetate and copolymers of methyl methacrylate) have been used in coating applications to achieve minimal drug release in the oral cavity and complete dissolution in the gastrointestinal tract.

Other taste-masking approaches have evolved over the years too, such as microencapsulation, the addition of pH-modifying agents and viscosity enhancers, suspensions, complex formations, solid dispersions, use of taste suppressants and potentiators, and dry coating bitter APIs. Although the use of these technologies has grown over the years, relative growth has been marginal compared to that of coating technologies.

What are the main challenges in using polymers to achieve effective taste masking?

The biggest challenge is identifying the right polymer – there is a lot to be considered! The formulator should take into account the API solubility, particle size, shape, dose and desired drug release pattern, as well as whether the polymer is water soluble/insoluble or if its solubility is pH-dependent. Formulators must also consider the polymer's hydration mechanism – is it swelling (delays diffusion of the bitter API) or gelling (increases viscosity to minimize contact between the active and the bitter tongue receptor), and other aspects such as coating film thickness.

The chemical and physical properties of the API play an important role when taste-masking. Its solubility, the dose at which it needs to be administered and the particle size and shape are very important considerations. A bitter API with a high solubility in saliva (pH 6.2 to 7.0) will be more difficult to taste-mask compared to an API with low solubility. Similarly, low particle size APIs in substrates with irregular shapes will be more difficult to coat than spherical ones. The dose is another important factor when utilizing sweeteners, microencapsulation or solid dispersion technologies for taste masking. High doses will limit the amount of sweetener that can be added to the formulation and polymer solid content when creating a solid dispersion.

"The chemical and physical properties of the API play an important role when taste-masking. Its solubility, the dose at which it needs to be administered and the particle size and shape are very important considerations."

What key innovations have helped alleviate taste-masking challenges?

There has been innovation in the polymers themselves and in materials combinations to achieve the desired taste-masking performance. Also, patients will always prefer taking one dose instead of multiple doses to achieve the same outcome. In

this regard, polymers that can mask bitter actives at high concentrations and/or be combined with pore formers for sustained-release applications (e.g., water insoluble polymers like polyvinyl acetate with gastrosoluble pore formers such as calcium carbonate) are gaining significant interest as a means to overcome taste-masking challenges.

At the same time, technologies have also evolved such that multilayer coating is now an alternative to formulate immediate and modified release drug products that contain bitter APIs.

BASF recently introduced a new copolymer that is suitable for taste-masking as well as moisture protection. Kollicoat® Smartseal (methyl methacrylate and diethylaminoethyl methacrylate) is a film-forming polymer designed to be insoluble at typical saliva pH for efficient taste-masking, but completely and immediately soluble in gastric (stomach) media at pH < 5.5. The polymer is available as an aqueous dispersion (Kollicoat® Smartseal 30 D) and as a powder (Kollicoat® Smartseal 100 P), which can either be re-dispersed in water or dissolved in organic solvents.

An additional consideration when selecting for the right polymer for taste-masking, is the material's cost-of-use. This includes taking into account any additional excipient that needs to be added to the formulation for the taste-masking to be effective, processing steps and times, current containment and safety measures, among others. In this case, Kollicoat® Smartseal outperforms all others because it was designed with the end-user in mind. The polymer is manufacturing site friendly because its processing is safe (does not require the addition of strong acids or harsh surfactants), it has a great smell, and it efficiently masks taste even at very low coating levels, which translates to material savings and process time reductions.

Are pharma manufacturers reluctant to use newer excipients?

Yes! Innovation in pharma excipients has been relatively slow. Some pharmaceutical companies see it as a gamble to utilize novel or innovative excipients in formulations because of the drug filing process. In the US, for example, excipients are regulated as part of the overall submission, rather than individually. Due to this, the natural tendency is to use novel excipients when all other options have failed or when it is unique in its class. Nevertheless, innovation for excipients continues, with examples like Kollicoat® Smartseal for taste-masking and moisture protection and Soluplus® for the formulation of poorly water-soluble drugs via hot-melt extrusion technologies.

What can be done to make it easier for manufacturers to embrace innovation in ingredients?

Open dialogues between pharmaceutical manufacturers and excipient suppliers are very important, and the latter should work closely with regulators to push for faster updates to the FDA Inactive Ingredient Database (IID). The FDA defines a novel excipient as a material that has not been previously used in an approved drug product in the US (i.e., not listed in the IID) for the intended route and level of administration, or an excipient previously used in an approved drug product but now at a higher level of use than previously listed in the IID. Unfortunately, the IID database is not regularly updated, and new registrations can be queued for months before they are visible to the public. This comes at an additional cost to innovators – an even longer return-on-investment. During this time, industry has no way to know if a novel excipient is acceptable for use early in development because no data is available prior to NDA approval.

Where is there room for further improvement in taste-masking?

Forty percent of American adults have difficulty swallowing tablets, even though most have no problems with food or liquid. If you add to this a child's aversion to medications and note the increasing trend of companies to develop a drug product acceptable by all population segments (pediatrics, adults and geriatrics), then it's evident that effective taste-masking is crucial. Taste-masking approaches have advanced significantly but I'd like to see more innovation in taste-masking new technologies for dosage forms such as multi-unit pellet systems (MUPS), chewables, gummies, orally dissolving tablets and films, and sachets. Currently, there are few polymers that can efficiently accomplish this, but as expected, published applications are scarce to maintain a competitive advantage.

NEW FRONTIERS IN ADC DEVELOPMENT

Though setbacks have prevented antibody drug conjugates from reaching their true potential, many in the industry remain confident in the ability of these products to boldly go where other therapeutics have failed to. But will these therapeutics live up to ever-growing expectations? Here, we explore the thoughts and predictions of five pharma industry experts.

By Maryam Mahdi

MEET THE EXPERTS

Gianluca Franguelli

Vice President, Drug Substance Development, Recipharm

Chris Martin

Chief Executive Officer and Director, ADC Therapeutics

Courtney H Morget

Senior Scientist III, Manufacturing Sciences, Purification, AbbVie

Thomas Rohrer

Associate Director of Commercial Development Bioconjugates, Lonza Pharma & Biotech

Ian Schwartz

Global Technology Consultant, Bioconjugation at Sartorius Stedim North America

THE ADC FIELD HAS SEEN MANY SETBACKS. WHAT IS THE PHARMA INDUSTRY'S CURRENT VIEW OF THE FUTURE OF THIS THERAPEUTIC CLASS?

Gianluca Franguelli: Ultimately, the development of an ADC will always be far more complex and less predictable than that of a small-molecule new chemical entity (NCE) – and the industry needs to embrace this hard truth and invest in more fundamental research before embarking on expensive clinical programs. Many drug developers are pressured to rush forward to generate profits for shareholders, but this needs to be balanced by a good business case and good understanding of the ADC.

Most new ADCs under development focus on oncology, and I believe this will be the case for the foreseeable future; the targeting ability of ADCs makes them particularly compelling for cancer where you need to treat disease tissue without harming healthy tissue. Generally speaking, cancers for which curative treatment options are scarce or unavailable represent promising areas of investigation because the hurdles to market introduction are somewhat lower. I hope that currently ongoing phase III studies will be fruitful, so as to give the industry additional arguments in favor of ADC research to present to shareholders. If no new ADCs can be introduced in the next five or so years, investment may gradually fade.

Chris Martin: The full potential of ADCs has yet to be reached, but I really believe that the coming years will be exciting for everyone in the industry, as well as patients. There is still a lot of interest in ADCs, evidenced by the fact that AstraZeneca recently paid up to $6.9 billion in upfront and potential milestone payments for a fifty percent interest in a Daiichi Sankyo HER2-targeted ADC.

One of the big hurdles that has hindered progress is the prohibitively high costs of clinical trials, which limits the number of optimal combinations and sequences of ADC therapies that can be investigated, or delays entry into clinical practice. The problem has not gone unnoticed by regulators, who have been looking for solutions that balance the benefit and risk to patients. As legislation is put into place to help guide the industry, we should begin to see the barriers to progress rapidly lift.

Courtney Morget: The future is positive. While oncology has been the epicenter of ADCs so far, we're seeing more happening in other therapeutic areas, such as immunology. The fact of the matter is that as long as there is an unmet medical need, ADCs can be beneficial. But we, as an industry, must remain adaptable. As more and more accelerated programs for ADCs emerge, it will become crucial to have robust plans for commercialization in place.

Thomas Rohrer: I agree with Courtney. The industry's attitude towards ADCs remains positive. During the 2018 ADC World Summit, held in San Diego, the FDA indicated there are 115 ADC programs under IND, and it is estimated three late stage programs will move to approval in 2019. I would say that these figures indicate the industry's positive position on the targeted therapeutic approach offered by ADCs!

However, there is still plenty of work to be done to maintain the optimism felt by the industry. Pharma needs to simplify its supply chains by manufacturing all intermediates (including large molecules, highly potent small molecules and linkers required for the development process) and the drug substance under one quality system, which will reduce the risk and timeline for completion of process development and subsequent clinical trials. Further to this, technical flexibility is required to support companies, many of which are in the early stages of clinical development.

WHY ARE YOU PERSONALLY SO EXCITED BY THE ADC SPACE?

Ian Schwartz: What I think is so exciting about ADCs is the concept of using the homing-like ability of a monoclonal antibody to deliver therapeutic molecules directly to the site of interest, thereby lessening the risks of off-target toxicities. The idea that a single linker-payload strategy could be an effective therapy for all disease settings has been disproven, and this encourages companies to innovate. We are seeing companies expand their ADC pipelines and explore not only new targets, but also new linker-payload combinations, mechanisms of action, and conjugation strategies. Further, the ADC field is growing beyond the oncology therapeutic area, for example antibody-antibiotic conjugates, and it's exciting to see what's next on the horizon.

Franguelli: For me, it is the scientific challenge. An exciting difference between a conventional chemotherapeutic and a bioconjugate is the level of interdisciplinarity required for the successful design of the therapeutic agent. To develop a classical NCE in the field of oncology, you must investigate its biological activity, mechanism of action, pharmacokinetics, metabolic pathways and a handful of other parameters to paint an essentially complete picture, which is complicated enough. The addition of an antibody and linker – as required with an ADC – bring further challenges. For example, to reach its target, a payload may require internalization and linker cleavage, which makes the margin of exposure (MoE) much more complex. In addition, you must understand not only the ADC's drug metabolism and pharmacokinetics (DMPK) profile, but also the payload. From both a synthetic and analytical stand-point, ADCs represent highly complex matrices. All of the above underpins the intriguing nature of ADCs and other bioconjugates as therapeutic agents and makes them exciting molecules to work with!

Martin: I am confident that ADCs can provide significant clinical benefit in patients with few therapeutic options. The ADC targeted approach provides the possibility that drug resistance can be reduced and that healthy organs or tissue can be spared during treatment. When I see an MRI scan with a complete response after two doses in a patient who has failed multiple other lines of therapy, I feel the excitement of having moved the frontier of cancer therapy one step further!

Morget: Like Gianluca, I find it exciting to tackle the challenges of ADCs! ADCs are at the intersection of small molecules and biologics. As there is also no "platform" for ADC manufacturing, we are constantly exploring new ADC designs and manufacturing technologies to meet those needs.

Rohrer: The ADC space represents one of the most interesting areas of exploration for my team when it comes to making significant improvements in patient care for unmet medical needs. Across the industry, we anticipate that some ADCs will have the potential to be curative. The promise of combination therapies, for example with immune-oncology drugs is very exciting as well. Secondary to improving the standard of patient care would be applying technology developed for unique payloads and engineered antibodies to reduce the toxicity associated with untargeted systemic administration.

WHAT HAVE BEEN THE GREATEST SUCCESSES FOR ADCS OVER THE COURSE OF THE LAST FIVE YEARS?

Rohrer: There have been some huge wins for ADCs. We've seen the approval of Pfizer's inotuzumab ozogmicin (a treatment for acute lymphoblastic leukemia) and Polatuzumab vedotin (large B-cell lymphoma), which received "breakthrough therapy designation" from the FDA, and the reintroduction of gentuzumab ozogamicin (a treatment for acute myeloid leukemia) to the US market. The industry continues to improve its understanding of the mechanisms of ADC toxicity and design of preclinical studies.

Schwartz: The commercial approvals and expanding marketing authorizations of Polivy, Myotarg, Besponsa, Adcetris, and Kadcyla are certainly remarkably innovative molecules and success stories. New conjugation strategies to increase therapeutic windows, such as site specific conjugation and new linker-payload combinations/mechanisms of action, have caught the interest of the entire ADC community.

Franguelli: ADCs have also advanced in ways that allow

them to address the needs of patients suffering from cancers for which there are very few alternative treatment options, for example glioblastoma. And we are learning a lot from failures too. Despite the preclinical prowess of PBD-type payloads and site-selective conjugation techniques, these have not translated to success in the clinic. While this caused setbacks for investors, however, the discoveries they yielded are crucial in the design of future ADCs.

I also believe we are seeing much needed progress in marketing authorizations. For example, Seattle Genetics' Adcetris was approved for additional indications, including the first-line treatment of Hodgkin Lymphoma (HL) in combination with conventional chemotherapy, proving that ADCs are not necessarily the second or third best treatment option.

Martin: Great drugs are built on the shoulders of good drugs, and the progression made in the quality of ADCs produced over the past five years is testament to this. And Gianluca raises an excellent point; the benefits to niche and often overlooked patient groups have been monumental. Looking at large B-cell lymphoma (DLBCL), loncastuximab tesirine (targeting CD19) and polatuzumab vedotin (targeting CD79b) are strong examples of how well these types of drugs can work. They are offering significant benefits to relapsed and refractory patients, and helping to shape the future of patient care.

ADCs are also improving therapy outcomes for patients with breast cancer, with Kadcyla helping Herceptin refractory patients. In addition, trastuzumab deruxtecan promises to extend the benefit to patients with low HER2 expression.

I hope we will see more soon – hopefully some from my own company! We currently have four PBD-based ADCs in clinical development, in six clinical trials, with two INDs expected to file in 2020 and a pipeline of PBD ADCs in research. Our lead ADC is ADCT 402, is in a pivotal Phase II clinical trial in relapsed or refractory diffuse large B-cell lymphoma and we plan to start a pivotal Phase II clinical trial for ADCT 301 in relapsed or refractory Hodgkin lymphoma later this year.

WHAT ARE THE BIGGEST CHALLENGES WITH DEVELOPING AND BRINGING ADCS TO MARKET?

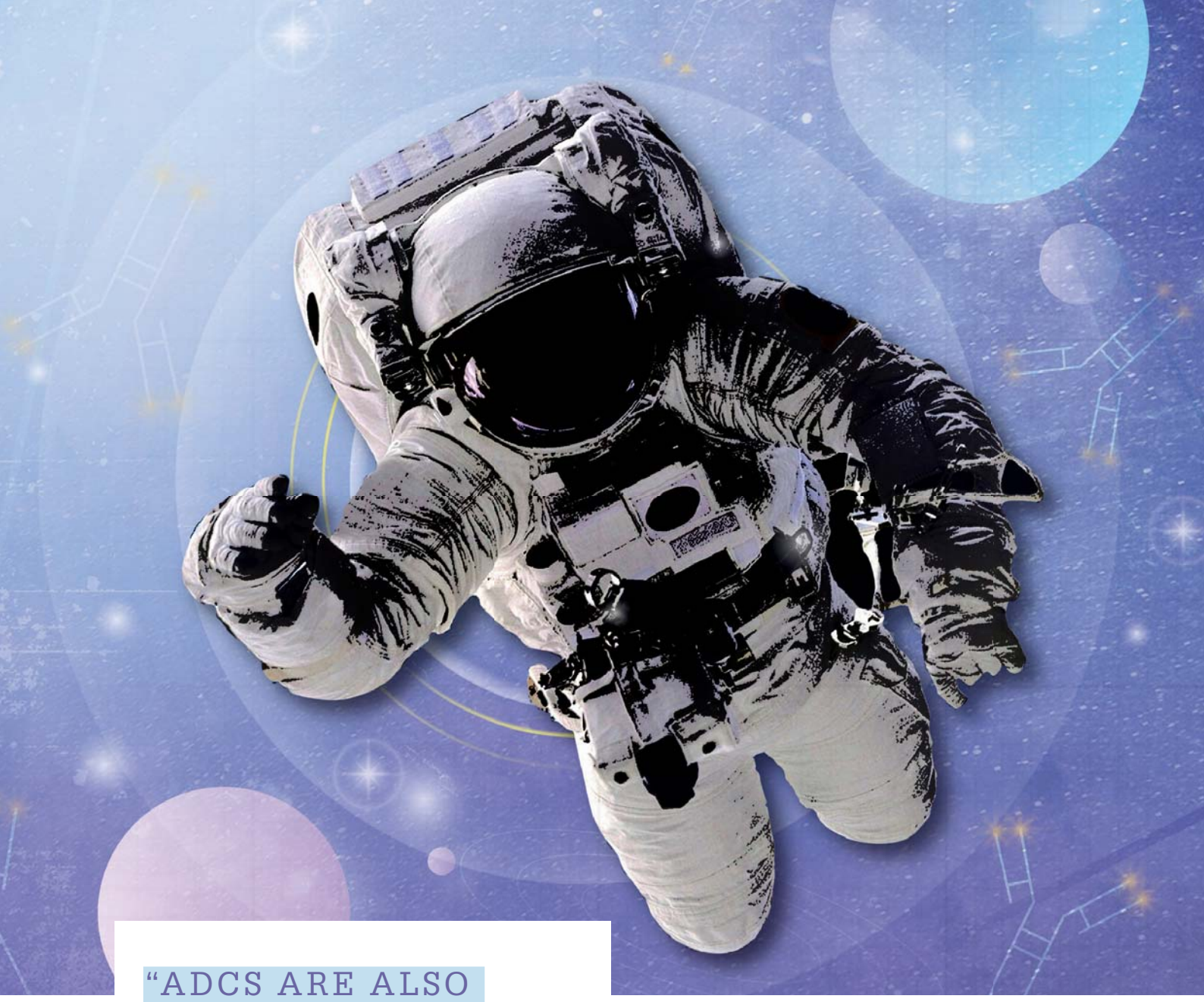
Franguelli: Many ADCs have failed to demonstrate therapeutic efficacy or safety. The single biggest challenge for the successful development of an ADC is the extreme difficulty in translating preclinical findings into predictions of clinical behavior. And the challenges are not confined to the design aspects of the development; ADC production combines the difficulties of generating a biotherapeutic agent and an extremely potent, small-molecule payload on large scales, with the additional challenge of chemically ligating one from the other in a reproducible fashion. Only a handful of highly skilled and extremely well-equipped manufacturers are able to successfully carry out this process.

Martin: Developing an ADC is seven parts science, two parts art, and one part luck! Simply put: it's complicated. And the challenge is heightened because most ADCs target difficult diseases, like cancer. Every tumor type has different target expression levels, and the heterogeneity of expression also varies. On top of this, each target has different levels of healthy tissue expression in different organs. Getting it right requires discipline and an experienced team.

Morget: The design and engineering of the molecule is key to its function, and there are many components of an ADC that need to come together to achieve the desired effect, resulting in a difficult balancing act to ensure the optimum performance of these drugs in vivo. Selecting the right linkers, designing new payloads and ensuring that conjugation sites are fit-for-purpose are all complicated activities. Many ADCs have missed the mark over the years because of a low therapeutic index.

Schwartz: As Gianluca notes, the actual manufacture of ADCs is also complex. Manufacture requires a multifaceted supply chain as each primary component of an ADC is frequently manufactured at different, specialized manufacturing sites and each requires their own complex raw material supply chains, and release/stability programs. For example, the antibody portion of the ADC requires a different technical skill set, critical starting materials (including master cell bank), manufacturing equipment and release/stability strategy then the small molecule components. Additionally, the manufacture of the small molecule payload requires a high level of containment and safety risk mitigation due to its toxicity. The antibody, linker and payload (or linker-payload) then need to reacted together and purified at the ADC bulk drug substance (BDS) manufacturing site and the BDS is then frequently shipped to a different site for drug product (DP) manufacture. In addition to payload manufacture, safety risks and cytotoxic waste disposal strategies also need to be considered and mitigated for both BDS and DP manufacture due to the presence of the free and linked payload. Further one should also consider the chemical compatibility of the product contact surfaces to solvents frequently used in an ADC manufacturing process.

These complex supply chains, frequent transcontinental shipping requirements, and the presence of potent small molecules (whether free or linked to the antibody) and solvents create the necessity for careful selection of manufacturing equipment and manufacturing sites, cleaning validation/waste disposal strategies, and storage/shipping logistics.



"ADCS ARE ALSO IMPROVING THERAPY OUTCOMES FOR PATIENTS WITH BREAST CANCER, WITH KADCYLA HELPING HERCEPTIN REFRACTORY PATIENTS."

WHAT NEW DEVELOPMENTS IN THE FIELD DO YOU THINK WILL HELP BOOST THE NUMBER OF ADCS AVAILABLE?

Franguelli: In my view, an area that represents one of the biggest hurdles for entry for any new player in the field is ADC analysis. However, providers of analytical equipment are increasingly focused on technologies that facilitate ADC analysis. One example of this is Waters' UNIFI, a software platform that merges liquid chromatography and high performance mass spectrometry data to allow for data acquisition, processing and reporting. The platform offers built-in ADC characterization capabilities.

Morget: Given that the manufacture of ADCs is so complex, outsourcing is an important option for the industry. As drug

"UNIVERSITIES SHOULD ALSO EXPAND THEIR TEACHING EFFORTS IN THE AREA IN ORDER TO PROVIDE THE INDUSTRY WITH MORE QUALIFIED ENTRY-LEVEL PERSONNEL."

developers dive deeper into ADC science and try out new approaches, CDMOs also need to keep pace and expand their technical depth in the field to alleviate concerns over technology handoff and assurance of supply. Some CDMOs are also making efforts to integrate the supply chain by allowing for consolidation of components (monoclonal antibody, linker toxin, conjugation and fill/finish) within key strategic partners to ease transfer requirements and accelerate time to market.

Martin: ADCs are at the early stages of becoming a mature technology. We are learning more all of the time, and I believe that the leading companies now understand which technologies to pair with certain targets and tumors, and how to develop them in the clinic. But there is no single magic bullet technology; rather there are a number of next generation technologies available; for example i) Synaffix conjugation technology – a platform that helps companies rapidly create competitive clinical-stage ADC programs for their development pipelines, ii) antibodies that only bind in the tumor microenvironment, iii) PBD ADCs to targets that have multiple mechanisms of action (like ADCT 301 targeting CD25 and ADCT 601 targeting AXL where immune suppressor cells, T-regs and M2 macrophages, respectively, express the target). There remains much to gain by maximizing the quantity of ADC delivered to a target site and, thereby the quantity of toxin delivered specifically to the tumor.

Rohrer: I believe that the development and design of pre-clinical trials, particularly as it pertains to off-target toxicity, will be essential to overcome many of the challenges we face with translating ADCs from the clinic to the bedside. The development of better pre-clinical models to aid in the understanding of absorption, distribution, metabolism and excretion (ADME) and DMPK of both the intact conjugate and its break down products will help technology developers further boost the number of ADCs making it to market.

My company is also doing a lot of work with site-selective conjugation vectors, which can help reduce off-target toxicity by manufacturing antibody targeting agents with a defined number and location of conjugation sites for the payload. This enables the production of homogenous ADCs with a higher

therapeutic index and help move more ADCs along the path to success.

Schwartz: I would highlight single-use technologies as a key development for the ADC field. Single use product contact surfaces for the manufacture of the monoclonal antibody component of the ADC and the ADC BDS have many advantages. For example, looking at capital expenditures, costs are lower for a single use facility compared to a stainless steel facility; utility requirements are lessened and the overall facility footprint is smaller, meaning it can be built faster with less overheads. You can also maximize the use of production suites by significantly reducing preparation, cleaning and changeover time. For many ADC manufacturing platforms, you could execute two multi-product batches per week in a single use suite as compared to one batch per week with a week of change over for a stainless steel suite. It's also important to point out that single use product contact manufacturing equipment has often been designed to be chemically compatible with the solvents commonly used in ADC BDS manufacturing processes.

Courtney mentioned the value of outsourcing for ADC manufacture; the benefits mentioned above can be hugely important to contract manufacturers. Further, a single use ADC manufacturing platform lessens the risks associated with multi-product facilities, while enabling flexibility to manufacture an array of different types of novel ADCs. Single use manufacturing equipment is often supplied as a modular system, enabling a flexible manufacturing process flow. Further, should these novel ADCs show promise in the clinical, a single use manufacturing platform can be rapidly and predictably scaled up or scaled out while satisfying regulatory requirements for commercial approval and market demand.

HOW CAN POLICY-MAKERS, REGULATORS AND OTHER INDUSTRY STAKEHOLDERS HELP SUPPORT THE SUCCESS OF THE ADC SECTOR?

Franguelli: Funding agencies must invest in therapeutically oriented, non-clinical research of ADCs and other bioconjugates to yield knowledge and patent-free technologies. Universities should also expand their teaching efforts in the area in order to provide the industry with more qualified entry-level personnel. More generally, institutions of higher education should define therapeutic bioconjugates as a major component of any oncology research and facilitate undergraduate and graduate students' entry into the field. To date, this has rarely been the case, but a change in this area will significantly contribute to the future success of ADCs.

Morget: With many ADCs, there is the opportunity for accelerated timelines. In these situations, programs benefit from more frequent interactions with the regulatory agencies. By engaging in a dialogue, we can ensure we are meeting the needs of the patients as well as the agencies, in a timely manner.

Rohrer: I agree with Courtney; meaningful conversations will always bring about positive results. If the industry is able to maintain or improve its engagement with regulatory agencies, we will see the continual enhancement of pre-clinical studies for off-target toxicity and therapeutic efficacy. This will allow for the development of better combinations of linkers and payloads early on in the therapeutic development process.

I would also perhaps like to see the FDA adopt a more liberal approach to the use of the breakthrough therapy designation. This could help with the upfront costs of developing ADCs.

WHERE DO YOU SEE THE INDUSTRY GOING NEXT?

Franguelli: The future trajectory of the industry is dependant on the outcome of all of the phase II studies that are currently underway. The financial pressure on the industry to generate profitable new products in the medium term will force them to focus on available technologies and invest in concepts already proven to take NCEs to market. Hopefully, industry efforts will be fruitful and encourage life science innovators, both large and small, to continue to pursue new approaches towards improved cancer treatments.

Martin: I expect there will be a substantial number of ADCs approved in hematological and solid tumors in the coming years. Combinations of these drugs with immune-oncology therapies, cellular therapies, receptor tyrosine kinases inhibitors and other small and large molecule therapeutics should broaden the applicability of these drugs and extend clinical benefit.

Rohrer: I think a significant number of new payloads and linkers will appear which diverge from the current technology platforms. As the field grows, we will see broader applications for bioconjugation technology with novel therapeutics being developed for cell therapies, vaccines, antibiotics and more.

Schwartz: I see the industry continuing to explore new targets, linker-payload combinations and conjugation strategies. I also look forward to see more applications of ADCs beyond the oncology therapeutic area. From a manufacturing point of view, I expect to see single-use manufacturing as the primary strategy for accelerating clinical development timelines while allowing for manufacturing flexibility. Finally, I predict that we will continue to see expanding marketing authorizations of existing commercially approved ADCs, positive clinical data from novel molecules, and additional commercial approvals of novel molecules in the near future.

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How to Commercialize an Orphan Drug

Orphan drugs present a number of unique challenges for pharma companies looking to commercialize their products in the US. Collaborating to find patients for trials, improving diagnosis, demonstrating value, engaging with caregivers and developing specialized supply chains are just some of the things to consider.

By George Chressanthis and Animesh Arun

Orphan drugs (ODs) for rare diseases (RDs) present pharma companies with the opportunity to address a substantial unmet medical need. There are approximately 7,000 RDs, and only about five percent have effective treatments. In the US, around 25-30 million people are affected by a RD; many are often chronic and deteriorating conditions, with the majority starting in childhood and frequently resulting in early death (1). This creates significant economic and social burdens for patients, caregivers and healthcare systems.

The global problem of how to encourage drug development in the area of RDs was addressed with the Orphan Drug Act of 1983 in the US, and similar legislation in the European Union (Regulation 141/2000 on Orphan Medicinal Products, 2000). There's little doubt that the Orphan Drug Act worked to stimulate R&D in the orphan field – there were only two orphan therapies approved by the FDA in 1983, but the average number approved each year in the following 10 years was nine, and the average for the ten years preceding 2018 was 36 (2).

But commercializing ODs presents unique challenges, requiring different solutions. Here, we explore those differences and suggest ways in which pharma companies can navigate the commercialization landscape.

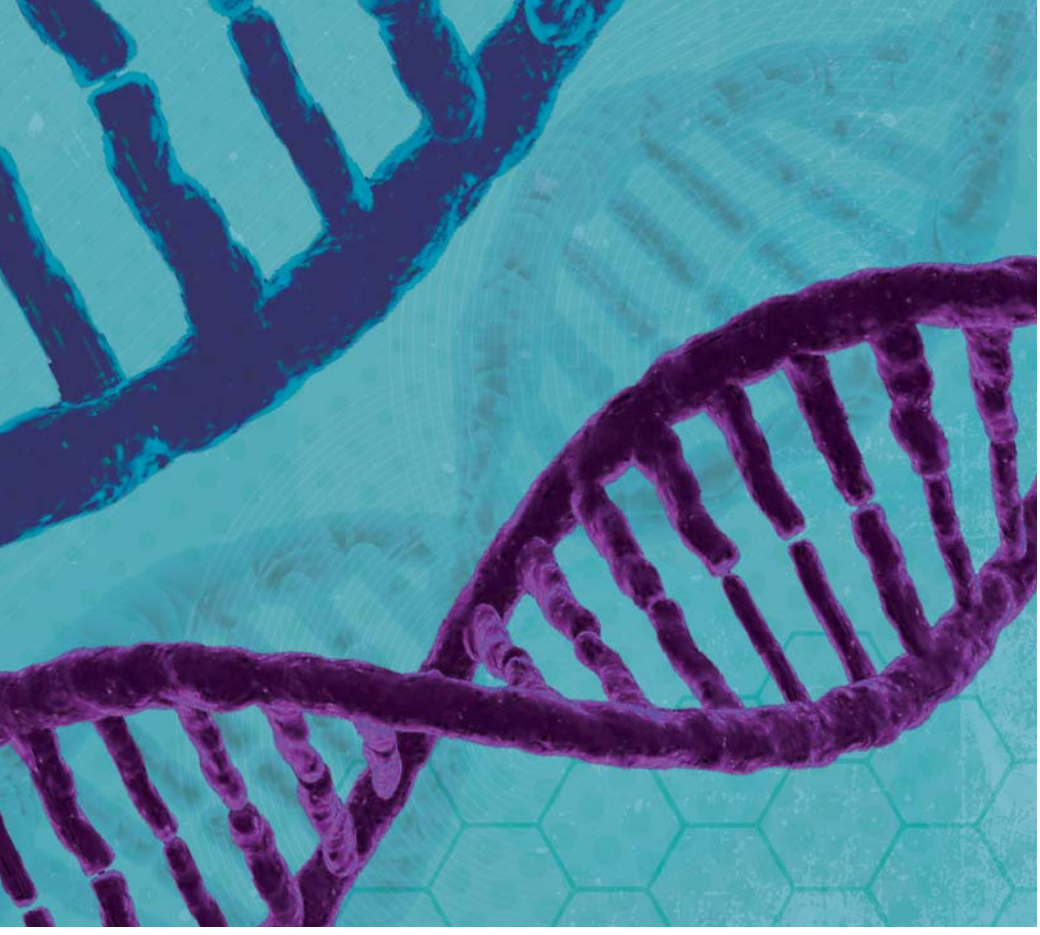
Finding patients and dealing with diagnosis

The successful commercialization of ODs requires a range of strategic and tactical elements to be implemented by pharma companies. Starting from the clinical trial stage of the product/project lifecycle, the first major challenge is patient recruitment. While finding appropriate patients is always a challenge for conducting clinical trials, this is especially acute for RDs, given the small populations involved. Pharma companies must develop strong relationships with all key Rare Disease Patient Organizations (RDPO) and research hospitals (e.g., children's hospitals, key academic research hospitals, etc.), which puts pressure on external medical affairs teams to foster relationships with key opinion leaders (KOLs) and RD experts.

Another key element is the diagnosis and treatment of RD. Unfortunately, many RDs go undiagnosed (3). Again, collaboration is key. Pharma companies must work closely with major research centers focusing on RDs, governmental agencies, RDPOs, and other companies, and data sharing is crucial. There also needs to be an international network for data and information sharing for undiagnosed patients.

Due to the length of time it can take for patients to get a correct diagnosis, it is common for patients to cycle between physicians for months or years (4). This means that pharma companies must make it easier for patients to access information, make it more affordable for patients to conduct necessary tests to determine their RD, and work with payers on the cost-effectiveness of providing healthcare subsidies to support faster detection of RDs. In addition, artificial intelligence (AI) and machine learning (ML) techniques can be beneficial to determine the attributes associated with an accurate RD diagnosis to shorten this pathway and help define metrics that physicians and patients can use to diagnose RDs accurately and quickly.

These points illustrate the need for pharma companies to develop a more



"Companies must also engage with governmental agencies and policy decision makers to address the economic and social impact of RDs."

patient-centric (rather than the current physician-centric) approach to RDs. Patients diagnosed with RDs are highly motivated, engaged, and informed so a strong digital and social media presence is recommended. There may also be a role for patient support infrastructure, such as patient hubs, to help pull-through patients by providing patient support for gaining access to therapy, and continued engagement with patients and physicians to help drive adherence to the prescribed therapy.

Pharma companies should also develop an extensive database of physicians by RD and share such information with patients. One reason for patients having longer diagnosis times for their RD is not being able to find a physician expert who can accurately diagnose and treat their RD. Expertise in RD diagnosis and treatment tends to be concentrated among a small subset of specialists, often in academic hospitals.

Market access and patient affordability

When it comes to affordability, pharma companies need to develop strong health-economic models for RDs to demonstrate the value (private health insurance and government) of subsidizing patient healthcare costs (5). Health economic and outcomes research (HEOR) and real-world evidence (RWE) analyses must be closely connected with commercial modeling. The often chronic and debilitating nature of RDs results in significant healthcare costs. Given the small patient populations, drug costs can also be an issue. Drug price elasticity analysis combined with HEOR/RWE is necessary to determine the economic burden to patients, as well as to payer plans and healthcare systems if these RDs go untreated. This means that performance-based contracts for ODs are much more likely than for non-ODs. Thus, the ability to link and track HEOR/RWE analysis with these payer contracts will be critical, as will the use of AI/ML technology to produce ongoing updates on projected health and economic outcomes.

In addition, the healthcare coverage of RDs significantly varies by plan and region; and patients often absorb a significant amount of the cost of the treatment (drug and overall healthcare costs). A payer registry for health plan coverage of RDs must, therefore, be shared with patients so they can plan accordingly on the cost-outlays required to obtain treatment of their RD. A payer registry can also be of benefit to a pharma company in planning their payer strategy and tactics necessary to support RD patients (e.g., the distribution and amount of copay support and discounts/rebates to payers/pharmacy benefit managers, or PBMs).

Strong database management is also important. The small number of patients with RDs will mean that the ability to link databases without losing data is paramount. This database capability will affect a wide range of clinical, on-going HEOR/RWE analyses for payer contracts, and sales and marketing activities.

Finally, mechanisms must be in place to allow for continued real-time monitoring by pharma companies of patient medical progress while being treated. Wearable and implant devices have already become more widespread to monitor patient progress with various conditions. Such devices

Top Tips

To successfully commercialize orphan drugs, you must:

- find the right patients for rare drug clinical trials
- work to improve rare disease diagnosis and treatment, and market access, more broadly
- produce accurate pre-launch forecasts
- develop an "informative" sales and marketing plan
- engage with governmental agencies and policy decision makers
- collaborate effectively, cross-functionally, in-house

will be even more critical given the cost of ODs for payers to subsidize coverage and/or for pharma companies to provide real-time patient information to support performance-based payer contracts.

Pre-launch preparations and supply chain development

Stronger efforts are needed by pharma companies pre-launch to ensure a successful OD launch. The small number of patients for each OD means the margin of error regarding accurate forecasts based on projected diagnosed patients, from a financial standpoint, can be substantial. An inaccuracy of just a small number of patients can have significant financial implications. Further, epidemiology-driven forecasts must estimate testing rates, diagnosis rates, as well as trends and leverage points to drive testing and diagnosis rates. Further, there may be an initial one-time "bolus" of untreated patients who had exhausted other treatment alternatives. This places greater importance on the validity and data used in prevalence and patient flow models to develop accurate patient forecasts.

When it comes to supply chain development, understanding the distribution of ODs through specialty pharmacy and buy-and-bill channels is important. The delivery of ODs to patients with RDs will likely take a different pathway than drugs for traditional non-OD conditions. This means capturing ODs going through specialty pharmacy channels and administered in non-office-based retail channel settings (e.g., hospitals, clinics).

In addition, specialized supply chains may be needed for certain OD treatments. In some cases, notably gene-and-cell based-immunotherapies, a two-way supply chain with specialized "treatment sites" is needed to collect cells from patients, manufacture the immunotherapy, and ship the manufactured cells back to a specialist site that can administer the therapy and manage any patient complications.

Sales, marketing and engagement

Pharma companies must go beyond the drug when it comes to providing patient support. For example, the majority of RDs affect children, so the role and needs of caregivers are paramount. Social and economic support programs for caregivers will be necessary for the continued engagement and treatment of RD patients. In some cases, diseases may be progressive and eventually terminal, and treatments may be palliative. Great sensitivity to patients and caregivers must be applied in the design of patient materials and their touchpoints with patient support infrastructure, such as patient hubs and clinical educators.

In addition, engaging in "patient-journey" analysis is critical for pharma companies to understand RD patient needs. The patient-journey for those with RDs can be long and arduous; pharma companies need to identify the crucial leverage points, and intervene to help prevent or ease roadblocks that can impede diagnosis and treatment (6). This also means the patient-journey must be geographically incorporated into the go-to-market model, target selection, and territory alignment design of sales representatives – including accounting for the layout of healthcare systems and payer health plans. Further, the role of healthcare providers in the patient journey is crucial, so companies need to bear in mind segmentation and the tonality of messaging directed at healthcare providers.

Sales and marketing strategy and tactics must be strongly "informative" in intent as opposed to the current "persuasive" approach often used by pharma companies. Companies must stress value-based messaging using scientific/clinical/medical information and evidence given the complexity of the RDs, the sophistication and expertise of physician specialists, and the well-informed nature of patients and caregivers. Aim for a strong linkage to personnel in medical affairs who can deliver peer-to-peer engagements with physician specialists, and small sales forces that are highly specialized and capable of delivering complex scientific/clinical/medical messages. Their backgrounds must be medical science liaison (MSL)-like in their ability to engage physician specialists at an advanced level.

Companies must also engage with governmental agencies and policy decision makers to address the economic and social impact of RDs. It is essential that pharma companies have a continued presence at public policy forums to highlight the economic and social burdens of people and society due to RDs. Further, pharma companies should promote policy actions that can be taken by the government to encourage continued development of new therapies and ease the burden of patients, caregivers, and the healthcare system due to RDs. Given the context of improvements in overall public health, there are constrained

resources available for healthcare. Spending on RDs needs to be considered in this overall context of affordability and what you get for each healthcare dollar.

Finally, the preceding commercialization elements illustrate the need for greater cross-functional collaborations from scientific, clinical, pre-launch, launch, and post-launch phases of the product/drug life-cycle than what is typically seen in a pharma company.

ODs present a range of unique challenges for pharma companies looking to successfully commercialize in this space. Issues around diagnosis, medical and economic burdens, pricing and the role of caregivers mean a carefully considered strategy is needed. In many ways, the commercialization of ODs for RDs represents a special case of the industry's shift to specialty medicines and how pharma companies must differently respond to these new challenges.

George Chressanthis is Principal Scientist, and Animesh Arun is Senior Director, both at Axtria, USA. This article has been co-published with Axtria: https://bit.ly/2XOWA4Z

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Perpetual Preparedness

With a no-deal Brexit still a real possibility, Merck continues to prepare for the worst-case scenario.

By James Strachan

In April, the European Council granted the UK an extension of the Article 50 deadline to October 31. This averted a no-deal exit whereby the UK would become a "third country" overnight – at least for the time being. Since then, the British Prime Minister, Theresa May resigned, prompting a leadership contest. At the time of writing, we still have little idea how the first stage of the Brexit process will conclude, with deal, no deal, and perhaps even no Brexit, all still on the cards. This means pharmaceutical companies must continue to prepare for the worst case scenario – that the EU Treaties will cease to apply to the UK on October 31.

We speak with Frithjof Holtz, an expert in Advocacy & Surveillance in Regulatory Management at Merck Life Science, and head of Merck Life Science's Brexit mitigation project to find out which issues have troubled Merck the most and what they have been doing – and continue to do – to mitigate the risks.

When did your preparedness planning begin?

Our colleagues in the UK identified Brexit as a key topic for the company quite early on, so we began monitoring the regulatory and political developments in the UK. At the beginning of 2018, we realized that no-deal was a real possibility, which is when we started to set up more global activities. We created a joint workshop that included the UK organization, experts from the European side and consultancy agencies to discuss what the impact of a no-deal scenario would have for our global operations. The first step was to identify the problems, prioritize them and then work out what we could do to mitigate them.

What were the main problems you identified?

We divided the different issues into a few key workstreams. One of those was regulation – initially our main concern. Would the UK develop its own REACH legislation? Would the rules around the manufacturing or registration of pharmaceutical ingredients change? Obviously, the life science industry is highly regulated and a lot will depend on what the UK does following a no-deal exit. For example, registering APIs separately in the UK could take some time if the registration process was only revealed shortly before the exit date and if it differs from EU27 regulations.

We also quickly realized that a no-deal Brexit would have significant trade and supply chain implications. Merck has a complex supply chain and we had to think carefully about how to mitigate new customs checks at ports such as Calais or Dover, both for the movement of finished products and raw materials – those produced in the UK and exported for manufacturing in the EU and vice versa.

Many of our products are "drop-shipped" directly from a warehouse in one country to a customer in another country. That is only possible if customs clear the supply before it gets to the customer. With no deal, simple courier shipments become much more difficult as each one would require a customs clearance and the use of an intercompany invoice. This takes time and money, while hindering any kind of drop-shipment process currently set up. We have worked closely with our freight partners to develop processes to allow a group of shipments to be collated and then cleared across customs as a single shipment. This will help process shipments quicker and is cheaper, but it is only on offer from certain providers. For some countries and processes (for example, hazardous goods or specially regulated products), even this process won't work and so we will need to ship to a warehouse in the receiving country to ensure the goods can be cleared, and then ship the product to the customer (restock). This will add cost, complexity and significantly increase lead time.

"With no deal, simple courier shipments become much more difficult as each one would require a customs clearance and the use of an intercompany invoice."

What took 24 hours could take several days or more.

Overall, we expect an increase in the workload required to manage the activities linked to customs clearance (payments of tariffs and taxes, processing of paperwork and so on). Of course, the size of additional resources will depend on the final agreement. There would be additional issues around recuperating VAT too, as well as in tracking profitability of UK-sold products.

Dealing with many of these issues will require significant investment in our IT systems.

In parallel, we are also monitoring potential challenges for EU citizens currently working in the UK to minimize potential impacts in terms of attraction and retention of high-skilled staff.

How do you plan to mitigate these issues?

There are a lot of uncertainties around whether or not there will be a deal by October 31, so we have to prepare for the worst-case scenario – significant port delays. We have already started increasing buffer inventory in our UK and EU27 warehouses. For most stocked and forecastable products, we have increased our inventory on both sides by approximately one month and, for some specific, higher risk products by up to four months. This means that even if there are border delays for these products there should be no or minimal delays in supply to our customers. When it comes to raw materials, Merck keeps sufficient safety stock to cover short-term delays, but we have increased our raw material safety stocks by up to one month in most instances. Of course, there may be some complications with fresh materials, so we have also worked with our suppliers on their preparedness – sending out a questionnaire to ask whether they would consider using alternative suppliers. This was dealt with by our central procurement group, which is connected to our broad global network. We have also increased our internal lead times to factor in potential delays at customs.

Changes have also been made to the supply chain (for example, splitting the UK and EU supplies for certain products), where doing so reduces overall risk. Last year, we also announced that we would be investing over €8 million into an expanded UK distribution center. Although this was unrelated to Brexit, it

Merck's UK Footprint

- Merck employs almost 1300 people across 12 sites, spanning R&D to manufacturing, testing, distribution, sales and marketing. They have clinical trials in approximately 70 sites.
- Merck's Gillingham site ships out more than 1.9 million units of products annually for research and biotech production.
- The Livingston site is a Centre of Excellence for the production of monoclonal antibodies for blood typing. Some 72 million blood typing tests are performed annually in the US, Europe and Japan and, of these, 65 percent use antibodies manufactured in Livingston.
- The Haverhill site is a Centre of Excellence for the manufacture of custom oligonucleotides. It is the UK's number one supplier of DNA molecules for research.
- Merck's BioReliance service business employs 400 staff across three sites in Central Scotland. The Scottish sites helps clients with contract safety testing and biomanufacturing across the globe, with 85 percent of revenues coming from outside the UK.
- Merck has 20 percent of its global venture capital invested in the UK. They invested £8.5m in early health research collaborations in partnership with institutions across the country in 2017.
- In 2018 and 2019 thus far, Merck has invested over €8 million in its LS Distribution facility in Gillingham.
- Merck has recently completed a £2.7 million expansion to its Irvine, Scotland biopharmaceutical production facility. The site is Merck's only location where both liquid and powder cell culture media are manufactured.

should mean we are well placed for any challenges post-Brexit.

When it comes to chemical regulations in the event of a no-deal, our UK legal entities, holding a registration under EU REACH, will lose their registrations. This is of course true for all UK companies. This would mean that many new EU registrations and nominations of Only Representatives (OR, a person or legal entity established physically in the EEA that is responsible for complying with the legal requirements for importers under REACH) will be required within existing supply chains to back up our supplies to our EU customers. It also means that our own EU affiliates would legally change their role in the supply chain from "Downstream Users" to "Importers" overnight if the supplier is a UK based company. As I mentioned, we are working with our suppliers and investing a lot of resources into our REACH preparedness, but we can't guarantee there will be no disruption. A permanent or transitory continuation of REACH in the UK, as it is foreseen in the event of a deal Brexit, would be helpful to ensure that registrations held by UK companies remain valid and European supply chains will not significantly be affected.

We are also updating our IT systems so that a group of single courier shipments can be cleared as one transaction, as well as ensuring that the data can be sent to our courier via an interface, which is a significant job. Other changes range from simple updates (e.g., ensuring our paperwork and systems reflect the fact that the UK is an "export" country, or setting up new Northern Ireland "routes") to more complex changes (e.g. ensuring our paperwork is compliant in relation to an Irish branch that we have set up).

Finally, we have set up a crisis management team of six people. Experts in supply chain, customs, tax and regulation have been brought together to help deal with any issues that may arise as a result of a no-deal Brexit. In the event of a no deal Brexit, they would be meeting on a daily basis to closely monitor the situation and deal with urgent issues arising with the import or export processes. The team is currently on standby and is ready to go within one hour so that our activities are responsive. They are also connected to our customer service teams who can distribute information.

Has anything changed after the extension of the March 29 deadline?

In a word, no – everything remains constant. We are still preparing for the worst-case scenario.

Our life science business has more than 20 manufacturing sites in EU27 and five in the UK. And before the March 29 deadline, we mapped our manufacturing supply chain for risks, placed POs early on our suppliers to ensure forward visibility, and moved delivery dates to build buffer inventory before that deadline. We will have similar plans in place for October 31.

Would things change if the deal was

"Dealing with many of these issues will require significant investment in our IT systems."

agreed? Certainly, some of the plans for a no-deal exit on October 31 would be put on hold, but we still wouldn't know what the final deal would be. We therefore continue to prepare for the hardest possible Brexit (the UK, minus Northern Ireland, could still leave the EU without a trade deal or mutual recognition agreement in place after the two-year implementation period, for example). The only major change would be if the UK were to have a second referendum and stop the Brexit process entirely.

As a company, what learnings, if any, have you taken from this process?

Our main concerns at the beginning of the process, as I mentioned, were the regulatory impact – especially around raw materials and registration activities. But, considering our expertise and flexibility, we found that the impact on that end is less critical than we first assumed, with supply chain and customs issues, plus IT emerging as the more significant challenges. There were a number of factors that cropped up throughout the process of setting up the risk mitigation workstreams, such as the link between VAT recuperation and IT.

More broadly, I think we have also learned more about how to deal with a potential crisis. Proper monitoring of regulatory and political developments is key, as well as bringing in experts together as part of a project and having the commitment of top management. The head of the Brexit mitigation team reports directly to the Senior Vice Presidents for supply chain & production as well as quality and regulatory. We also share weekly updates in writing and meet regularly as a team. This ensures a short decision path from upper management, which allows us to be flexible and responsive. We were ready to go before March 29 and will certainly be ready to go before October 31. Overall, I think we've developed skills that could be applied to other challenges in the future.

What role has communication played in your Brexit mitigation plans?

Clear communication is essential – both internally and externally – to mitigate risk. I've already mentioned how we've put systems in place to facilitate quick decision making from upper management, but we've also created feedback loops with our customers and suppliers, so that we're constantly identifying potential issues and putting in place mitigation plans. To this end, we created a Brexit dossier (1), which has been downloaded more than 1500 times. The dossier went through several development cycles and we plan on publishing a third edition to provide further information on specific topics.

Reference

1. *Merck KGaA, "BREXIT FAQ" (2019). Available at: https://bit.ly/2XnV120.Last accessed, July 4, 2019*

A Biosafety Revolution

Biopharma manufacturers have been using the same assays for viral safety testing for decades, but new analytical technologies and molecular approaches offer a faster and more reliable approach. Until the next revolution...

By Afshin Sohrabi, Martin Wisher, and Audrey Chang

Monoclonal antibodies and other biopharmaceutical products, as well as their manufacturing processes, are inherently at risk of viral contamination, making viral safety testing critical. Viral safety testing is mandated by regulators worldwide, and although technologies for biomanufacturing have rapidly advanced, viral testing methods remain largely the same today as they were thirty years ago. Traditional virus detection approaches – cell-based assays – have served the biopharma industry very well over the years, but they have limitations; for example, some assays have long turn around times such as 28 days. In addition, although cell-based assays can detect contaminants, they generally cannot directly identify them and it can be slow to obtain results.

Albert Einstein once said, "Once we accept our limits, we go beyond them." In an age where speed is the key to success, we believe it is time to accept the limitations of traditional testing and to focus on newer technologies that focus on speed, sensitivity and reliability. Faster assay results will lead to more rapid batch disposition, reduced interruption of processing, and also meet the needs of more intensified processing – a key capability given the increasing interest that manufacturers are paying to continuous manufacturing strategies.

The molecular revolution

Although traditional assays remain the standard approach to biosafety and virus testing, biopharma manufacturers are increasingly being drawn to molecular methods such as broad specificity polymerase chain reaction (PCR) and next-generation sequencing (NGS), to expedite viral safety testing.

NGS

Of all the molecular methods available, we think it's fair to say that NGS is the one that excites the industry. Many biopharma organizations employ NGS extensively in early stages of development for cell line characterization. Although the technology has been available for well over a decade, its use in biosafety testing is much more recent – and has only become feasible as sequencing costs have lowered and implementation methods have become standardized.

NGS is so effective as a molecular tool because it enables de novo identification of both known and unknown agents (viral, bacterial, or fungal) with precision and sensitivity. Merck was the first to provide a GMP compliant NGS offering paired with a fully validated bioinformatics platform. However, despite these advantages, currently NGS tends to only be used where traditional testing approaches struggle or fail – for example where a product may be incompatible with cell-based viral detection approaches. However, for newer virus-based therapeutic products, where traditional assays are more challenging, NGS is an attractive alternative to meet virus testing requirements.

PCR

PCR enables detection of DNA or RNA sequences in vitro. It has been used in biosafety testing for the past twenty years, with the biggest advantages being that it is rapid (results available in a few hours) and highly sensitive. The largest issue with traditional PCR, however, is that small changes in the sequence of the target organism genome may result in a failure to amplify and potentially, a false negative result. The application of PCR in biosafety testing has evolved, with quantitative real-time PCR and, more recently, digital PCR approaches, allowing for more sensitive detection and more accurate quantitation of nucleic acid levels.

Other approaches are also enhancing the potential of PCR methods for virus testing. At Merck, for example, we are working on broadening the detection capability of PCR by developing degenerate primer sets that can broadly detect the

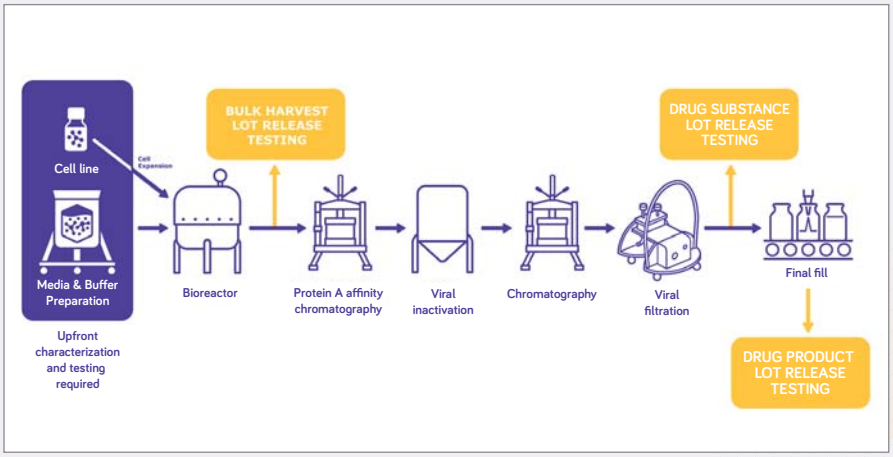

Figure 1: Lot release testing steps required for monoclonal antibody production.

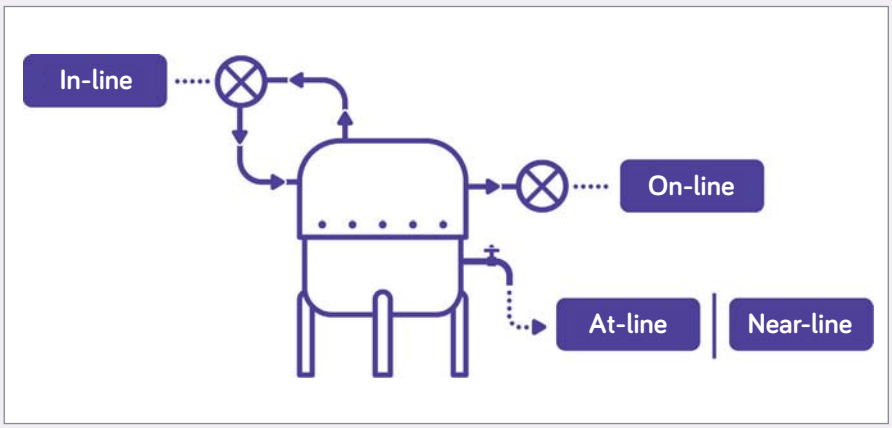

Figure 2: Diagram of the potential testing points from the bioreactor. In-line: bioreactor material constantly monitored. On-line: direct sampling of bioreactor for automated testing. At-line: sample removed for testing within manufacturing suite. Near-line: sample removed for testing within manufacturing facility.

seven families of DNA viruses and 14 families of RNA viruses relevant to CHO manufacturing. This novel approach using familiar technology enables us to identify a contaminant in a single test, rather than having to perform multiple different PCR tests. In our view, this expands the breath of detection while keeping the sensitivity and speed of PCR, opening up a huge opportunity to accelerate biosafety testing.

The next revolution

As both NGS and PCR methods evolve, they present clear opportunities to accelerate virus testing, which is meeting the needs of an industry that is looking for real-time decisions and information on the quality of the drug being manufactured. Indeed, these methods and other rapid testing technologies, such as biomonitoring and pyrogen detection, enable biopharmaceutical manufacturers to control their most important commodity – time.

A central conflict that we often see is that, although willing, biopharma manufacturers are often hesitant to implement new testing technologies due to concerns over regulatory implications. However, the regulatory documents on biosafety testing encourage the implementation of methods where it is demonstrated that the method is as good as, or better than, an existing technology; and that it meets the intended purpose of testing. The good news is that with the rise of cell and gene therapies, regulators are more frequently exposed to alternative and rapid testing strategies as traditional approaches are often not compatible with these modalities and the newer methods offer the only viable option for viral safety testing.

As any manufacturer will tell you, development of testing methods is only half the story. At Merck, we are investing on the development of new biosafety methods and we also validate the performance of these tests to ensure they meet stringent GMP standards, thus bringing the confidence drug manufacturers need to use them.

Testing methods and approaches will continue to advance but the next revolution in viral safety testing may come sooner than we think. As biomanufacturing is moving to connected, continuous, intensified, and more automated processes, the notion that these highly developed manufacturing processes can wait for the time-to-results from traditional adventitious virus assays seems unlikely. The processes of tomorrow are looking for testing that can provide real-time test results enabling fast lot release, without compromising quality.

A current buzz in the industry is in-line testing, where testing is performed within the bioreactor environment for both ongoing monitoring as well as bulk harvest lot release. Realistically, not all technologies can be implemented this way and, to meet the needs of rapid time to results, some tests must evolve from being run in a testing lab away from the manufacturing site, to being able to be run close to the manufacturing line. We call this near-line testing. As the technologies develop, they can be brought ever closer to the manufacturing process, with testing on the manufacturing floor, or at-line. Our current thinking is that the closest these test technologies can get will be on-line, where a sample is taken from the process and consumed within a fully automated test. It is only with this evolutionary approach that virus testing timelines can reduce from days to hours, thus enabling intensified and ultimately continuous manufacturing processes (Figure 2).

Our teams of technical experts have been proudly supporting the biopharma industry for over 70 years with BioReliance® biosafety services and are committed to developing tests and services to support the evolving biologics market. Our experts understand the different needs of the processes that comprise drug product manufacturing and will work with you to design a solution that fits your needs.

Afshin Sohrabi, Ph.D, is Head of Near Real Time Testing Lab; Martin Wisher is Senior Regulatory Consultant; and Audrey Chang, Ph.D, is Head of PSS R&D. All are focusing on the BioReliance® biosafety portfolio at Merck. The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

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Foresight is 20/20: Lessons Learned with Claudia Zylberberg

Claudia uncovered a gap in the market for high quality ancillary materials during her time in the human plasma industry – and combined that with her belief in the future of cell and gene therapies to found Akron Biotech. Here, she reveals the lessons learned along the way and offers her perspective on the now booming advanced therapies industry.

A gap in the market is good, but a gap in an emerging market is better

I am originally from Buenos Aires, Argentina, where I began my doctoral work, which eventually became a cross-institutional PhD project that took me to the University of British Columbia in Vancouver. Following a move to the United States, I completed two postdocs in Florida before taking a job in the human plasma industry with a company called Nabi Pharmaceuticals, where I worked in bioinformatics and recombinant protein development.

At Nabi, we were working on recombinant vaccines for S. aureus. One of the critical components used during the manufacturing process, an enzyme, was causing a number of quality-related problems. I went to visit the vendor, and they told me that they couldn't manufacture it at a higher grade or in a more stringent environment to improve its consistency because the cost was too high and there wasn't the market for it. Essentially, it was "take it or leave it" – and we couldn't make the vaccine without the enzyme. I realized then and there that there was a gap in the market for reliable, high-quality materials for the production of biologics and advanced therapies, so I left Nabi to set up Akron. While Akron was getting off the ground, I actually co-founded a stem cell bank with the idea that, in the future, you might be able to make use of younger, and potentially healthier, stem cells. Even then, I was excited – and literally banking on – the future of cell and gene therapy. It was clear to me that the field of regenerative medicine was about to take off in earnest, and that for these therapies to be successful, the market would need high quality ancillary materials. Akron has been growing steadily since 2006 on the hypothesis that high quality ancillary materials would be critical to the clinical and commercial success of these life-saving therapies.

Never underestimate the importance of quality – especially for living therapies

When I started Akron in 2006, the industry was still in its infancy. Since then, and especially with the first CAR-T approvals, I have seen the industry evolve to the point where the scientific questions are being answered. There is a tremendous amount of excellent research driving the field forward, and we have seen some of these early findings yield incredible clinical advances. In many ways, the debate has now moved to the important questions of how we can reduce costs while maintaining high quality standards, thereby ensuring that patients have access to safe and effective therapies. Ancillary materials play a crucial role when it comes to cost and quality.

At Akron, we develop and manufacture ancillary materials as well as provide specialized services to accelerate the development and commercialization of advanced therapies. Our aim is and has always been to develop and manufacture high quality products that we think are, or will be, essential for the industry's continued growth.

I was recently on a panel where a representative of the FDA articulated just why the quality element is so important. He pointed out that cell therapy products cannot be sterilized, which means that what you put into the manufacturing process is crucial to the final product's quality. And we see this idea reflected in FDA guidance, which discusses the need for greater detail on the source, quality and manufacturing of ancillary materials. And this trend is global. Indeed, other national regulatory agencies are pondering the same sorts of questions, and in the transnational arena, ISO has put together an ancillary material standard (a technical document) that we, along with others from Europe, Asia and the US, helped to create.

But quality is also closely tied to cost. Today, we're seeing a great deal of interaction between developers' supply chain teams and their suppliers – it's a much closer and stronger relationship than in the past. And that's because some of the components that go into a cell therapy are extremely difficult to find, so sourcing

"It was clear to me that the field of regenerative medicine was about to take off in earnest."

isn't easy. And there's a lot of risk involved because the quality standards haven't yet caught up and aren't set up for the fact that these new products can't be sterilized. Manufacturers must build expensive and time-consuming measures into their supply chains to mitigate that risk. We are all walking a fine line, trying to increase quality while containing cost. Ancillary materials will thus play an important role in streamlining manufacturing and reducing costs – even I had not appreciated how important they would become when we first started the company.

"I love what I do and I think passion is vitally important. The field has a great deal of promise – especially for patients who don't have many options."

Ask yourself: what legacy will I leave?

I spend a lot of time working with industry organizations and regulatory bodies. Sitting around tables, sharing thoughts, listening and challenging one another is what will make the industry grow. The industry as a whole is new and we need to work together to facilitate its development.

I love what I do and I think passion is vitally important. The field has a great deal of promise – especially for patients who don't have many options. One of my main drivers is thinking about what legacy I will leave. In the early days of the cell and gene therapy industry, I was frustrated because it seemed like everyone was speaking a different language. I felt that I needed to participate in the discussions by sitting on advisory boards and writing papers in an attempt to harmonize standards and practices in the industry. And I hope that bringing the industry together so that we can move forward faster will be part of my legacy.

Engaging With Your Peers

Claudia is active within a number of cell and gene therapy industry organizations, including:

- Centre for Commercialization of Regenerative Medicine, Member Board of Directors
- National Academy of Sciences, Member Regenerative Medicine Forum
- International Society for Cell and Gene Therapy (ISCT), Member of the Strategic Advisory Council
- Standards Coordinating Body, Member of the Board
- Alliance of Regenerative Medicine Foundation, Member Board of Directors
- ARM Alliance of Regenerative Medicine, Member of the Board
- BioFlorida, Board of Directors and Co-Chair of the Biobusiness track
- Theradaptive, Advisory Board Member

Claudia Zylberberg: "It's interesting to see how industry organizations have evolved over the past decade. For example, ISCT used to be made up of hospital-based academics and doctors – usually technical specialists. Now you see an increasing number of industry representatives. The influx of industry people started with smaller companies, usually spun out from universities. Now you see the likes of Novartis and Pfizer at the table because they're interested in how to incorporate these new therapies into the big pharma model. I think these industry forums are where you really see the industry's incredible rate of growth and get energized for the road ahead."

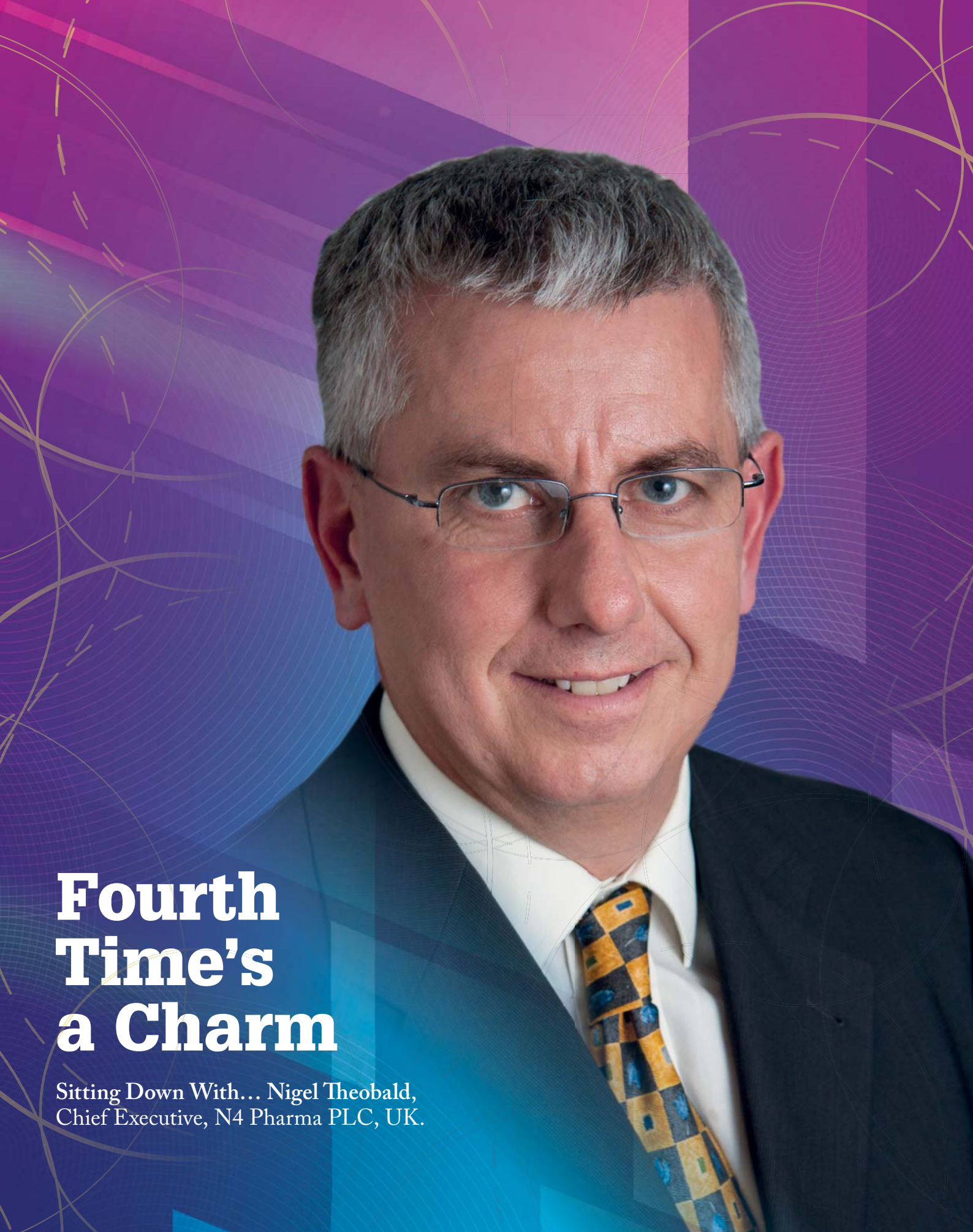
It's also about being part of something bigger than yourself. I am passionate about education, whether it be for scientists, business leaders or patients; this is why I chose to get involved in the newly formed Alliance of Regenerative Medicine Foundation, whose primary purpose is to educate. But this also extends to the next generation: I actually write children's books about science. One book I published a while back called "You're Full of Genes" was interesting because it was read by both children and adults, who wanted to learn or brush up on the basics. I believe a more educated public on the science of genes and cells can only help our industry – plus I really enjoy it. I would love to pursue it further (if I had more time!).

Witness the strength of street knowledge

I always knew I was going to set up my own business – it was just a matter of time. In the beginning, I felt a little under-utilized given everything I'd learned during my time in academia. I felt there wasn't much space to adjust, but once I'd made the switch there was no going back. Industry is a completely different environment to academia and adjusting to it can be challenging – though over time I have learned to really enjoy it. I had to learn business on the fly. I didn't have time to pursue an MBA when I could've used it most – early on, when knowledge and connections are most important to getting a new business off the ground. So I learned the hard way. I've picked up some bumps and bruises along the way, but I do believe that business is best learned in practice – on the street. Everything is nice and clean in theory – you don't truly learn how to run a business when you don't have any skin in the game.

Be persistent – but don't bang your head against a wall

I'm proud that I was able to emigrate to the US and make a success of a business – really from scratch. If there's one thing I've learned, it's that you must persevere. I wanted to give up many times, especially during the economic crisis in 2008. It happened just after we had started the company and there were certainly moments when I thought it might be easier to give up. At these times, you have to be honest with yourself; sometimes you have to move on and admit that what you're doing isn't working. But you also have to be sure that it's for the right reasons. I think success comes from knowing, not hoping, that what you're doing has great potential, and then persevering through the hard times to make it a reality.



Fourth Time's a Charm

Sitting Down With… Nigel Theobald,
Chief Executive, N4 Pharma PLC, UK.

Tell me the story of your career before N4 Pharma...

I'm not a chemist or a biologist – I studied economics at the University of Southampton in the UK. Early in my career, I worked at Boots the Chemist, initially marketing baby products (which was handy, because I had two young kids!). I then moved into the healthcare and medicines branch, and eventually became Head of Healthcare Product Development just before I left back in 2001.

My goal was always to have my own business at the age of 40. And I set one up just as I turned 41 – so I was on track, give or take a few hours! My initial consulting company produced contacts enabling me to set up my second business, a specialist distribution company for the European market – a really challenging sector because of the competition from a number of big players. Following that, I was asked by some investors to set up and run a company called Oxford Pharmascience, which developed a new ibuprofen formulation that reduced gastric irritation. The company grew significantly but my aim was always to set up and make a success of my own business. So I sold my shares and used the funds to found N4 Pharma – my fourth company, hence the name.

Does your economics background give you an advantage as a CEO in the pharma space?

I think it gives me a different perspective. I might not necessarily understand the ins and outs of a given technology in great detail, but I am able to focus on why someone might want to use a system, which is crucial. It can be easy, with all the amazing technologies out there, to lose sight of what it takes to successfully develop and commercialize a product. I passionately believe that we shouldn't do things in this space just for the sake of science. And that was the approach we took with N4 Pharma, speaking with a number of scientists to evaluate their technologies and see whether they had commercial traction or not. And that approach eventually led us to Nuvec.

What's the story behind Nuvec?

After evaluating a number of technologies, we agreed an exclusive commercialization deal with the University of Queensland for a nanosilica system for delivering vaccines and therapeutics. The original Queensland technology works like a hollow, porous practice golf ball that moves slowly through the air – these holes allow the vaccine inside but slows down its release from the particle. The original plan was to develop a vaccine delivery system for hepatitis B to reduce the number of doses per day from three to one. But we decided to go down the DNA and RNA delivery route as there was a great deal of investment in that area. The system didn't work for DNA and RNA, but it just so happened that the Queensland team had a version with spiky hairs on the silica surface that could attract and protect DNA and RNA from the nuclueus; we have called this Nuvec.

We have done a great deal of in vitro work and some early preclinical in vivo studies show that it can safely travel to cells, get across the cell wall, break down in the cell to produce antibodies and doesn't drift to the liver (as it stays at the site of injection). As we've carried out further in vivo experiments we found that our CRO partners were working slightly differently to our original successful in vivo study. So we're taking a step back to make sure the antigen loading protocol is fully standardized before embarking on further in vivo studies. These are some of the challenges of working without an internal R&D team!

What are the secrets to success as an entrepreneur in the healthcare/pharma space?

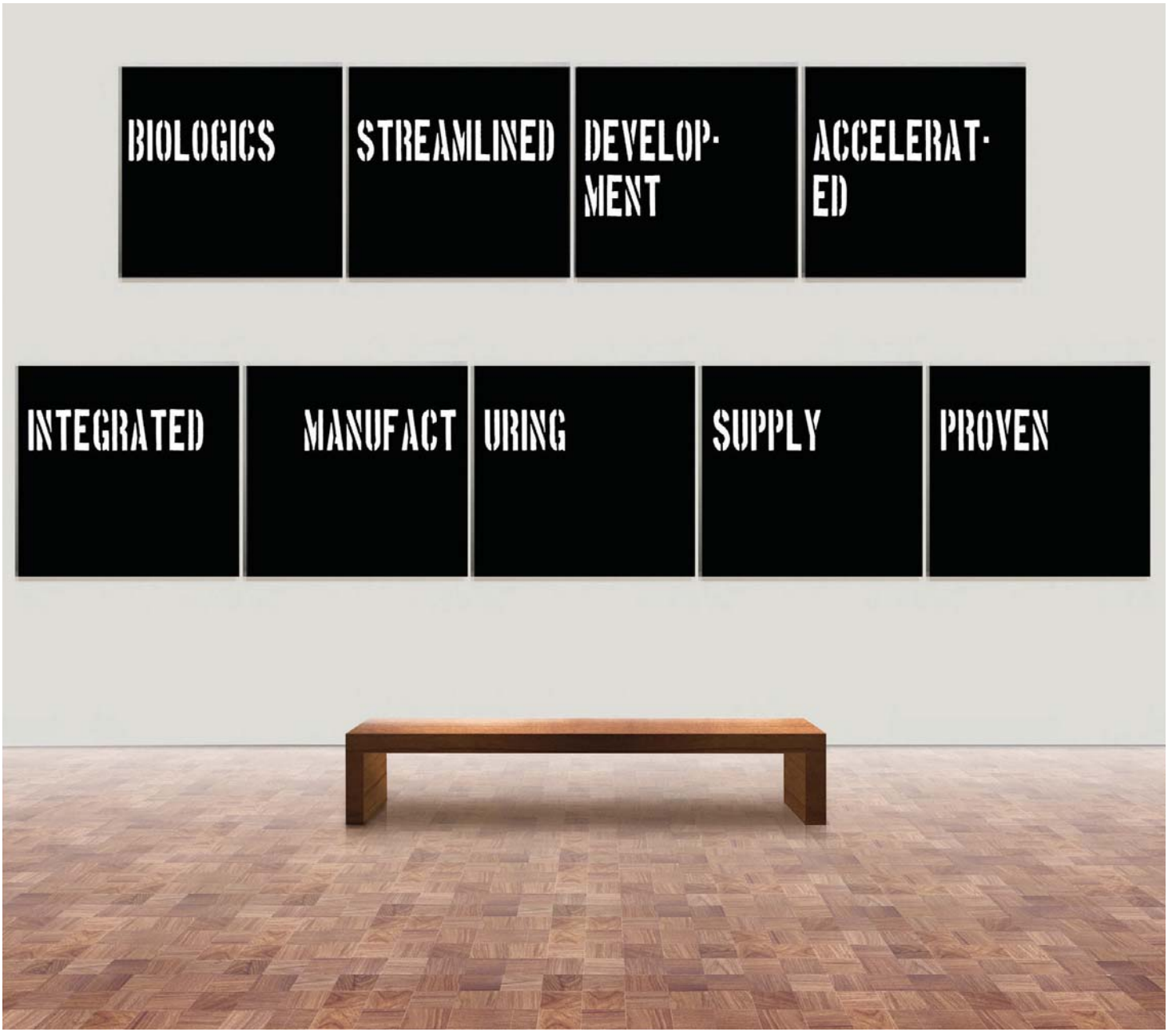
It's interesting; I don't think the secret is necessarily being a good entrepreneur. The key is getting access to capital right from the get go. In fact, and this might be controversial, you could say the secret to success is to be American! The American model basically involves sitting down in front of investors and explaining what your idea is and how much money you'll need to turn it into a success. If they like the idea, they will give the money upfront and tell you to go away and do it. In Europe, you might get a fraction of that money upfront, then another fraction a year later, then more two years later, and so on. It's a slow, target-driven approach; and as a result, European companies sometimes struggle to get the right level of funding to develop their life science assets. Overcoming these problems is key to success.

What advice would you give an entrepreneur in this space?

Form partnerships that are truly mutually beneficial – so that your success and your partner's success are co-dependent. I remember a company from my time at Boots that had developed an improved version of ibuprofen. They started working with a new Indian company to make the product for them and their approach was to create such a strong partnership that the success of both companies really hinged on the success of the product – it was in nobody's interest to suddenly switch suppliers and start undercutting each other. In the end, they both became very successful.

What's one thing you wished you knew when you started your career?

Honestly, nothing! If I knew then what I know now, I wouldn't have become the person I am today. In any case, if I did hear something mind-blowing 20 or 30 years ago, I don't think I would have quite realized it so I doubt it would have changed things!



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