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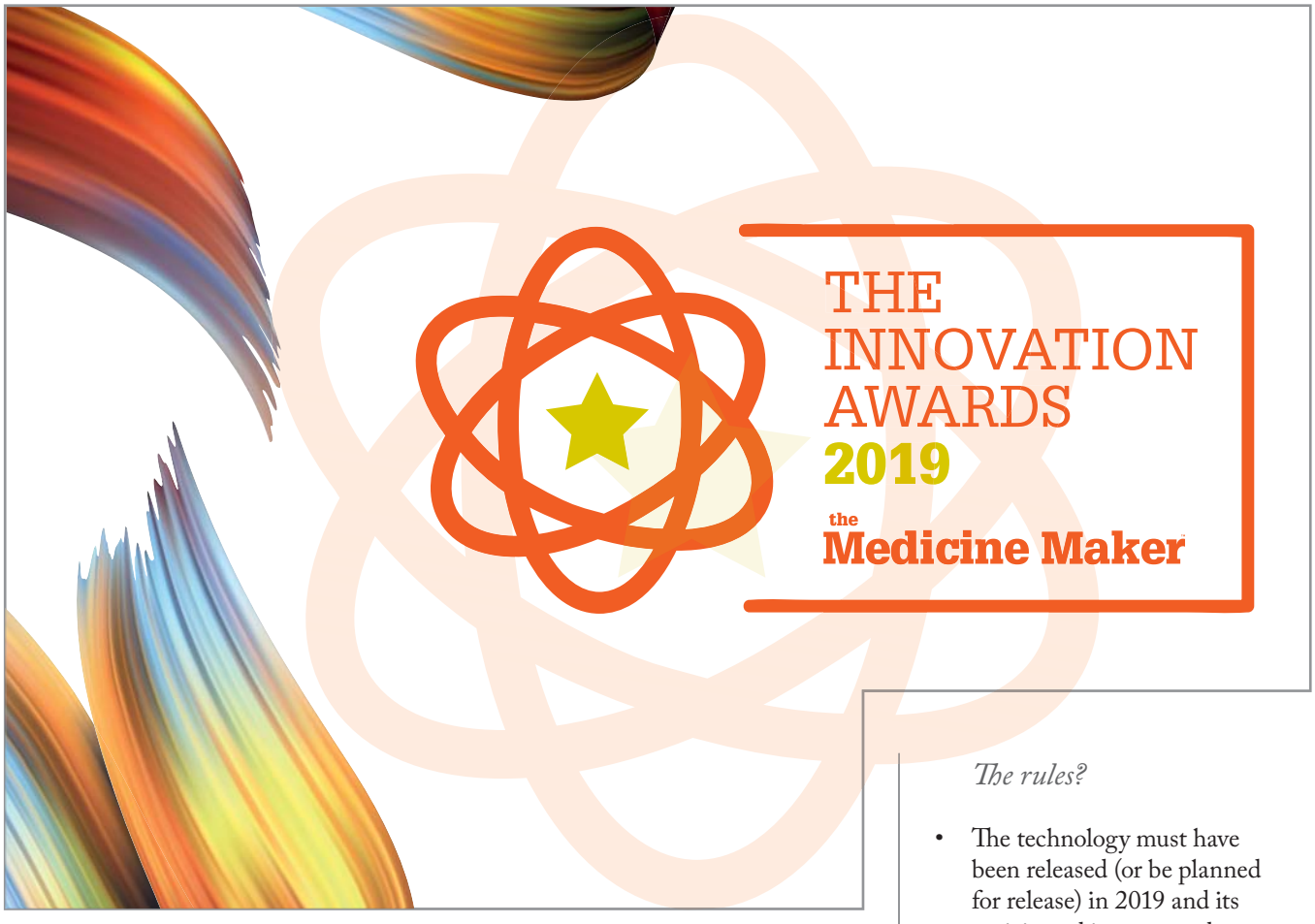


Nominate Now for The Medicine Maker 2019 Innovation Awards

Do you want to share the story behind your technology in a future issue of The Medicine Maker?

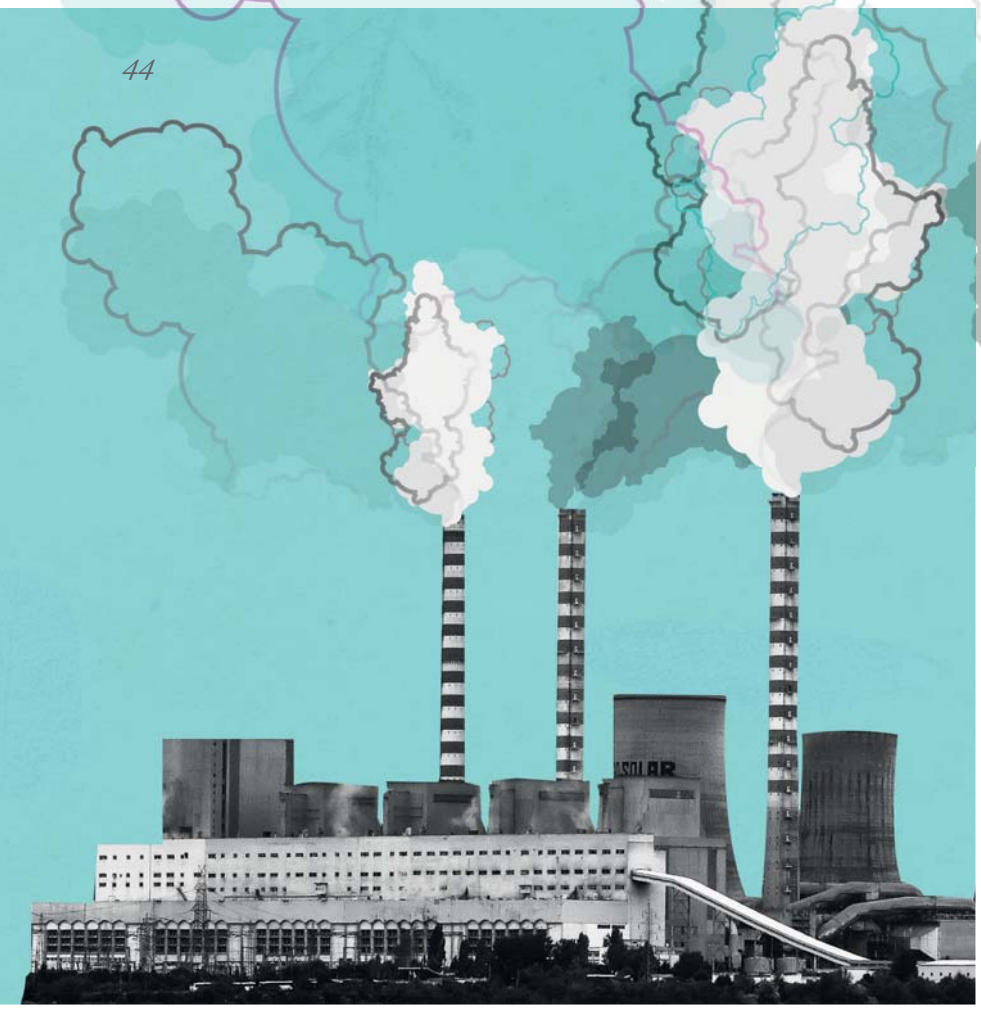
In our December 2019 issue, The Medicine Maker will showcase the top 15 technologies released throughout 2019. The final winner will be decided by a public vote and be given the opportunity to tell the story behind their innovation in a 2020 issue of The Medicine Maker.

The nomination form for the 2019 Innovation Awards is now live: tmm.txp.to/innovations19-noms

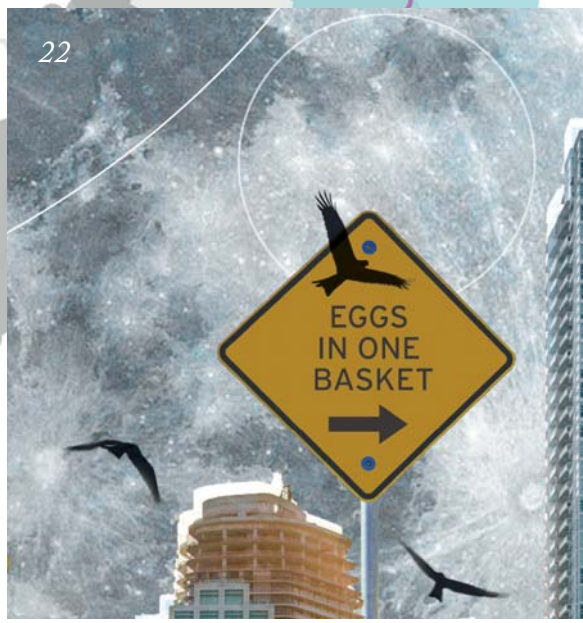
The rules?

- The technology must have been released (or be planned for release) in 2019 and its anticipated impact on drug development and manufacturing should be significant.
- The innovation can be a piece of equipment, IT software, formulation technology, drug delivery method or any other product or service that you think could fit the bill.
- The deadline for entry is October 25, 2019.

Contents



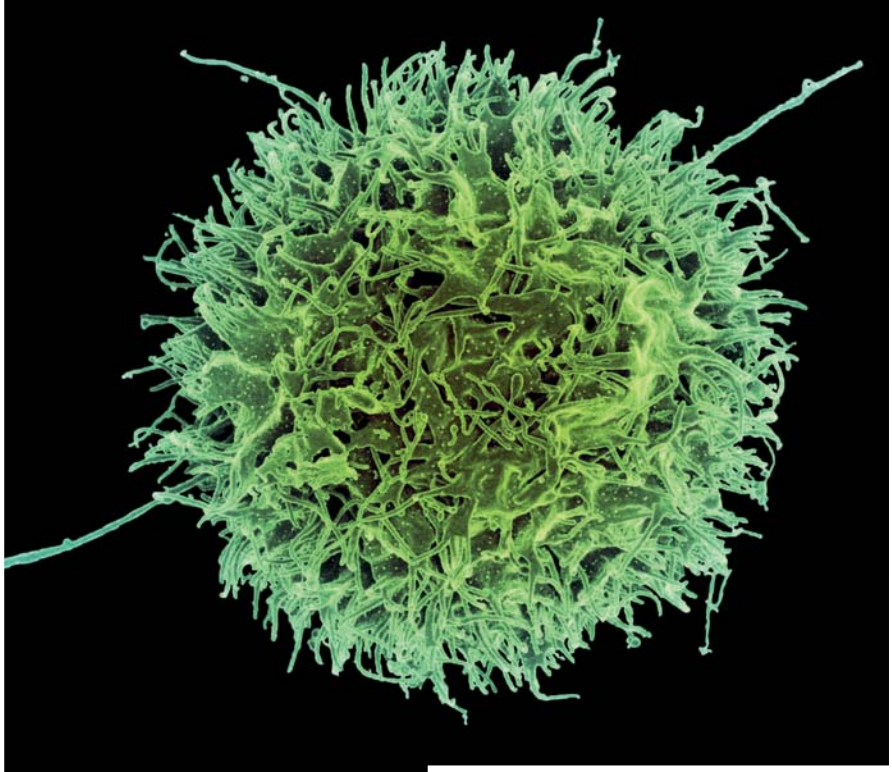
44



22

On The Cover

Decisions, decisions… experts discuss the challenges of choosing outsourcing partners.



12

50

Best Practice

NextGen

Reports

Sitting Down With

the **Medicine Maker**

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

General enquiries:
www.texerepublishing.com
info@themedicinemaker.com
+44 (0) 1565 745200 sales@texerepublishing.com

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Waking the Sleeping Giant

Will the antibiotic crisis kill us all?

Most professionals in the pharma industry are well aware that the lack of innovation in antibiotic development is a serious problem. But, with few solutions, a head-in-the-sand response is too tempting. The business reality of the situation is pretty clear: there is no profit in antibiotic R&D and making drugs at a loss is not good for a company's future.

That said, there is no shortage of fascinating work on new antibiotics happening in the research community – and there are plenty of untapped natural reserves that may harbor promising new avenues (fish slime, soil, and fungus, to name just a few). There are also many government sponsored initiatives and funding opportunities designed to kickstart the development of promising new antibiotics. But given that the industry has been talking about the antibiotic apocalypse for years (indeed, the topic was featured in the very first issue of The Medicine Maker: https://bit.ly/2YwuJXE) and little has changed, it's high time for a serious reassessment. New research will be useless if there are no commercial prospects enticing enough to wake the sleeping giant. With the collective intelligence and technologies of the pharma industry, we could work our way to treasure-trove of new antibiotics. But "treasure" means different things to different stakeholders…

I was interested to see an announcement in the UK about a new subscription payment model that aims to incentivize the development of new drugs for resistant infections. Instead of a drug company being paid based on the volume of antibiotics sold, companies would still be paid even if the drug was stored for reserves. The country's National Health Service is calling for companies to identify products to be considered for the initial phase of the test. The project will be evaluated from the very beginning, and the findings shared with the rest of the world so that other healthcare systems can test similar models.

It is refreshing to see the problem being looked at from a different angle – and to see a healthcare system stepping up. But it would also be good to see (big) pharma being more proactive in suggesting other innovative approaches that could help fund R&D for vital – though currently commercially unattractive – products.

Stephanie Sutton
Editor

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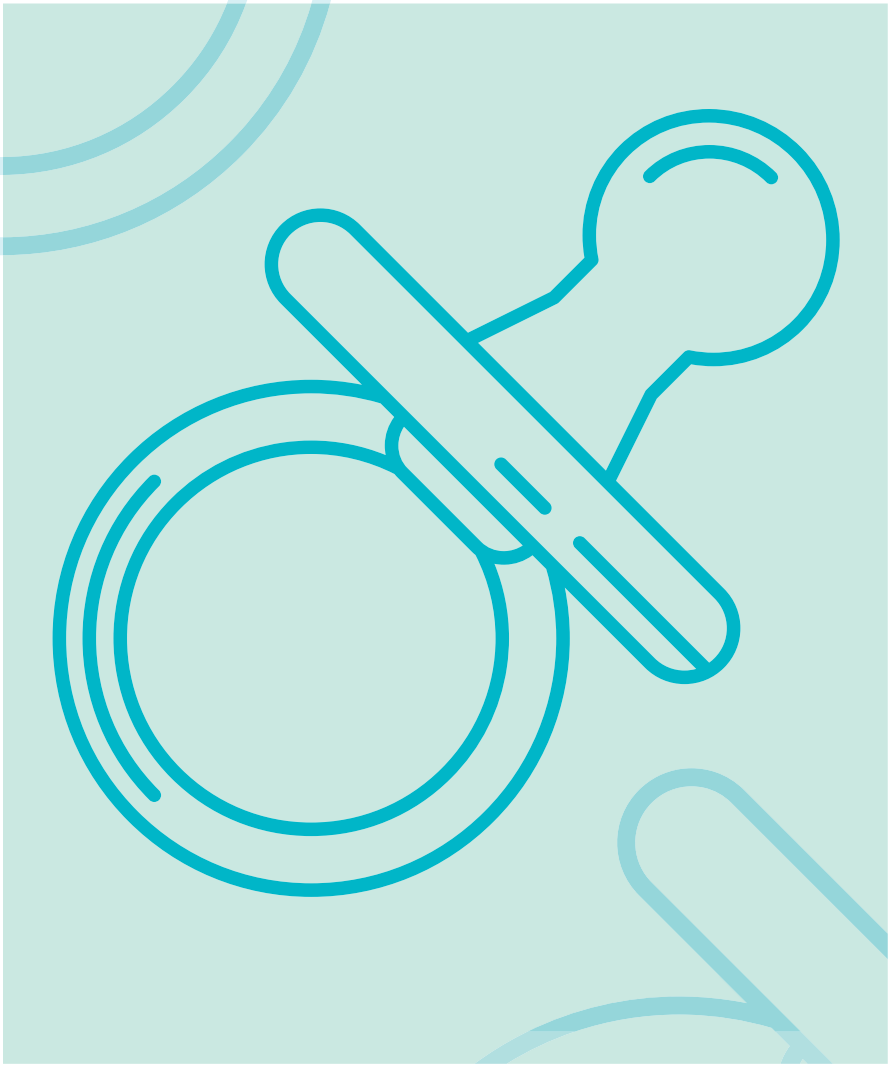
Upfront

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



Doing it for the Kids

Pfizer aims to improve pediatric clinical trials with increased investment

Looking to improve medicines for children, Pfizer is investing £5 million in its Discovery Park site based in Kent, UK. Pfizer has a long-standing relationship with Kent County Council. "Since 1954, we have invested in manufacturing and advanced science capabilities. Our priority is to continue to ensure that the local area remains a hub of scientific excellence and a vibrant life science community," says a Pfizer spokesperson.

Pediatric clinical trials can often be limited by the complexities associated with the demographic. Patients who fall into the category can be divided into several age groups, with each presenting different physiological characteristics with different pharmacokinetic and pharmacodynamic parameters. Dose flexibility and formulation, as well as

poor patient compliance due to potential issues with taste-masking, can also hinder the success of trials.

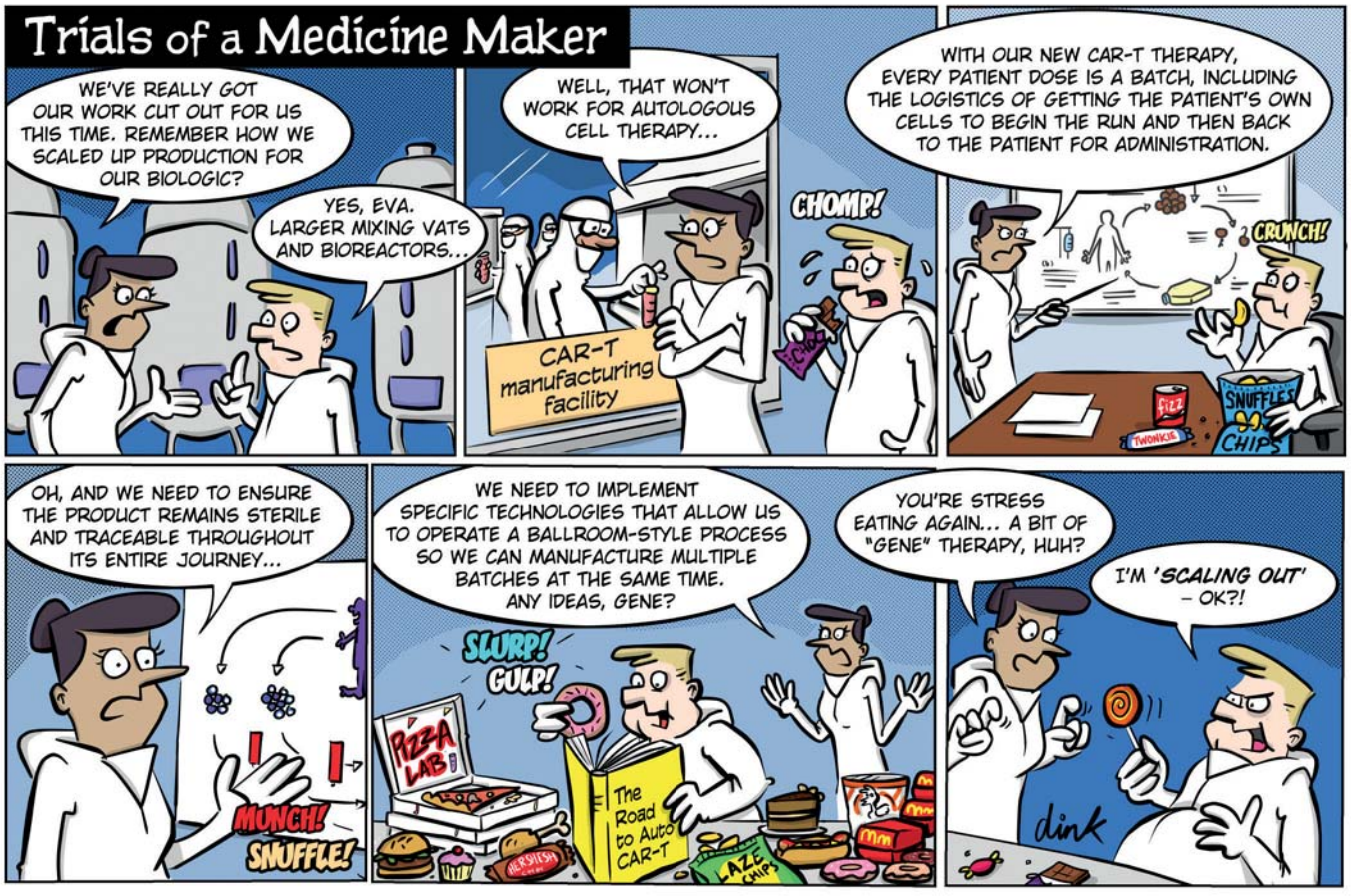
Pfizer hopes to deploy highly-specialized manufacturing technologies at the Kent-based site to help its scientists explore innovative ways to make medicines more palatable for children and to modify release technologies to make them better suited to young patients.

"Existing release technologies are made to be used in adults and cannot be effectively scaled down to meet the needs of a pediatric population," the spokesperson explains. "We aim to develop manufacturing technologies which can be scaled up or down to provide more efficient manufacturing solutions for highly-varied and unpredictable clinical trial demands."

The company plans to commission the new manufacturing technologies toward the end of the year and expects to supply medicines for enhanced clinical trials from 2020. They are interested in hearing from and partnering with companies and research institutions who "share their vision of improved pediatric technologies and patient-centric design."

Since 2018, Pfizer has invested more than £36 million into advanced manufacturing and innovation at the Sandwich site. And despite industry-wide uncertainty around Brexit, it seems that Pfizer is committed to the UK. "Thanks to its scientists, universities and industry, the UK is a world leader when it comes to R&D. Private investment is key to this long-term success. This latest round of investment builds on a series of investments we have made over the past few years and will help secure that legacy for years to come," said Pfizer.

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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Inside the World's Most Expensive Pharmaceutical Market

Costs in the US have doubled for almost half of top-selling branded medicines over the past six years

The sky-rocketing prices of drugs in the US has been highlighted to a global audience in recent months; the price hikes of much-needed drugs, such as insulin and Humira, have become the subject of much debate. With a single vial of Humalog, a branded version of insulin, costing $274 in 2017 (1), many Americans are priced out of access.

"While high prices are of no benefit to the average citizen, they are even worse for the 12 percent of adults who fall into the category of being uninsured or underinsured. These patients pay based on the list price of the drug, and not on the "true," post-rebate prices. As the gap widens between list and post-rebate prices, these patients pay disproportionately more," says Nathan Wineinger, Director of Biostatistics and Assistant Professor at Scripps Research.

Wineinger is first author of a paper recently published in The Journal of the American Medical Association that outlines the growing trend for inflated Rx drug prices in the US (1). In their evaluation of 49 common top-selling branded drugs, the researchers found that 78 percent of the drugs that have been available since 2012 have seen an increase in insurer and out-of-pocket costs by more than 50 percent, and 44 percent have more than doubled in price.

Previous research has found that the prices of top-selling branded drugs in other developed nations pale in comparison to the US where, spending on drugs per capita is anywhere between 54 and 209 percent higher than other high income countries (1).

"Legal protections grant large pharmaceutical companies market exclusivity and limit competition. The fact that US law prevents adequate negotiation against these high costs also contributes to the US' unmatched drug pricing policies," explains Wineinger.

The US experienced record levels of growth in drug pricing between 2014 and 2015 as several innovative products made their way to market. Though spending slowed in 2017 due to lower price increases for protected branded products, net pharmaceutical drug spending still reached $324 billion (2).

As manufacturing volumes increase and the research conducted on currently available branded drugs is scant, how are the prices being justified? Some industry players and advocacy groups argue that lowering drug prices would have a knock-on effect on R&D, impinging on the US' capacity to back innovative research. But Wineinger disagrees. "The contention that excessively high prices and spending are necessary to foster innovation has not been shown to be true," he says. "Public funding of research substantially contributes to the development of new products. Yet the notion that there would be a drastic drop in innovation in the event of cutting drug prices seems to be widely held."

Peter Bach, Nancy Yu and Zachary Helms, all based at the Memorial Sloan Kettering Cancer Center, empirically tested the claim that premiums earned from charging US patients and taxpayers more for medications than other western countries fund research. They found that the premiums earned were substantially higher than the amount spent by companies on R&D (3), meaning there are billions of dollars not being invested back into research.

Another issue associated with US drug pricing is the impact of US patents, which reduce competition from generic drugs. Drug patents filed in the US are granted exclusivity rights for 20 years from the date of application and the FDA extends a five-year period of exclusivity for any NCE, even if it lacks patent protection. Many drugmakers also take advantage of the opportunity to extend their exclusivity rights, monopolizing the drug patent sector and blocking the introduction of more affordable generic products.

"When generics enter the market, the overall cost of specific drug products drop as competition increases," says Wineinger. "However, manufacturers may take advantage of patent laws to extend the exclusivity of a product, maintaining high costs. The original patent for Humira, the number one selling product in the world, expired in 2016. Yet biosimilars will not be available until 2023 due to patent extensions."

Recently, the Trump Administration has moved to enforce drug list pricing in TV adverts, but will it make a meaningful difference? Wineinger thinks that much more needs to be done. "Health is an inelastic right for all, or at least it should be. Patent laws need to be revisited to bring about impactful change," he argues. "We also need greater negotiating powers so that the economic and clinical value of pharmaceutical products can be

thoroughly assessed. What we pay as a society should be proportional to the inherent value of a given product."

In May, the House of Representatives in the US passed several bipartisan bills to lower drug prices. The aim of these bills was to allow the American public better access to affordable and generic medications and prise away some of the influence that manufacturers of branded drugs have over the industry. But it is not believed that the bills will make it through the Senate because they lack enough Republican support, mainly due to the fact that the bills also include provisions to bolster Obamacare.

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Celebrating Young Talent

Georg Winter wins the Young European Investigator award for his work on undruggable targets

Eppendorf recently presented the 2019 Young European Investigator award to Georg Winter, Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria. First established by the company in 1995, the prize recognizes the innovative contributions made to biomedical research by Euopean scientists.

Winter developed a novel method for targeting specific proteins for degradation using heterobifunctional chemical compounds to specifically recruit ubiquitin E3 ligases to intended protein targets for destruction. The disease-relevant proteins that were the focus of the research had been deemed thus far "undruggable." According to Eppendorf, the work has led to significant excitement in the pharma industry because of its potential to be used for new cancer therapeutics and other indications.

Winter has received prize money of €20,000 and credits his colleagues and mentors for their support and collaboration. "I've had many close and fruitful collaborations with other talented researchers whose advice and mentorship made a world of difference to my investigations," he said.

Eppendorf is now accepting applications for its 2020 award. Nominations will be accepted from October 1, 2019 until January 15, 2020. The Young European Investigators award is open to candidates aged 35 or younger.

More information about the award can be found at: https://bit.ly/2yfWIjx.

Innate Response

Can the innate immune system be reprogrammed to fight cancer? Inmune Bio believes the answer is yes

There are two parts to the human immune system: adaptive and innate. There are many therapies designed to improve the adaptive immune response against cancer (for example, vaccines, CAR-T cells and immune checkpoint inhibitors), but far fewer efforts focus on boosting the innate immune system response to cancer. According to Inmune Bio CEO, RJ Tesi, if medical practitioners only have access to therapies targeting the adaptive immune system then it's like trying to fight with just one hand... Tesi wants to bring the innate immune system into the ring. We asked him more about the company's research.

What inspired this approach to treating disease?

Early in his career, our founder, Mark Lowdell, determined that NK cells – not T cells – are responsible for eliminating minimal residual disease (MRD). Cancer relapse, the disease that kills the most patients, is caused by MRD. At the time of his discovery in the late 1990s, this finding was considered very controversial, but today it is well accepted – and attempts to improve NK cell function are gaining traction in the clinical and drug development community.

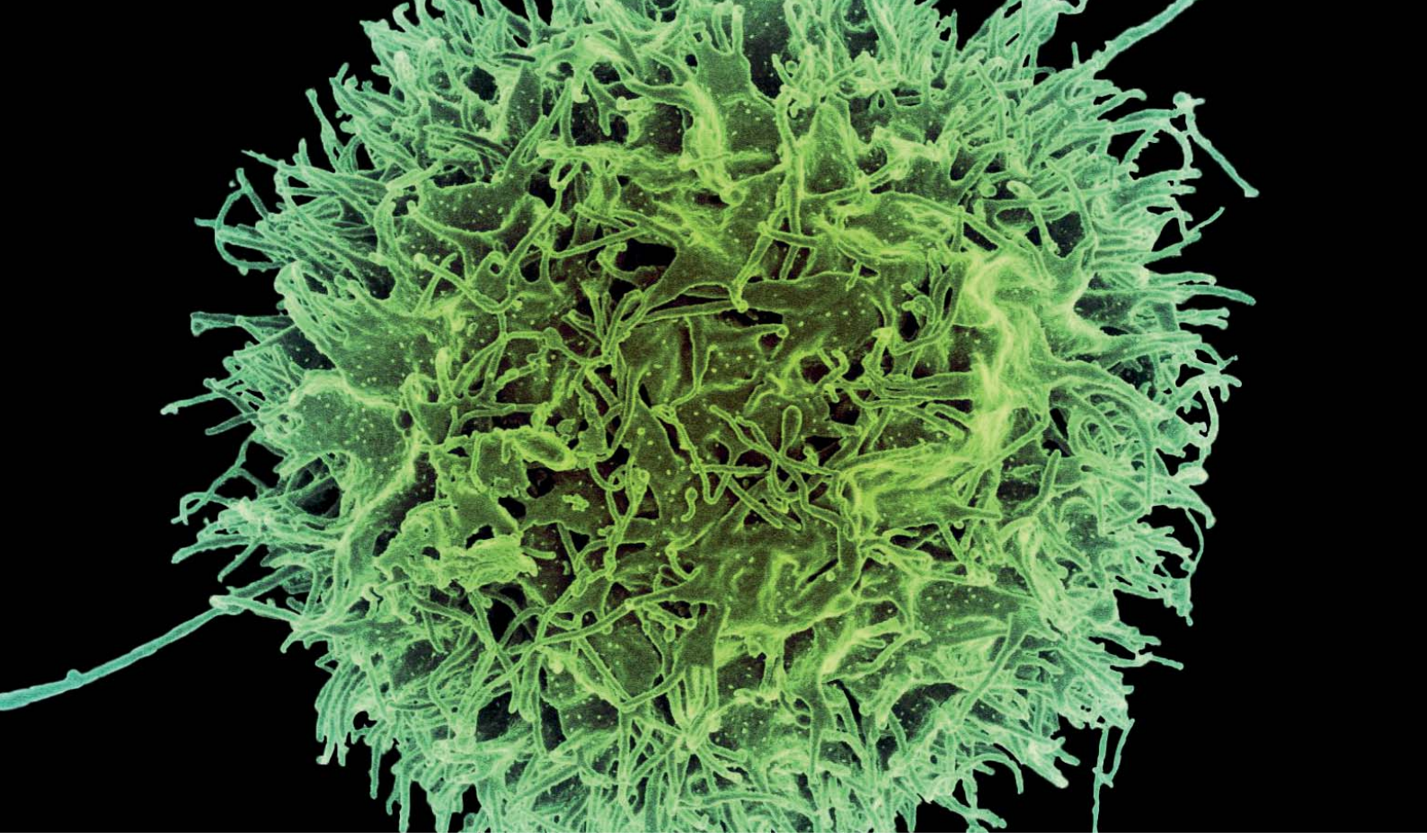
Inmune Bio was founded on INKmune, our first program, but we haven't stopped at NK cells. Both microglial cells, the immune cells of the brain, and myeloid derived suppressor cells (MDSC, the cells that protect cancer from immunotherapy) are part of the innate immune system. We have been targeting microglial cells and MDSC with Xpro1595 and INB03 respectively in an attempt to treat Alzheimer's disease (AD) and cancer.

How far have you gone down the translational path?

All our programs are in phase I. The INB03 program in cancer is enrolling patients and the Xpro1595 program for AD is screening patients for the trial. We hope to enrol the first patient soon. The INKmune program will be enrolling patients in the fourth quarter of 2019. By the end of the year, we will be enrolling patients in three phase I trials!

Why do you think this approach is a promising avenue for fighting Alzheimer's?

AD and dementia are caused by nerve cell death and synaptic dysfunction. Without synapses, nerve cells cannot communicate. Even if you have good nerve cells, if there is synaptic dysfunction then you will get dementia. Synaptic dysfunction means weaker, fewer or otherwise malfunctioning synapses. Neuroinflammation is caused by activated microglial cells, which secrete inflammatory cytokines that kill nerve cells and cause synaptic dysfunction. The "master" cytokine is soluble TNF (sTNF) – this is the main



cause of nerve cell death and synaptic pruning. Xpro1595, a second generation highly selective inhibitor of sTNF, targets sTNF (the bad TNF), while leaving trans-membrane TNF (the good TNF) intact. I think this unique pharmacology separates it from currently available non-selective TNF inhibitors that block both the good and bad TNF. Xpro1595 has been shown to reverse the symptoms of AD in animal studies. Our data with Xpro1595 was so impressive that Alzheimer's Associated gave us a $1 million grant under its Part the Cloud to RESCUE initiative, which aims to accelerate the transition of research into clinical practice.

Other than animal data, we have other hints that targeting sTNF is a great way to prevent AD. Patients with rheumatoid arthritis (chronic inflammation) have an eight-fold increase in the risk of AD compared to other patients, unless they have their rheumatoid arthritis treated with a TNF inhibitor. Patients treated with anti-TNF therapy have a lower risk of AD compared with other patients! This confirms that TNF is a target.

Unfortunately, all is not good. As currently available TNF inhibitors block both sTNF and trans-membrane TNF, there are increased risks of infection, cancer and multiple sclerosis. Thus, they trade one disease for another. The advantage of Xpro1595 therapy should be that the patient gets all the advantages of targeting TNF without the serious side effects.

How are you approaching the challenge of clinical translation?

Translation from mouse to man is a scary problem for small biotech companies like ours… We attempt to manage risks in two ways. The first is to identify the subset of patients that will respond to our treatment – and to not presume that every patient with a diagnosis has the "type" of disease that could be treated by our therapy. For example, the patients we enrol in the AD trial will be selected for patients who have inflammation as part of their disease. This means we have a very good chance of selecting patients with microglial activation as part of the pathophysiology driving their disease. Ultimately, this is about precision medicine; improving the chances that you will include patients that will benefit from therapy and exclude patients who will not benefit from the therapy. This is good medicine.

Our second strategy is to use biomarkers of drug effect to ensure our drug is doing what it is supposed to do. For instance, after patients are treated with INKmune, we expect their NK cells to be able to kill cancer cells. We have a simple bioassay that should demonstrate that INKmune therapy is doing what it is supposed to be doing – priming the patient's NK cells to kill their cancer.

What are the company's plans for the remainder of 2019?

Our primary goals are to get patients enrolled into the XPro1595 trials. One thing drives value – clinical data! And we spend every hour of every day thinking about how to move our programs forward!

GDUFA 2020

GDUFA fees for 2020 have been decided – and include a significant price drop for finished dosage facilities

Generic Drug User Fee rates for fiscal year 2020 (beginning October 1, 2019) have been published by the FDA (1). The fees specify what companies must pay for Abbreviated New Drug Applications (ANDA), Drug Master File (DFM) submissions, annual active ANDA holdings, and API and finished dosage form facilities. Compared with the previous year, the fees for Finished Dosage Form (FDF) facilities have dropped by around 6 to 7.4 percent.

GDUFA fees help fund the FDA review process, including research activities for investigating new methodologies and tools for the development of generic drugs. In fiscal year 2018, the FDA's Office of Generic Drugs awarded 13 new research contracts and 11 grants for research projects on generics, including complex active ingredients, formulations and dosage forms; complex routes of delivery; complex drug-device combination projects; and tools and methodologies for bioequivalence and substitutability evaluation. GDUFA has also helped fund the development of 136 new product-specific guidelines as a roadmap for generic drug development (2).

When the user fees were first introduced, they were structured in a way that unintentionally created a large fee burden on contract manufacturers. Since then, the Pharma & Biopharma Outsourcing Association (PBOA) has been advocating to ensure the GDUFA program – and other FDA programs – are fair to the contract manufacturing sector. You can read more about PBOA and its effect on GDUFA fees in a previous cover feature of The Medicine Maker, "Standing Up for the Invisible Manufacturers," featuring Gil Roth, President at PBOA.

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Type	*Fee Category*	*Fee*	*Percentage Change from Previous Year*
	ANDA	$176,237	-1.4%
	DMF	$57,795	+5.1%
Facilities	API (domestic)	$44,400	+0.4%
	API (foreign)	$59,400	+0.3%
	FDF (domestic)	$195,662	-7.4%
	FDF (foreign)	$210,662	-6.9%
	CMO (domestic)	$65,221	-7.4%
	CMO (foreign)	$80,221	-6.1%
GDUFA Program (generic drug applicants)	Large size operation	$1,661,684	-10.8%
	Medium size operation	$664,674	-10.8%
	Small business operation	$166,168	-10.8%

Table 1. Generic Drug User Fee rates for fiscal year 2019

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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

Full SPaeDD Ahead

Advances in pediatric drug development have been slow. We can do better if we collaborate.

By Andrew Parker, Head of Business Management, at Catalent Nottingham, UK.

It's true what they say about strength in numbers; pooling both resources and expertise allows those collaborating to better tackle the challenges associated with complex research and development. The result is an approach greater than the sum of its parts.

In my view, collaboration is particularly crucial in areas of drug development with great unmet medical needs, such as the pediatric field. Over the past few decades, pediatric drug development has not kept up with the progress made by medicines tailored to adults, and there are many limitations that disincentivize companies from formulating medicines specifically for children. Children's physiological make-up will alter as they age, with factors such as the composition of intestinal fluids, gut permeability and metabolism all changing over time. In addition, there is a distinct lack of methodologies and clear guidelines available to support pediatric medicine development.

Collaboration can help solve some of these problems. I'd like to draw attention to the SPaeDD (Smart Paediatric Drug Development) project in the UK, which has brought together academic research institutions and pharmaceutical companies and contractors, including Catalent Nottingham (formally Juniper Pharma Services), Pfizer, AstraZeneca and Aston University. Co-funded by Innovate UK, this project ran from 2014 to 2018 to refine and clarify best practices for pediatric drug development. The project focused on research areas considered critical for pediatric drug development, including drug exposure, taste, and medicine acceptability.

"Consolidating knowledge relating to drug exposure, taste assessment, and acceptability is critical for addressing the unmet medical needs of children."

It is crucial that drug developers can accurately predict exposure of drugs for children. Children are not just small adults – they have a very different physiology that can affect absorption, distribution, metabolism, and excretion profiles for drugs. Accurately predicting and understanding this exposure can greatly accelerate the drug development process. Unfortunately, this is something that the industry doesn't have a great hand on with respect to a harmonized approach and methods. The SPaeDD project tackled this by creating a predictive mathematical model for age-related biorelevant dissolution testing for pediatric formulations. The successful outcome highlighted how predictive models can inform our understanding of exposure, due to the clear effect of age-related physiological parameters on oral dosage dissolution.

SPaeDD also considered taste assessment and taste masking. This is important when developing medicines for children because children are notorious for their aversion to unpalatable foodstuffs and medicines, which makes the administration process for parents and adults very difficult and stressful! The pediatric drug development process is, unfortunately, no easier, with a distinct lack of in vitro and in vivo taste assessment tools hindering progression along the pipeline. The SPaeDD project comprehensively reviewed the available tools used to evaluate bitter tasting medicines. This aided the consortium in fully understanding the gaps in the toolkit currently available to help direct research. A technical review also helped create an open access quality target product profile (QTPP) for taste masking – supporting future pediatric drug development projects. By reviewing and analyzing all past literature in this critical area of work, the SPaeDD project created an excellent springboard for future research projects to hit the ground running.

"The SPaeDD project has resulted in the development of a number of novel and refined toolkits, which should facilitate the development of pediatric medicines."

The final output of the SPaeDD project was to improve understanding of pediatric "medicine acceptability." This is the overall ability of an individual to use a medicinal product as intended. Factors like appearance, volume, smell, complexity of modification before administration, and the required dosing regime all fall under the acceptability umbrella. Prior to the SPaeDD project, there was no guidance on how to conduct or report on acceptability testing. To address this, the consortium used a systematic literature review to create an algorithm that generated data concerning the acceptability of a range of formulations across the pediatric age range. By providing a systematic approach for dosage form selection, this tool will help guide size and volume selection for particular dosages.

Consolidating knowledge relating to drug exposure, taste assessment, and acceptability is critical for addressing the unmet medical needs of children. The SPaeDD project has resulted in the development of a number of novel and refined toolkits, which should facilitate the development of pediatric medicines. I have no doubt this would have been impossible to achieve in the same timeframe by one company alone! From computer algorithms to in vitro modeling, the SPaeDD project required a diverse skillset that could only be found through a multi-partner consortium. And it has reaped great rewards, with the publication of a wealth of literature already receiving regular citations (1). Moreover, the tools created have received great interest from industry – it has certainly been beneficial for pediatric medicine research efforts at our company.

Collaborative approaches are continuing to transform the field of pediatric medicine. For instance, programs such as the European Paediatric Formulation Initiative bring together pharmaceutical organizations, hospitals, and academic institutions to resolve issues associated with pediatric formulations. Another example is the Catalent Applied Drug Delivery Institute partnership with the Department of Pharmacy Practice at Rutgers University. This collaboration aims to identify diseases that require pediatric-friendly formulations, and to build awareness and advocate for targeted translational research. For each of these programs, there is one crucial common feature: the ability for all organizations involved to draw on unique strengths and resources to achieve an overall aim. We can make huge strides forward if we collaborate.

Reference

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We Must Focus on Science, Not Geography

In times of political and social upheaval, maintaining our links across borders and working closely together is more important than ever.

By Steve Arlington, President of The Pistoia Alliance, UK.

We're just over the halfway point of 2019 and it's fair to say the year has already been one of tumultuous political and social change. Whether it's Brexit in Europe or continued fractured politics in the Americas, we are experiencing a time of great change, during which organizations dedicated to maintaining links across borders become increasingly important. My organization, The Pistoia Alliance, is a non-profit group formed in 2009 by representatives of AstraZeneca, GlaxoSmithKline, Novartis, and Pfizer, with the goal of lowering barriers to innovation in life sciences R&D through collaboration.

Now, as we look forward to the next decade in life sciences, our mission hasn't changed. In fact, it has become even more imperative. To deliver new drugs and treatments to a growing global population, we must seek out more opportunities to collaborate. And to explore the potential of new technologies, such as AI, we will have to come together and agree international standards and protocols for use. At our recent European members conference in London, more than 250 attendees gathered to discuss these themes, as well as to take part in numerous workshops and discussions over three days. In my keynote address, I spoke about the growing need to focus on science, not geography. I talked about why it is important that the industry shows willingness to work cooperatively and to form links with global organizations; whether this means being more open to sharing pre-competitive data with peers, joining a working group to identify life science use-cases for blockchain, or agreeing a Unified Data Model for biological information.

We also heard from Professor Mark Caulfield, Interim CEO of Genomics England, a member of The Pistoia Alliance, on the news that the organization has sequenced more than 104,000 genomes – over 91,000 of which are accessible for research. Mark emphasized the vast potential these kinds of data hold for R&D, but cautioned that genomic data sets must be made available internationally to enable greater insights from analysis that will aid diagnoses and treatments for all patients. Mark explained that Genomics England currently holds more than 1.6 billion data points, which organizations around the world could benefit from, and that as it makes progress towards its next goal of sequencing five million genomes, it will be essential to work together to cut costs and share expertise.

Chris Molloy, the CEO of the UK's Medicines Discovery Catapult and a member of The Pistoia Alliance,

"When I first started my career in the 1970s, the importance of cross-disciplinary working became increasingly apparent, but without a group pushing for it, collaboration remained a challenge."

"Successful research relies on successful collaboration – some of the biggest breakthroughs in science have come from joint international efforts."

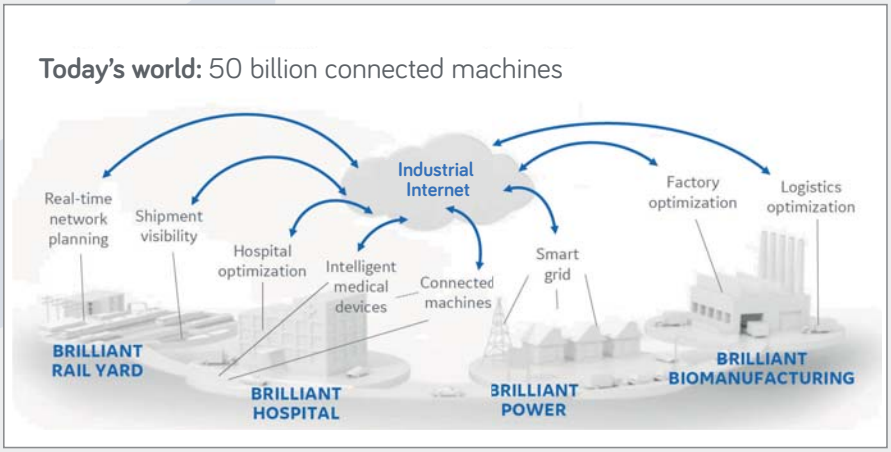
was another speaker. Chris discussed cross-border collaboration and data sharing, explaining why the life sciences sector must come together to improve how the industry manages "smart" data. He spoke about the fact that three-quarters of UK SMEs today go abroad to access patient data, and why it's essential those in the life sciences work with patient groups and regulators to change this. He also talked about unleashing the power of industry networks to get new therapeutics to patients faster and reiterated that this drive can't just be a UK-wide effort but must be linked globally, with scientists ready to share data and skills.

The drive to collaborate is a subject very close to my heart. When I first started my career in the 1970s, the importance of cross-disciplinary working became increasingly apparent, but without a group pushing for it, collaboration remained a challenge. This is one of the reasons I became President of The Pistoia Alliance, and today, my aim is to make a difference through the projects we work on. Our Advisory Board is made up of senior industry figures who also feel passionately about collaboration and provide guidance on priority areas. Our projects are very varied – including helping to develop the "Lab of the Future," our "Centre of Excellence" for AI in life sciences, and the development of a Chemical Safety Library to improve lab safety worldwide.

I am particularly passionate about seeing the industry launch affordable medicines that society really needs and I am working hard to bring together all the right stakeholders to meet this goal! Ultimately, successful research relies on successful collaboration – some of the biggest breakthroughs in science have come from joint international efforts. Science is too precious to be kept in one country, and the free exchange of ideas – while politicians continue to argue about physical borders – must be enabled.

The Future of Digital Biomanufacturing

Digitalization means a more productive and adaptive plant through the application of analytics to leverage connectivity and data – maximizing efficiency from people, processes, equipment and core systems. How? By facilitating data-driven decisions.



In May 2019, GE Healthcare brought experts together at its Uppsala, Sweden, site for Bioprocess Days: an event to discuss the future of bioprocessing. One of the key themes was the role that digital technology, analytics and data will play. This article was developed based on an interview with Jun Huang (Director/Team Leader; Process Monitoring, Automation and Control at Pfizer) who presented a case study on the "Industrial internet of things" at the event.

Digitalization means different things to different people. For me, it starts with connectivity and data. Pharmaceutical manufacturing generates a lot of data, and in many cases, operations are highly automated, but are they truly digitalized? I think many systems working in silos suggests they are not. For example, does your process control system talk to your quality system? Technologies like the industrial internet of things (IIoT) will release the data that is trapped in these silos by enabling connectivity between systems.

The idea is to combine and contextualize data from disparate sources and different core systems so that you can make it available to the people who need it; this could be an operator on the manufacturing floor, a plant supervisor or a senior manager. Your data would be unified in a central data hub and accessed by the people who need it.

This central data hub could be accessed through a persona dashboard – tailored to the needs of the individual decision-maker. For example, on the factory floor, people would be looking at operating the system in the best and most efficient way, so they might see some quite granular information. The plant manager, on the other hand, would care mainly about key performance indicators and higher-level metrics. And senior management will be keeping track of performance at the enterprise level, across various sites, enabling them to develop a long-term strategy for the entire network.

But a key question is, what exactly are these people supposed to do with all of this centralized data? Data is useless unless you can turn it into an intelligent decision. This is where analytics, AI and machine learning come in. IIoT enables connectivity, data gathering and contextualization, but you need analytics to tell you what to do with it and how to apply it to decisions regarding production.

At a process level, you can use IIoT in combination with advanced analytics in the existing process control system to improve process robustness and increase yield, ultimately enhancing productivity. In the quality and compliance department, the aim is to make sure the product is made within quality specifications. IIoT enables connectivity between quality and the production floor, allowing you to identify deviations quickly and make adjustments. Then at a higher level, real-time changes in demand could inform decisions about production.

These decisions could be made by an operator or a manager, or, in some cases, an automated process control system. Imagine developing a model

> *"Turning data into intelligent decisions is the goal of digitalization, but to do that, companies must create the right culture."*

that, based on data generated by the IIoT, could manipulate your process so that an economic target or quality measure is met. The model might be able to go beyond real-time monitoring and decision making by predicting deviations or failures before they occur, and take preventative action.

Overall, digitalization will drive unprecedented levels of visibility, productivity and quality by increasing the connectivity across systems, enabling more collaborative manufacturing and data-driven decision making.

Catalyzing a culture shift

Turning data into intelligent decisions is the goal of digitalization, but to do that, companies must create the right culture. In my view, it is the culture within a company that is the main barrier to digitalization in the pharma industry, as opposed to the technical challenges. New technologies are slowly enabling new ways of thinking and operating, but people must be receptive and mindsets must evolve with the technology.

Oftentimes, people in pharma are very busy and focused on their immediate priorities: from getting products out of the door to good safety standards – digitalization might not be top of their agenda. However, I've also seen other companies who are very progressive, innovative and proactive in adopting new technologies and who are seeing real success stories from their use. I think it's only a matter of time before digitalization becomes widespread within the pharma industry – the clear benefits will make it so. But the first step is perhaps to develop pilot studies or create user cases to demonstrate the value of digitalization to pharma businesses, before rolling out these new technologies and practices across sites.

Of course, it would be remiss of me not to mention the regulatory challenges of implementing, say, an AI-based GMP solution for commercial manufacturing. Working to ensure new solutions are in line with regulatory requirements is an important challenge to overcome, but a lot of positive conversations are happening in this area.

We've only scratched the surface of what's possible with digitalization. Technology continues to evolve, and the opportunities are almost endless. New technologies such as smart and wireless sensors that will transmit into your IoT platform to remotely monitor equipment, cloud computing, 3D printing, augmented and virtual reality will all be part of the digital revolution and I can't wait to see where they lead the pharma industry.

Read more on digital transformation in biomanufacturing: https://bit.ly/2KVZ7bz

Building the Brilliant Factory

Jun Huang believes we're still scratching the surface of what's possible with digitalization. As Chief Digital Officer at GE Healthcare Life Sciences, Ben Newton is also optimistic about the future. He believes that digital technology could be used to build "the brilliant factory."

What developments have had the biggest impact in your field over the past five years?

I am excited by the increasing sophistication of cloud-based technologies, which allow us to compute large amounts of data in the cloud remotely. We are also seeing the emergence of technologies that extract data from patients or equipment through wearables and sensors. Then, we also now have the ability to aggregate that data in a structured way so that we can start to make predictions about disease and manufacturing methods (big data). Coupled with the digital revolution has been an increase in our knowledge of disease processes and how to use the immune system to treat cancer and this could have a real impact on how we address disease. It's a fascinating time to be involved in the industry.

What is your vision for the future of manufacturing?

We need to bring all of the pieces that we are working on together under the roof of what we might call the "brilliant factory." Right now, many in the biopharma industry are working on optimizing the cell culture and upstream process by developing smarter ways to define the right kind of process for the production of antibodies and cell therapies. We're also defining the tools to separate and purify those antibodies cost-effectively with multivariate analytics tools. And to support manufacturing, we're developing digital twins to optimize and control processes. At the moment, we're doing these things somewhat in isolation but if we can bring them together in a single manufacturing setting, where every step is optimized, and the data is aggregated and analyzed by AI, you can create a system that can learn which factors are important for optimization and that is able to self-validate to automatically improve processes. This vision of a fully automated intelligent system is what we should be aiming for.

HOW TO FIND YOUR SECRET SOURCE

The complexity and scope of tasks within the (bio)pharma industry lend themselves to outsourcing – especially for small companies – but finding the right partner can be daunting. Do you opt for individual suppliers to form a specialist supply chain? Or do you choose the convenience of a one-stop shop? Here, we present perspectives generated at a Bio Integrates panel discussion.

By Stephanie Sutton


SPECIALIST SUPPLIER
DANGER OF COMPLEXITY
EGGS IN ONE BASKET

Whether you are a big pharma or small biotech company, the outsourcing question is almost bound to present itself at some point. Bigger companies will be familiar with the process – and even have special departments and personnel responsible for vetting different partners and managing relationships. But for smaller companies, with a limited budget and resources, outsourcing can be far more daunting. Will their presence or spending power affect the quality of service they receive? Put another way: will a small biotech receive the same care and attention as a pharma giant?

This very topic was raised at a Bio Integrates panel discussion in London back in May 2019, when big pharma, SMEs, emerging companies, startups and academic institutions all came together to discuss the major challenges impacting the pharma and biotech sectors. Jo Craig, Senior Vice President CMC, KaNDy Therapeutics & NeRRe Therapeutics, chaired a session titled, "One-stop shop or specialist supply chain: how do you select the right providers?", featuring Frank Ritacco (Thermo Fisher Scientific), David Molyneux (Alcami), Brian Fairley (SK biotek), Peter Sargent (UK National Institute for Health Research) and Detlef Behrens (Bay Pharma). The aim was to discuss the challenges smaller companies face in identifying the right outsourcing partners.

SMALL BUT VALUABLE

Small biotech companies are known for their innovation, but many simply do not have the cash reserves – or the certainty – to invest in their own manufacturing infrastructure, so outsourcing becomes the best way forward. With so many biotechs turning to outsourcing, they collectively make up a huge portion of a CDMO's business.

"I'd say that around 75 percent of our clients on the biologic side are new and emerging biotechs, so obviously they are very important to us! We have customers that range from big pharma all the way down to virtual companies," explained Ritacco, during the panel discussion.

"Similar to Thermo Fisher Scientific, a large percentage of our work comes from small pharma and biotech – around 80 percent," Molyneux added. "It makes good business sense to value the small clients as much as the larger clients. Alcami was founded when two companies, AAI Pharma and Cambridge Major Laboratories, came together. The two companies were previously leveraged towards a few large commercial partners, which posed a huge business risk. Although it is not uncommon for biotech companies to drop out of the market, CDMOs can fail to develop a resilient pipeline by only taking on the large volume partners and products, placing more emphasis on their business than the smaller clients. When Alcami was founded, the strategy was to instead diversify the portfolio by having a higher number of projects and to work with smaller partners, predominantly in the clinical space."

Small biotech companies are also important to Fairley at SK biotek, accounting for around 50 percent of its business. But working with large pharma is also crucial. Fairley said, "Everyone should spend some time working for large pharma. Our experience working with them is extremely important because these companies get into a lot of detail in a variety of areas. We have learned a lot from working with their experts – and I think they have learned from working with us too in terms of our technology and expertise. We are then able to translate that experience for the smaller biotechs and help them to accelerate their programs as a result. Biotechs may not necessarily have a depth of experience in CMC, and may require the expertise of chemists or analysts and so on to accelerate their pipeline."

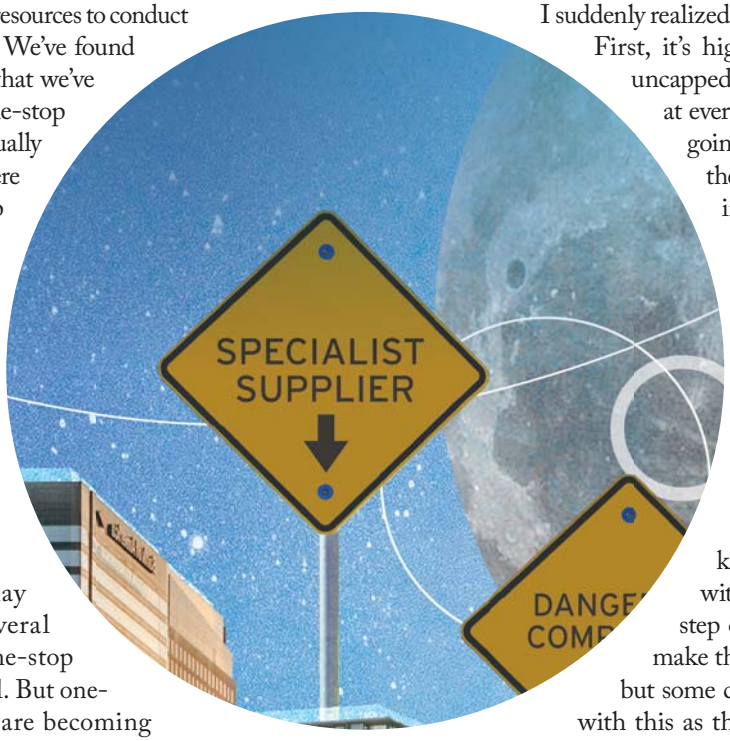
"I think it's important to appreciate that different companies will have different needs," explained Ritacco. "A lot of small, virtual companies, for example, tend to need a little more guidance and support when moving into commercial drug manufacturing processes. A big pharma company, on the other hand, often comes in with a well-built process that they want to replicate for manufacturing."

Sargent also believes that smaller companies tend to need more help with their products and processes. Unlike the other panelists, who work in commercial companies, Sargent's role lies with the UK's National Institute for Health Research, which is part of the country's wider research and health system. There he supports researchers and companies of all shapes and sizes – helping them to identify collaborators and set up trials to generate the clinical and economic evidence required for

market adoption of their healthcare products. "The NIHR engages with a wide variety of companies. As Brian said, I find that when you're talking to large pharma, they typically do know what they want and what is needed. They tend to already be connected to the various experts and will have gone down the clinical path many times before," said Sargent. "Not all small biotech companies are the same, but in most cases they do seem to need more advice and hand holding."

ONE-STOP SHOP OR SPECIALIST?

The audience – which included academic and research institutes as well as pharma and biotech – had a number of thoughts and experiences on the subject of outsourcing. One attendee said, "A small biotech company will often be seen as the small guy in the pond and may not have the resources to conduct truly thorough due diligence. We've found that the policies and services that we've had from some of the big one-stop shop service providers aren't actually up to what they'd promised. There may have been a relationship with a named person, but that person only turns up every three months, so you don't get any real benefit." Another attendee explained that, while a one-stop shop had benefits for a small company, there were concerns about how much of a service provider's attention they would receive.



"Many small biotechs may not want to deal with several different companies, so a one-stop shop approach may work well. But one-stop shop service providers are becoming larger and larger as the industry engages in more mergers and acquisitions. Can big providers really give priority to small biotech clients when large pharma are asking them to be 20 percent of their customer portfolio? Large pharma companies will likely be considered more important clients."

Behrens had an interesting take on the matter: "When I was in the CDMO industry, I was selling a fully integrated service because that was the solution. When I later moved out into procurement, I suddenly realized that it doesn't make any sense. First, it's highly risky to put everything uncapped and, second, no one is good at everything – it is just a fact. If I'm going into a fully integrated service then I have to make compromises in terms of selecting something for a certain step. And if I am looking from a biotech perspective, the customer is unlikely to have a simple white tablet. Biotechs tend to work with innovative projects and complex molecules, and will have a specific need for various services and technologies – and may be very keen to select the right provider with the right expertise for every step of the supply chain. This may make the supply chain more complex, but some companies are more confident with this as they know they have the right people – and may feel they have more commitment as these experts will often be at smaller companies."

"Individual suppliers can lead to overlaps and duplicated work, so in some cases time and money can be saved by having everything done by the same company."

But some companies may prefer the one-stop shop approach. The CDMOs on the panel were keen to emphasize the advantages. Individual suppliers can lead to overlaps and duplicated work, so in some cases time and money can be saved by having everything done by the same company. Molyneux said, "I have a point of contention with the title 'one-stop shop or specialist supply chain' because it implies that you can't have

THE EXPERTS

Frank Ritacco

Director of Scientific and Technical Affairs, Biologics Drug Substance Division of Patheon – a part of Thermo Fisher Scientific

"We are a global CDMO, which you could say is a one-stop shop. We can handle your biologic molecule all the way from DNA sequence through process development, drug substance and drug product manufacturing, packaging, labeling and even clinical trials. I joined Thermo in 2018, but before that I worked in both big pharma companies as well as small biotechs. I spent a lot of time at Wyeth working with small molecules, and then I moved to biologics at a small company called Unigene Laboratories, before ending up at Bristol-Myers Squibb in their biologics process and development division."

Detlef Behrens

Managing Director, Bay Pharma

"I would describe Bay as a classic biotech. We are virtual, so we are completely reliant on CDMOs. Most of my background lies in the CDMO industry in sales, but then I moved into procurement, procuring CDMO services. I have the perspective of outsourcing, or insourcing, and in talking to customers in both large and small companies."

David Molyneux

Senior Director and Global Head of Sales and Business Development, Alcami Corporation

"I'm a PhD chemist by trade and I have spent all of my career to date in end-to-end CDMO services. Alcami is a fully integrated end-to-end contract development and manufacturing organization that provides customizable and innovative services to pharma and biotech companies of all sizes. Alcami was established in 2016, but the founding base is considerably older, with the first going back to 1979."

Peter Sargent

Head of Business Development, The National Institute for Health Research, Office for Clinical Research Infrastructure (NIHR)

"Before I started at NIHR, I'd had a variety of different roles within industry, working in both R&D and commercial functions. I have experience in biologics development and manufacture, in vitro diagnostics, clinical research and drug development. With regards to my current role, I manage a business development team at the NIHR supporting companies to navigate the UK's complex health and research system. The NIHR is the largest funder of clinical research within the UK, managing over £1.2 billion per year for the Department of Health and Social Care. A large proportion of that goes towards funding researchers across the NHS and partner universities. It is these researchers and centres that can support industry in development of their products."

Jo Craig (Panel Facilitator)

SVP CMC, NeRRe and KaNDy Therapeutics

"Before taking on my role a year ago at the clinical stage biotechs, NeRRe and KaNDy Therapeutics, I spent over 30 years in pharma development in large pharma (GlaxoSmithKline). I was no stranger to biotech, however, having held a Board Observer role at NeRRe and KaNDy for the last few years. My facilitation, questions and interest in the area of 'Specialist Supply Chain or One-Stop Shop' stems from my experience across both large and small pharma."

Brian Fairley

Director of Business Development, SK Biotek

"I've had a career that spans across different geographies across Europe and the US, working for nearly twenty years in the CDMO space. I have been fortunate to be able to work with everything from small biotechs and one or two individuals with some IP, right through to large pharma companies. I've also had the opportunity to work not just in sales and lead sales for various CDMO organizations, but also to build an operational footprint for an organization in Europe and lead a number of operational functions."

both! If you have independent API and drug product, you can bring these together. Being that we were founded by merging two specialized organizations, we have experts in each area, which we then overarch with a structured offering to make sure they are properly integrated. A key thing our clients tell us – especially smaller clients who don't want to manage a big supply chain – is that they like the internal efficiencies you can get with a 'one-stop shop.' Being one doesn't necessarily mean you're not a specialist in each individual area; the real skill is in bringing those specialist areas together in a seamless, integrated way that makes their sum greater than the individual parts."

Pharma and biopharmaceutical development rarely runs smoothly, and being able to respond and react to issues as they arise is crucial to success. Some believe this can be more challenging with a specialist supply chain comprised of many different partners. "For example, you may lose a slot for the next part of your development if something goes wrong earlier in the chain," said Molyneux. "If you are working with a single provider then it's all on them and they have a responsibility to see the project through."

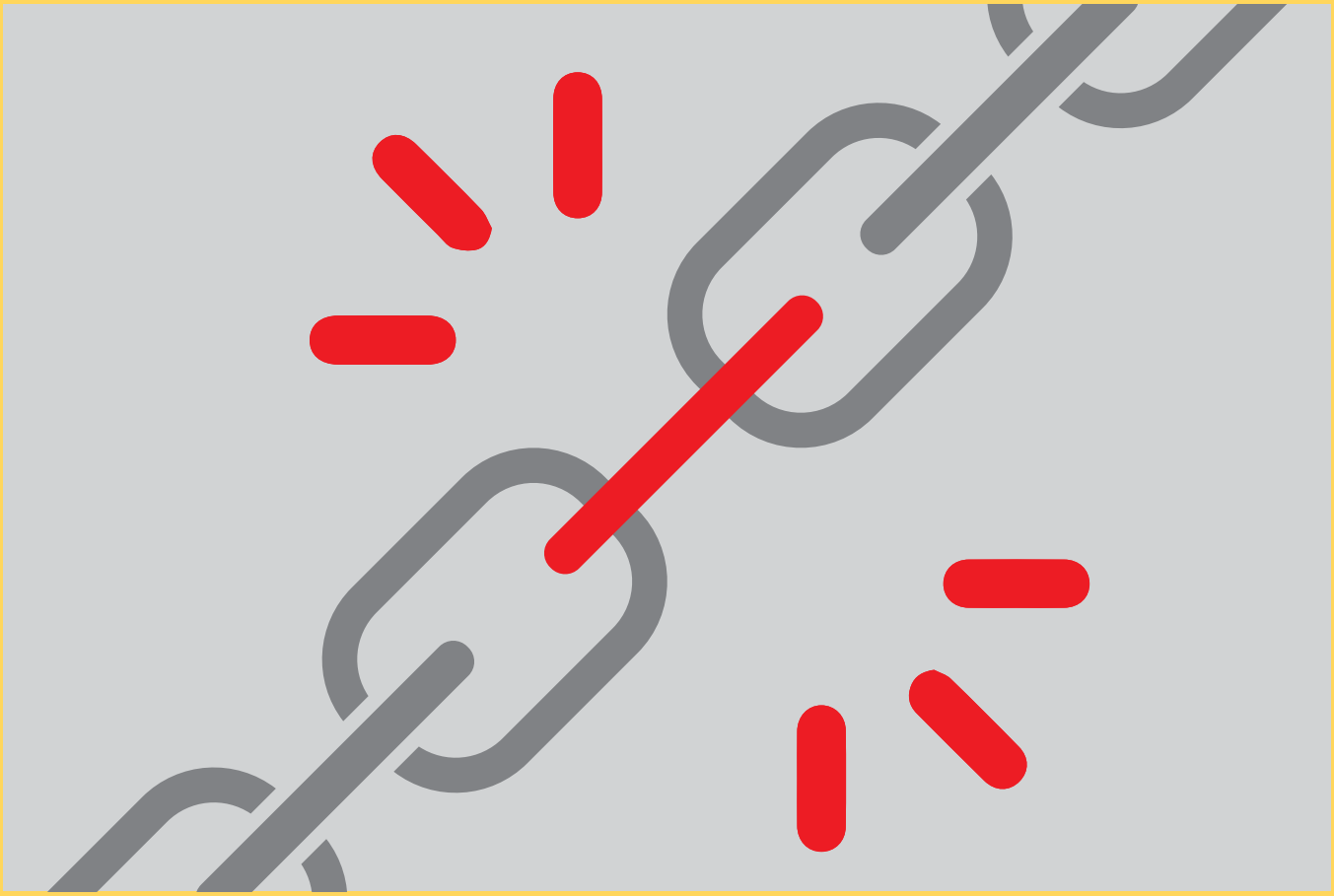
But Behrens pointed out that this isn't necessarily a big problem when using a specialist supply chain. "It's really about aligning your different suppliers. For sure, it is a bit more work, but if you talk with all your suppliers and make them aware of key issues early enough then it can still be aligned easily. In my company, I think we will likely end up with three suppliers (API, analytics and drug product). Three suppliers are very manageable. If I could find the right one-stop service provider – who really brings value without charging significantly extra on top – then I am open to considering it. But I haven't found them yet!"

PERFECT PARTNERS?

Ritacco believes that it is not so much a case of one-stop shop versus specialist supply chain – or large company versus small company; rather, it is about getting the relationship right. There must be a synergy between the sponsor company and the service provider – organizations with vastly different values and mindsets are unlikely to work effectively together. Ideally, the partnership should facilitate free-flowing innovation with a minimal degree of formality. "A good relationship is key whether working with a big company or small company but, in a way, it is perhaps more important for small pharma and biotechs because you have fewer people," agreed Molyneux. "Often this makes things easier from a decision-making point of view – people are often more reactive and you can get things done quickly in a small company – but it also means that when challenges arise, you have fewer resources to resolve the problem and prevent collateral damage. Having an open, honest dialogue and two-way relationship is incredibly important to fixing problems quickly."

"Pharma and biopharmaceutical development rarely runs smoothly, and being able to respond and react to issues as they arise is crucial to success."

Ritacco added, "If you're looking at potentially going to a one-stop shop then you already have a vision of what you need for your product and it is very important to know that you have a team with the depth of experience that can manage a project and get your product to the market. As David mentioned earlier, things can – and will – go awry! You need to know that the team you are working with is experienced enough to handle those problems, especially in the world of biologics where things can change when you scale your processes up."



THE WEAKEST LINK

During the panel discussion, one audience member explained that, in his experience, one of the most difficult areas to outsource was product design – a critical step that can cause a biotech to succeed or fail.

In response, Behrens pointed out the different mindsets between development and manufacturing personnel. "A requirement for development people is being creative and flexible. It is the complete opposite for manufacturing. I have worked with companies who try to do both with the same people and I don't believe this works because you can't bring in someone from manufacturing and expect out-of-the-box thinking because they have been trained to follow all documentation. If I am selecting a CDMO for just development or just manufacturing, then I look at whether they have a separate organization – and ideally a separate facility – with separate people."

Molyneux agreed; at Alcami, the vast majority of API development comes out of a facility in the Netherlands, but when the work is scaled up for large-scale manufacture it will typically go the US. "There is some scale of manufacturing capability within the Netherlands, but the groups are segregated," said Molyneux.

The challenge with segregation, however, is bridging the resulting gap. Here, a "middleman" can help ensure that the process is being designed with scale in mind.

As part of due diligence when selecting a supplier, Fairley also explained that it is crucial to ask questions about information flow and transfer. "For example, if you have a chemist and a manufacturing team, you want to make sure that the right processes are in place and that they are talking to one another to get the process right first time," he explained. "You don't want one department throwing a project over the fence to another department! Ask questions before you make your decision."

Ultimately, every company will be looking for something different from their CMO and the panel agreed that it comes down to getting to know the team, being comfortable with them, and feeling confident in their ability to help you navigate the problems you'll face en route to getting your molecule filed. A good relationship also involved flexibility. As an example, Behrens explained that his company had changed the design of their clinical study several times in a matter of months – and that this isn't unusual for small companies. CDMOs need to be prepared for this, but many may have their own way of working and their own guidelines, which are inflexible. "Biotech will also be driven by certain external perimeters, such as available cash. It is always a challenge if you need to reduce your spend as much as possible and still get your project through. CDMOs working with small customers need to be flexible. In my experience, smaller service providers are more flexible," said Behrens.

"The reality is that all programs will have their challenges and may require changes," said Fairley. "A CDMO is judged by how they communicate during those challenges, what solutions they produce, the options they come up with proactively, and then delivering on that. Whether you are a large CDMO or a small CDMO, customer service is crucial and is what really differentiates CDMOs. It's not the pots and pans or the reactors you own – it's about how you deal with problems and the creative solutions you come up with; how you interact with your partner and how you give them the highest level of service."

"Communication is definitely important," added Sargent. "And it's not just about communicating with NIHR; we encourage the companies we work with to speak to other stakeholders early within their development pipeline, such as MHRA and NICE in the UK."

CONTINUING CHALLENGES

Although many companies are satisfied with their outsourcing partnerships, there were members of the audience who were quick to point out that there is room for improvement from most players. "Some very, very big names in the field have been completely dreadful in true CMC, even though you would think it would be their bread and butter from their name and reputation."

"It is always a challenge if you need to reduce your spend as much as possible and still get your project through."

It's also perhaps fair to say that drug development is becoming far more challenging as therapies increase in complexity. Ritacco explained, "In my opinion, we are seeing a lot more movement in complex biological molecules. I've seen a shift from a field that was pretty dominated by monoclonal antibodies for a while to more complex, specific products, such as fusion proteins and antibody fragments – and then, of course, cell and gene therapies. A lot of customers are coming to us with products that are difficult to develop and manufacture. But there is also a shift, where possible, towards very standardized platform processes."

Sargent also points to the digital revolution. "Digital is an important trend to keep an eye on. AI algorithms, in particular, seem to be cropping up everywhere and there could be some key benefits for the drug development process. But, of course, one of the biggest challenges facing both pharma and biotech – particularly as therapies become more complex and expensive – is market access and reimbursement. But that is another topic for another day!"

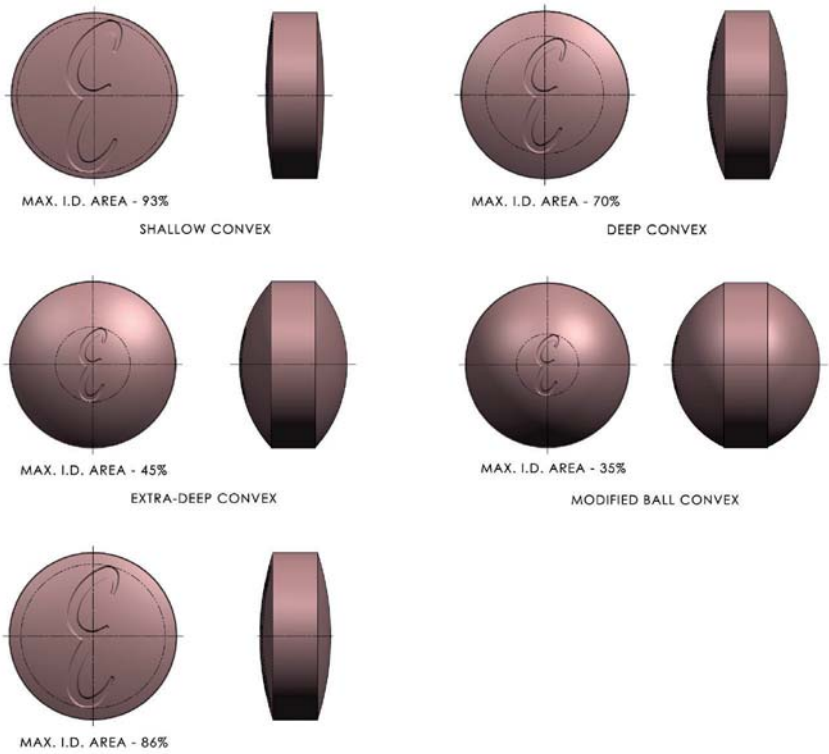
Born to Be Manufactured

Tablets are the preferred dosage form for both patients and drug manufacturers; the tableting process is well established and cost-effective, but the science and engineering go deeper than you expect. A number of aspects must be considered to design a tablet that is well suited for commercial manufacture.

By Jim Calvin and Andy Lapinsky

The manufacturability of an oral solid dose tablet can sometimes be an afterthought, given that most formulation conversations revolve around therapeutic efficacy (dose requirements and tablet format, such as conventional or bilayer tablet), the patient (swallowability and ease of use), and marketing (brand awareness and differentiation). But to make consistently good tablets, early design choices are often more meaningful than choosing good tooling and machinery. Different tablet designs require different engineering considerations and there are many factors that dictate how well a formulation will run in a given tablet press, and if the design a company has in mind for their product is actually practical from a manufacturing perspective. Certain designs used with the wrong punch, for example, create stresses that lead punches to wear out quickly, or result in tablet defects. Choosing in incompatible steel to the formulation compound being compressed can lead to abrasion of tool faces and die walls.

Tablets come in a very wide range of geometrical formations. There will always be a certain amount of weight that is needed in the tablet and from there you must consider the tablet's length, width, band thickness and cup depth.



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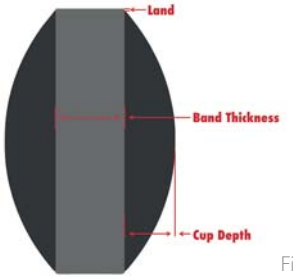

Figure 1.

Figure 3.

If the length and width are chosen incorrectly and the tablet ends up too small, the thickness has to grow to accommodate the necessary weight. This is actually one of the most common mistakes we see; as the tablet thickness grows, manufacturers often run into compression issues, as well as high ejection forces, capping and friability problems. Another common mistake is for companies to produce a small-sized tablet successfully, only to find it is then too small to add desired logos or other identifying text on the tablet surface.

The building blocks of good design

In our tooling design process, we use software to create a solid model to evaluate the stresses and strains that a given tablet shape will create on the punch tip. The computer simulations promote collaboration with product designers and timely iterations when changes to tablet geometries are still possible. This type of software can also be used to transfer an existing product to another geometrical shape through reverse engineering. Broadly speaking, there are a variety of tablet geometry aspects that need to be considered.

- Cup depth. A tablet's cup depth is the distance from the cup's lowest point (usually the center point of the tablet) to its highest point of the land. Some tablets will have a shallow depth and others will be concave. As the cup depth increases, the compression force that can be used on that tool to achieve tablet

hardness decreases. Too much cup height increases the distance for the compression forces to travel from the perimeter of the punch to the apex, or the punch's cup apex, and can lead to premature punch wear and tear, and even breakage.

- Land. The land is a narrow plain perpendicular to the tablet's band, creating a junction between the band and cup radius. Although the punch is made out of steel, the area at the perimeter of the tip is very weak so a land should be incorporated into the tablet to strengthen the punch and prevent nicks on the punch edge, which could cause compression issues (see figure 1).
- Band thickness. Too wide of a tablet band can cause high tablet ejection force, and issues with coating and non-uniform density. For all compression tooling, the two closest points are compacted first and this can create a dense area that locks air into the cup, leading to capping issues. If the band is too narrow, it can create high compression forces that may affect tablet hardness, density and cause friability problems, with tablets that are too thin being susceptible to chipping or tablet edge erosion in particular.
- Identification. The area available for identification on a tablet, such as the addition of a logo, depends on the cup radius and the style of cup, as well as the geometrical shape of the debossing, including the depth and angle needed. The flatter the geometry of the tablet's cup, the larger the available area for identification. If the debossing is placed too close to the perimeter of the tablet, you'll lose clarity of the debossing (see figure 2).
- Film coating. It is important to decide if the tablet will be coated at the very start of the design process because it can affect other aspects, such as debossing. For example, it is important to ensure the debossing is deep and wide enough that the film coating doesn't fill in the areas and make the identification unreadable. With certain shapes, film coating can also lead to twinning (see figure 3).

In addition to considering the tablet's geometry, we also advise paying careful attention to granulation. Where possible, try to ensure you have free-flowing granules that aren't abrasive – otherwise you'll be wearing down the tooling. Maintenance is important too – take care of your tools! Your operators need to understand how to set-up the machine and identify irregular operation. Once something starts wearing it needs to be addressed before there is a domino effect on other parts of the process.

The early bird

There are many aspects to good tablet design and it's fair to say that it is a very unique science. You need to understand your formulation, additional components, such as binders and other excipients, and your tools and machinery, especially when considering more complex layer tablets or core-tablets. Chemists and engineers should work together to answer the questions and ensure the final formulation will suit both sides. It is also important to consider the differences between the R&D phase – where you'll be working at low speeds and volumes – and the production phase where the pressures on the system may be different and possibly more challenging to maintain tablet quality at increased production volumes.

Many in the industry advise drug developers to consider their formulation strategy and impact upon manufacturing as early as possible. We also urge companies to give early thought to manufacturing process to avoid common issues such as picking, sticking, flashing, and high compaction and ejection forces (tips available at https://catalog.eliz.com/tooling-troubleshooting/). There are some "tricks of the trade" that can help compensate for bad tablet design and formulation, such as altering the press feeder speed to affect the hardness and weight of the tablet, but overall it is difficult to effect major change. In the case of multi-layer tablets, tooling design decisions complimentary to tablet press configuration are essential to robust layer definition. Regulatory authorities are strict and once performance qualification has been completed and the line is validated there isn't much that operators can do. Instead, it pays to get it right early on by considering the options before your design causes manufacturing issues.

Meet the Experts

Andy Lapinsky has been working for Elizabeth Carbide since 1989, taking on roles of increasing responsibility over the years. Today, he is the manager of engineering and CNC programming where he oversees the design of compression tooling and technical services for Elizabeth tooling customers.

Jim Calvin joined Elizabeth in the 1980s making tooling. Early in his career, Jim transitioned to Elizabeth-Hata International (press division) designing and building press control systems, working as a service technician and service manager, servicing and installing equipment, validating, troubleshooting and training. Today, he is General Manager of Elizabeth-Hata International.

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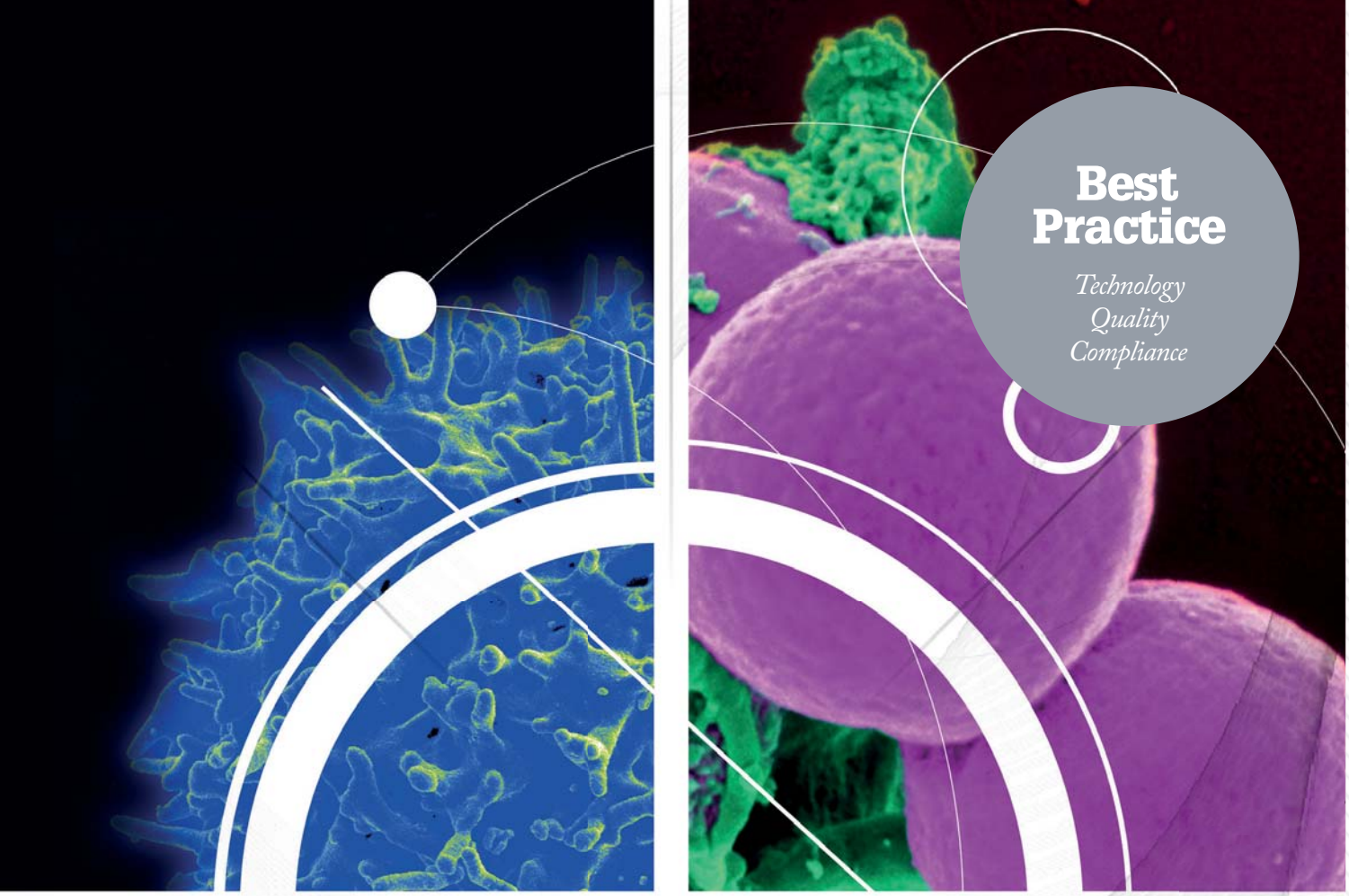

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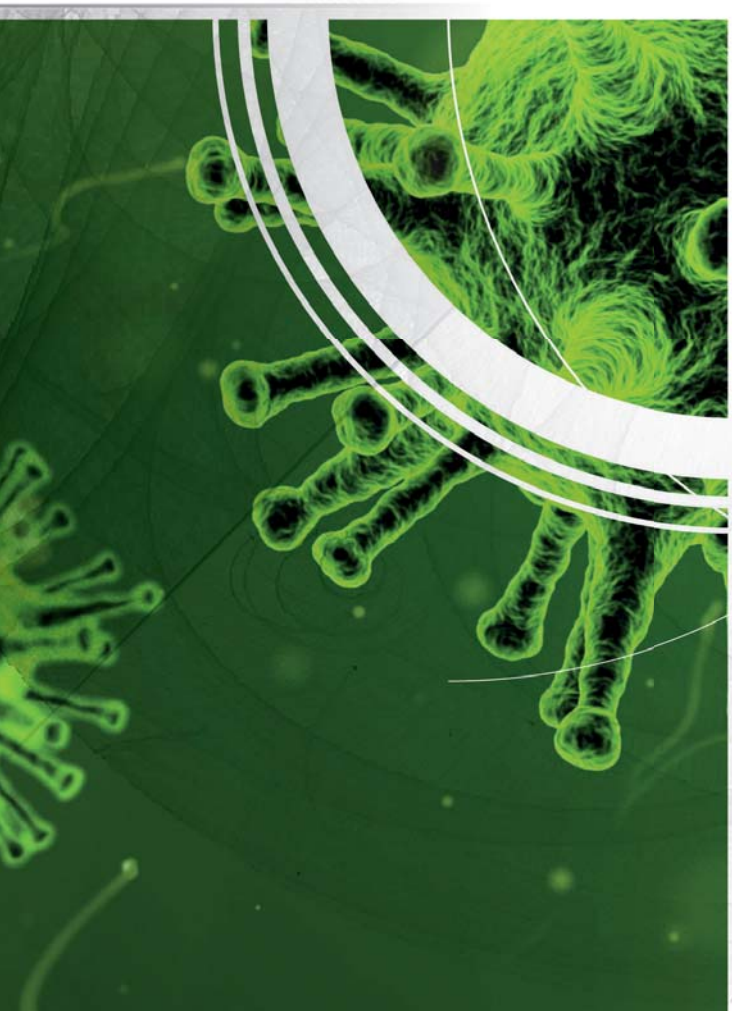
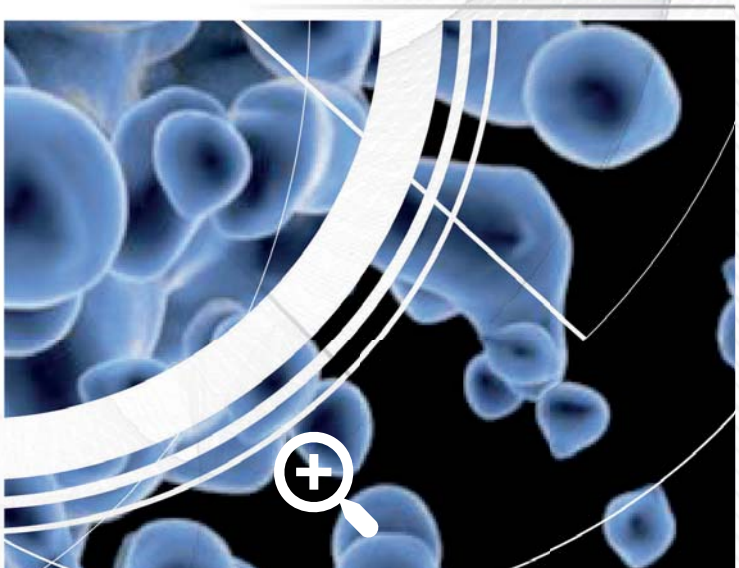
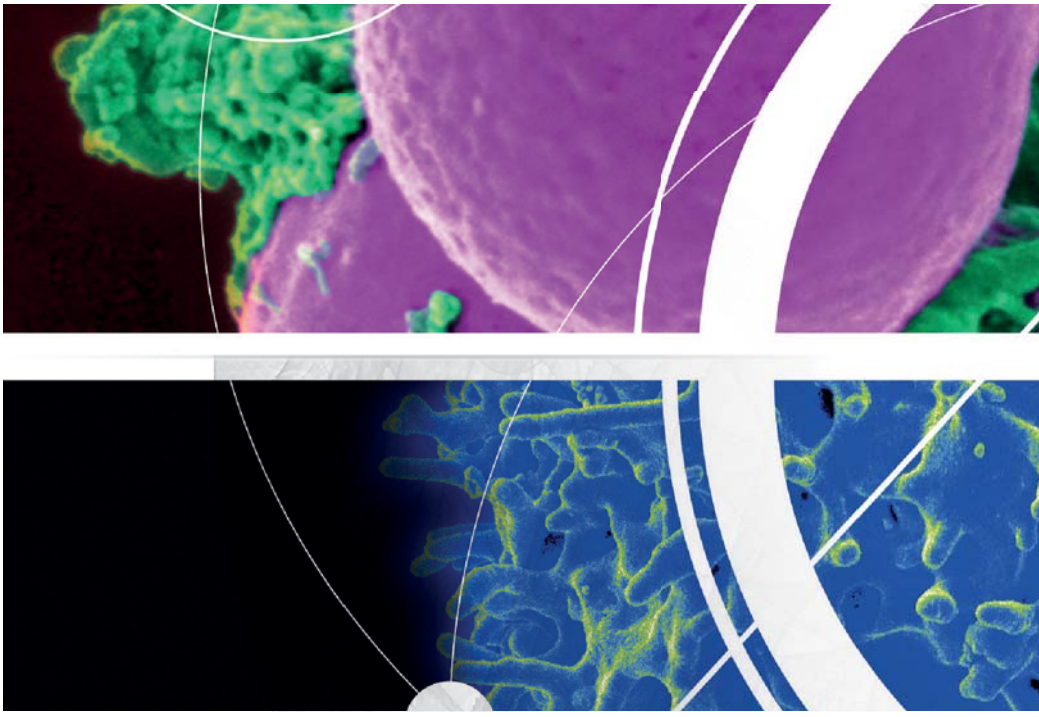




Advanced Medicines: Making it to Market

We've learned a number of lessons when it comes to developing and manufacturing cell therapies, including the importance of keeping our eyes on the end goal of commercial manufacturing – even at the earliest stages.

By Miguel Forte



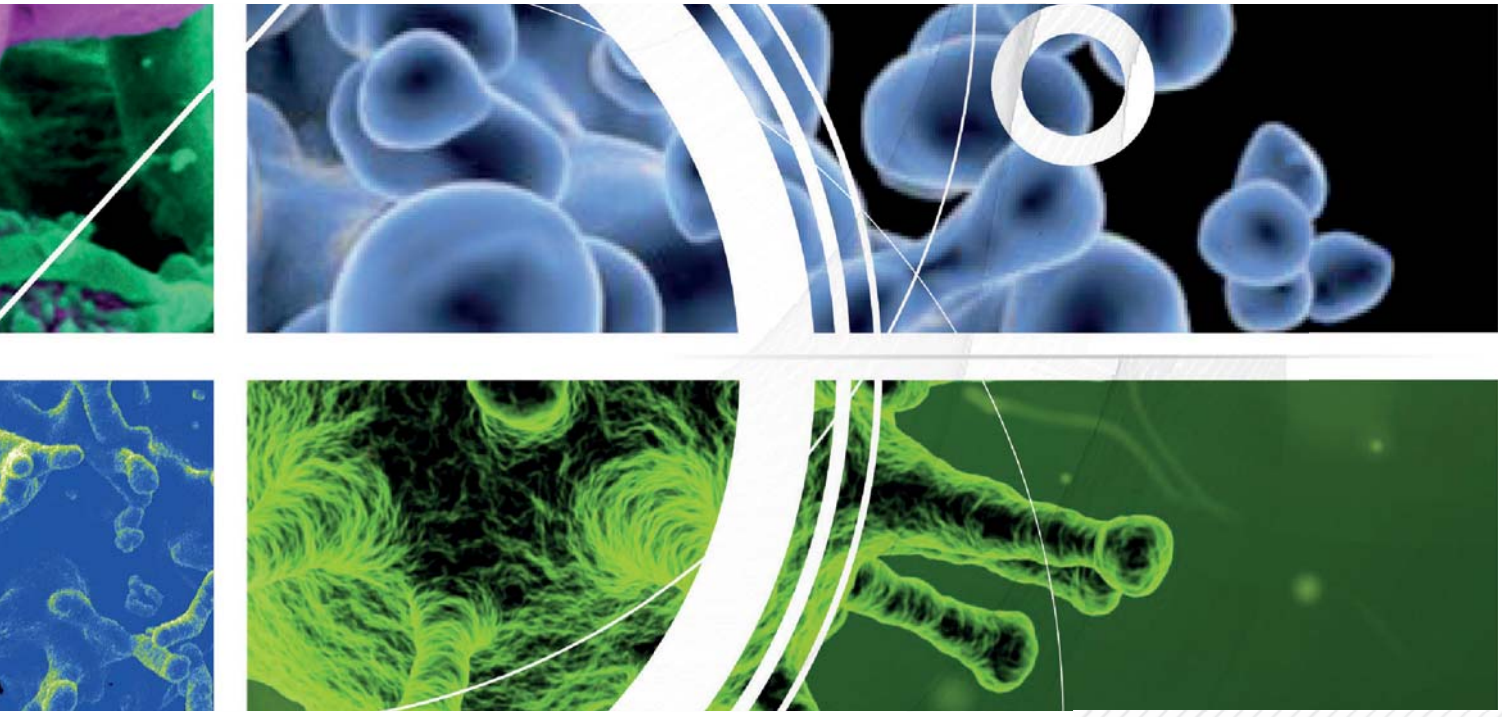
I think it's fair to say that some of the first cell therapies to hit the market have been a little rushed – but with good reason; don't we all want to bring life-saving products to patients as quickly as possible? In clinical trials, positive results demonstrated in patients have been the primary focus and so potential issues that have arisen haven't necessarily been given the full attention they deserve. During a cell therapy clinical trial, for example, it is not uncommon for companies to make an exception and treat a patient with a product that would not be released at a commercial manufacturing level (depending on the problem) – particularly when the experimental therapy may be a patient's only chance of life. When it comes to scaling up production, a manual and complicated process that worked for a small number of patients becomes a problem and questions also arise about how exactly you define product characteristics.

When the industry began pursuing biopharmaceuticals, they were described as being "three dimensional" – but cell therapies go a significant step further in terms of complexity and can be said to have a life of their own. Putting process controls in place when you have huge inherent variability from different patients' source materials is difficult. And yet, despite the challenges, we've already seen fantastic results in the clinic. Continuing to learn from marketed cell therapy products and developing new solutions will allow us to continue to improve the quality of life of cancer patients globally.

Manufacturing matters

When I accepted the position of CEO at Zelluna Immunotherapy (see sidebar: Zelluna Ambitions), my first move was to hire a Chief Technology Officer. Why? In my opinion, manufacturing is crucial. As an industry, we are still learning about how best to manufacture these promising therapies and discovering the best technologies for the job. We can't afford to wait until it's time for commercialization; manufacturing and scale up must be considered early on so that you can reach patients smoothly. Because of this, my second move was to develop our short and long-term manufacturing strategies. I decided early on that it would be best to open our doors for discussion with organizations that could help with our process development, ensuring that we

"You don't manage your business today; you manage your business with a forward-looking perspective."



were ready for manufacturing when the time came.

At recent conferences I've attended, one of the hot topics on the minds of budding advanced therapy developers is outsourcing. Some people are of the opinion that it can be exploitative; however, it is often the only option available to small and medium companies. In fact, roughly 60 percent of companies outsource their manufacturing processes to CDMOs. Most of us rent our first home rather than buy it and the same logic can be applied when choosing to use the manufacturing facilities of CDMOs! Certainly, working with a CDMO is a good de-risking strategy and can free up valuable cash flow for the sponsor company. But the pros and cons of going it alone versus outsourcing should always be considered; for example, with outsourcing, you are not always in full control and the price per unit may be more expensive. If you do decide to go down the outsourcing path, just make sure the company is a good cultural fit; a CDMO will always have a mind of its own but there needs to be good synergy in beliefs and working practices to foster a long-term relationship.

The best advice I can offer? You always need to have the long-term perspective in mind. You don't manage your business today; you manage your business with a forward-looking perspective. In an ideal world – with endless investment(!) – we would all want to build our own manufacturing facilities because we would retain the value. In most cases, however, we must accept the risks and consider what long-term commitments are appropriate.

Our conversations with external organizations helped us to evaluate options and integrate solutions, such as automated closed systems, into our manufacturing plans from the outset, ensuring that we would be able to produce cost effective, easy-to-use

Zelluna Ambitions

Zelluna was built on the back of 30 years of research carried out at the Norwegian Radium Hospital on T cell receptors (TCRs) that began in the early 1990s. Today, we are focused on developing TCR-based adoptive immunotherapies and we have created a varied portfolio of both CD4 and CD8 T-cell therapies, with the intention of directing them against TGFβRII frameshift mutations and the universal cancer antigens, hTERT and RAS. In essence, this allows us to tackle a plethora of cancer types. Our lead TCR candidate, targeting hTERT, is expected to enter sponsor studies in 2020 and several of our other candidates are at the preclinical trial stage.

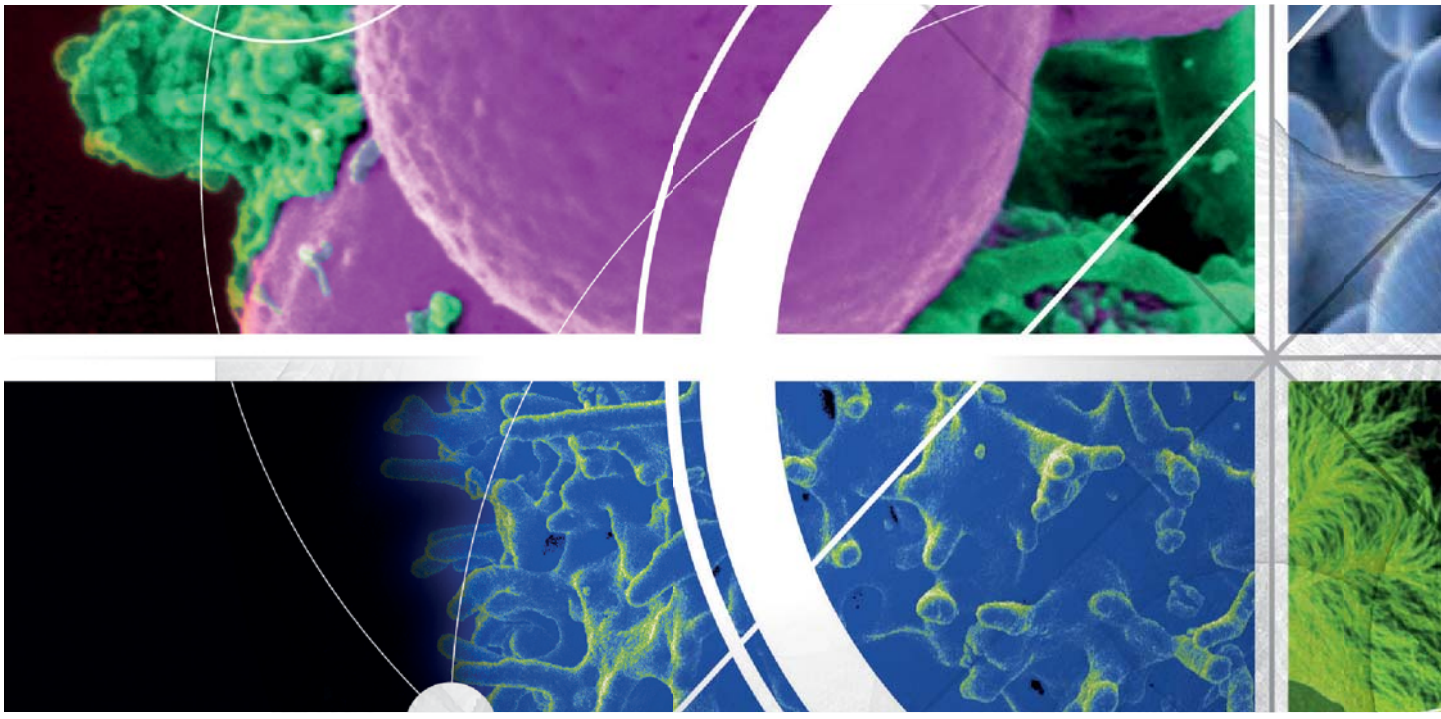
A Little Knowledge is a Dangerous Thing

The Internet and other readily available resources present patients with the opportunity to learn more about their medical conditions, empowering them to actively participate in decisions made about their own health. But with this newly found empowerment comes new responsibilities for pharmaceutical companies.

The information patients come across on the Internet or social media is not always pertinent to their specific conditions – and, depending on the source of the information, may not always be reliable. The consumption of information can often do more harm than good if it creates skewed perceptions about what therapies are truly available for a patient to use. Managing the flow of information surrounding particular products is, therefore, essential to protecting patients and preventing them from developing a distrust of the industry. Many cancer patients, for example, were of the belief that they could be cured by taking Kymriah, not realizing that the medication was only approved for use in patients suffering from B-cell acute lymphoblastic leukaemia and diffuse large B-cell lymphoma. As an industry and as individuals, we have a duty to ensure that we do not instil a sense of false hope in patients. While the success of Kymriah was significant, it has only been dampened by allowing misconceptions about it to penetrate public opinion.

Information platforms today can also be used for the discussion of unproven therapies – a huge danger to patients. Global organizations like the International Society of Cellular Therapy (ISCT) have taken a clear stance against the use of unproven cell therapies and the society's Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapy has entered into dialogue with the FDA and is fighting to make interventions against unproven products and share effective strategies within the pharma industry.

Patients often do not distinguish between someone dying from an unproven therapy and someone dying from a proven therapy; and if this continues, we could reach a point where patients do not want to access real treatment. The industry must take a stand against unproven therapies to protect patients and the integrity of real medicines.



"As you reach the commercialization stage, you need to ensure your process is robust and repeatable."

products as and when we reached these stages of the drug development pipeline. Automated and closed systems are well accepted as being the best way forward for manufacturing cell therapies and it pays to consider this early on.

Capturing a moment in time

The road to commercialization is rarely free from obstacles for any therapy, but for advanced medicines, such as cell and gene therapies, there is still much more for us to learn and, therefore, potentially more hurdles in our way. In development, processes can be tweaked and adjusted, but once you reach approval, the regulators approve a "photograph" – and that photograph must be repeated perfectly again and again for each batch. As you reach the commercialization stage, you need to ensure your process is robust and repeatable. Regulators aren't interested in the negatives you've produced – they want the final, perfect, polished and impactful photograph. It's easy for companies to get ahead of themselves because their product offers promise, but if you don't have a plan for manufacturing and commercial roll out then you'll hit many more bumps in the road.

Some have said that regulation in the pharmaceutical industry borders on being too stringent, but ensuring public trust should always be at the forefront of all of our minds when developing these exciting therapies (see sidebar: A Little Knowledge is a Dangerous Thing). Unfortunately, the hype of cell therapies has led to unscrupulous players joining the field, offering unproven therapies to desperate patients. Clearly, we need thorough and rigorous regulation because, in developing immunotherapies, we are ultimately playing with the very nature of our cells. At Zelluna, we have endorsed the FDA's position on the rigorous scrutiny of all cell therapies. In supporting the work of such organizations, we hope to contribute to the global effort to restore the public's trust in pharma and ensure that only the best – and safest – therapeutics reach patients.

Miguel Forte is Chief Executive Officer, Zelluna Immunotherapy, and Chief Commercialization Officer and Chair of the Commercialization Committee, International Society of Cellular Therapy.

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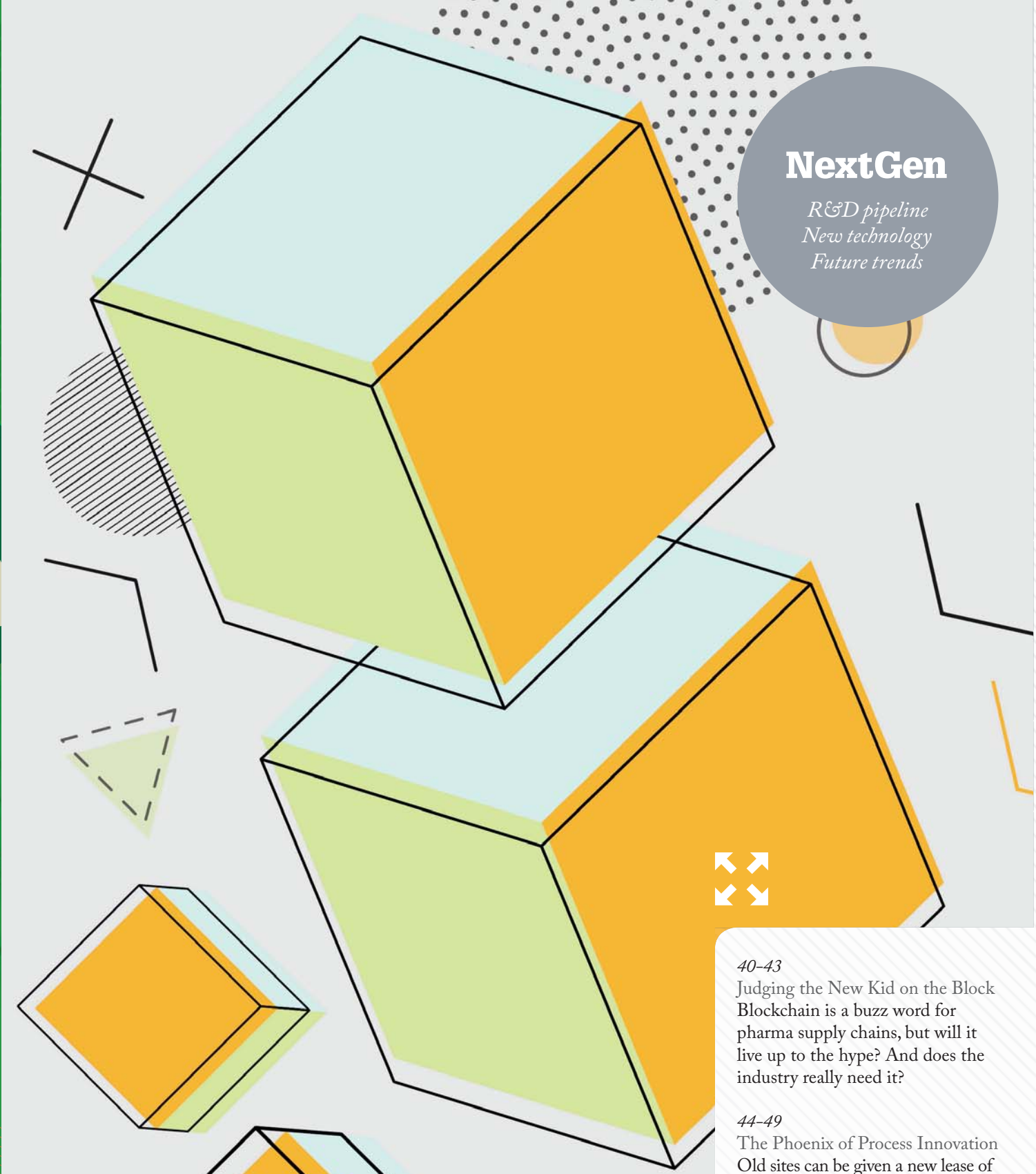
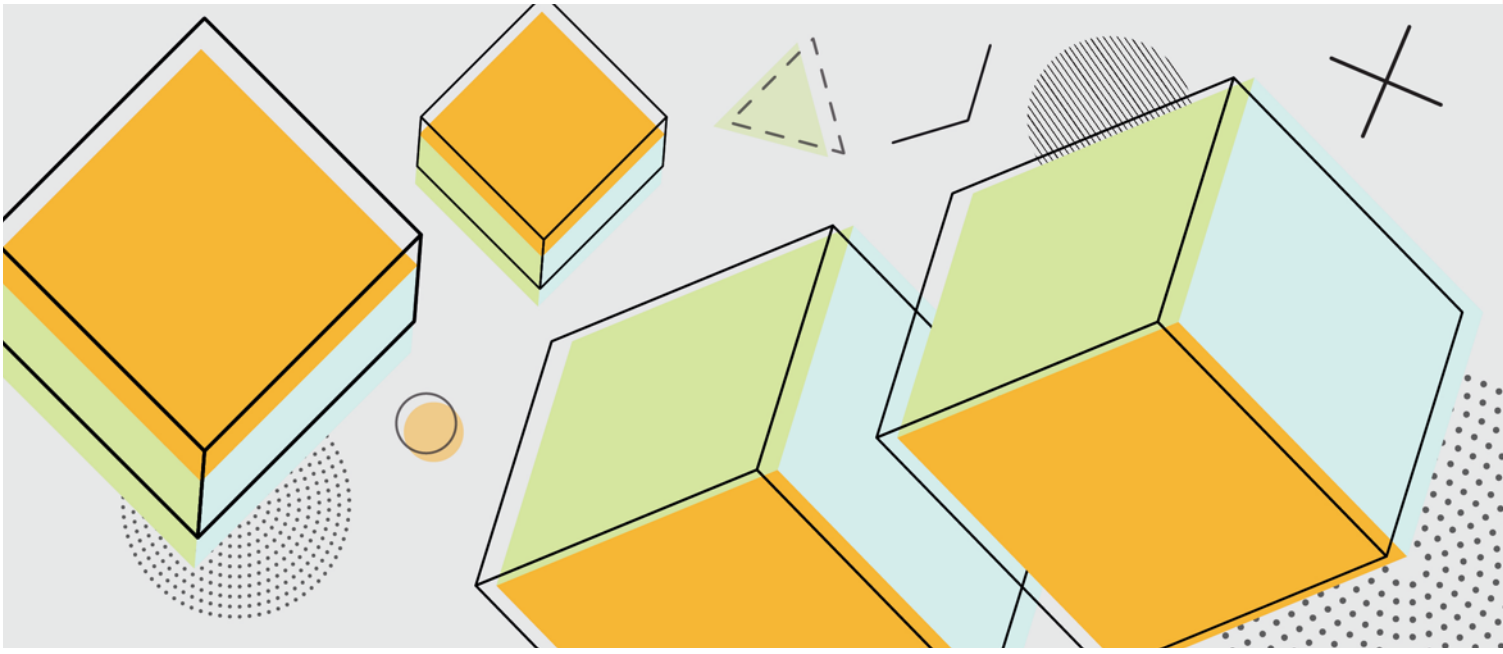




Judging the New Kid on the Block

Can blockchain truly make a difference? Or is the novelty of the ledger technology its main selling point?

With Pasi Kemppainen

A new era in supply chain compliance is being embraced by the pharmaceutical industry. The implementation of the requirements of both the EU Falsified Medicines Directive (FMD) and Drug Supply Chain Security Act (DSCSA) have made companies on both sides of the Atlantic turn to serialization systems and other digital technologies to improve the efficiency and transparency of their supply chain management. In many cases, companies are using Level Four and Five serialization systems. Level 4 is an enterprise system and Level 5 is a network system, such as a global network enabling the management of all serialization and regulatory data with partners, customers and regulatory authorities. Both types of solutions – as well as other options – are widely available from serialization solution vendors.

But now it seems there is a new technology that may go above and beyond a network system: blockchain. While some pharma companies are keenly researching and investing in the technology, others are questioning whether blockchain is just an on-trend talking point with little value. The debate is complicated by the fact that many within the industry aren't exactly sure what blockchain means. Simply put, blockchain is a decentralized digital ledger that can be used to record transactions across different computers. It is made up of a list of cryptographically secure "blocks" of data. What sets the technology apart from other ledger and database technologies is its capacity for data management and distribution within a network. Once something is recorded in the ledger it cannot be edited, altered or removed. In other words: it's a single source of truth for parties who find themselves unable to trust the integrity of data or each other.

For pharma, blockchain could help prevent the sale and distribution of counterfeit medicines and medical devices, and improve the transparency and traceability of clinical trials. Others in the industry are also exploring the potential of blockchain to help with recalls or compliance. In many ways, blockchain is a truly fascinating concept backed up by a complex mathematical model.

When examined more closely, however, I believe that the technology may not have the capacity to live up to the expectations the pharmaceutical industry has of it.

(Not) on the same page

The beauty of blockchain is that it is an immutable and secure ledger technology. Tamper-proof and fully distributed in nature, its appeal lies in the fact that centralized controlling parties can potentially be done away with. Though these qualities are desirable, the ability of blockchain to work for pharmaceutical

Complete Visibility

With John Hogan, Senior Vice President of Engineering, TraceLink, a company that focuses on track and trace and serialization.

Blockchain was thrust into the spotlight as the underpinning technology behind cryptocurrency. Since then it has been positioned as a general-purpose solution for many problems that, in my opinion, it is not necessarily suited for. Specifically, blockchain is best suited for applications that have a need for complete visibility into transactional data for all participants, immutability, and non-repudiation. In a nutshell, it is perfect for parties that don't know or trust each other!

There are a handful of use cases in the pharmaceutical supply chain that may be good candidates for blockchain technology. For example, the FDA is working with various partners, including UCLA Health, IBM, KPMG, Merck Sharp & Dohme, Walmart, and TraceLink on various blockchain and distributed ledger projects to support the track and trace of drugs and/or digital recalls. This is a novel use case for blockchain given the highly sensitive transactional data that is shared about medications making their way up and down the pharma supply chain, which helps to ensure there is a carefully tracked and encrypted record affirming every medication bottle's' integrity and pedigree.

But my advice is that, given the specific benefits and costs of blockchain, it is best to carefully consider the most applicable use cases for your company's specific business objectives before jumping on the blockchain bandwagon.

companies may be limited due to the general lack of interest of the industry for the technology standards and shared data. Pharma companies are notorious for keeping their cards close to their chests; information sharing is seemingly a painful process for some! In other industries, the willingness to share data has contributed to success. Take telecoms for example; 5G is a global standard already rolled out in major markets across the world, marking the start of a faster, more innovative era in mobile networking. This couldn't have happened without the desire of various groups and companies to work within industry standards and share useful data. Nokia, Huawei and Ericson are all competitors, but as 5G has now been introduced, it will be available on all of these companies' platforms and devices. The pharma industry is very different. The IT solutions that pharma relies on are highly company specific with very little industry collaboration and standardization.

In addition, a lingua franca is essential for the growth of blockchain, particularly when it comes to interoperability (the ability of computers or devices to share and make use of data) and integration. Because blockchain is still relatively new to the pharmaceutical industry, many vendor companies and start-ups are taking a stab at developing their own solutions in an attempt to be the first to market. But as the implementation of blockchain is highly vendor specific in pharma right now it will inevitably lead to data discrepancies between companies as the type of data one company holds won't necessarily match anyone else's. To help illustrate the issue further, take the example of cryptocurrency platforms Bitcoin and Ethereum. They both rely on blockchain to work, but they don't operate in the same "language" so information sharing across the two platforms is difficult. Therefore, technology agnostic data standards like GS1 EPCIS are even more relevant for the pharma industry than blockchain itself. DSCSA standards call for the "interoperable exchange of data" and I expect the biggest challenge will be how data semantics are addressed by blockchain solutions rather than the data sharing.

In the EU, there is also GDPR – the General Data Protection Regulation – to consider. GDPR Article 17 states that "the data subject shall have the right to obtain from the controller the erasure of personal data concerning him or her without undue delay and the controller shall have the obligation to erase personal data without undue delay." As blockchain platforms are inherently non-reversible, their use is a source of contention in terms of data protection.

For companies looking to develop their

own blockchain solutions, considerations must be made during the early stages of development as to how to navigate this issue and possibly correct or omit entries. But the question arises of how the authenticity of records will be maintained if such alterations are permitted or required. Companies will have to work to address conflicts with European law to gain and maintain the public's trust – (and many members of the public already view the data collection with an air of scepticism).

Another inherent problem for blockchain is the fact that it is a slow and costly platform by design with large data sets and number of users. The technology relies on a transaction consensus mechanism (protocols that ensure that all the devices reliant on the technology are synchronized with each other and agree which decisions are legitimate and, therefore, safe to be added to the blockchain), which prevents it from truly being applicable to real-time performance management. Though there are proprietary blockchain solutions to overcome these problems, they are controlled by private companies or consortiums, locked in by the respective proprietary rights that again contradict the blockchain interoperability, data semantics and platform openness. Effectively, these options aren't able to cut to the heart of issue and provide meaningful solutions.

Beyond the buzz

In many cases solutions already exist to tackle some of the issues that blockchain is being hyped to address – consider saleable returns, something that many have cited blockchain could help with. Saleable returns allow for verified products to be resold by wholesalers when they are returned by pharmacies. Historically, regulators have played a limited role in the process but by November 27, 2019, all wholesalers in the US will be required to verify Global Trade Item Numbers or GTIN (an identifier developed by GS1, a not-for-profit organization that creates standards on barcodes), serial numbers, lot numbers and expiry dates for their products. Failure to comply with these standards could have knock on effects for other areas of the supply chain, preventing manufacturers from adequately planning for demand – and potentially resulting in drug shortages. Currently, wholesale returns account for approximately two percent of overall sales, which, depending on the size of a company could account for a significant number of items for which a verification is required.

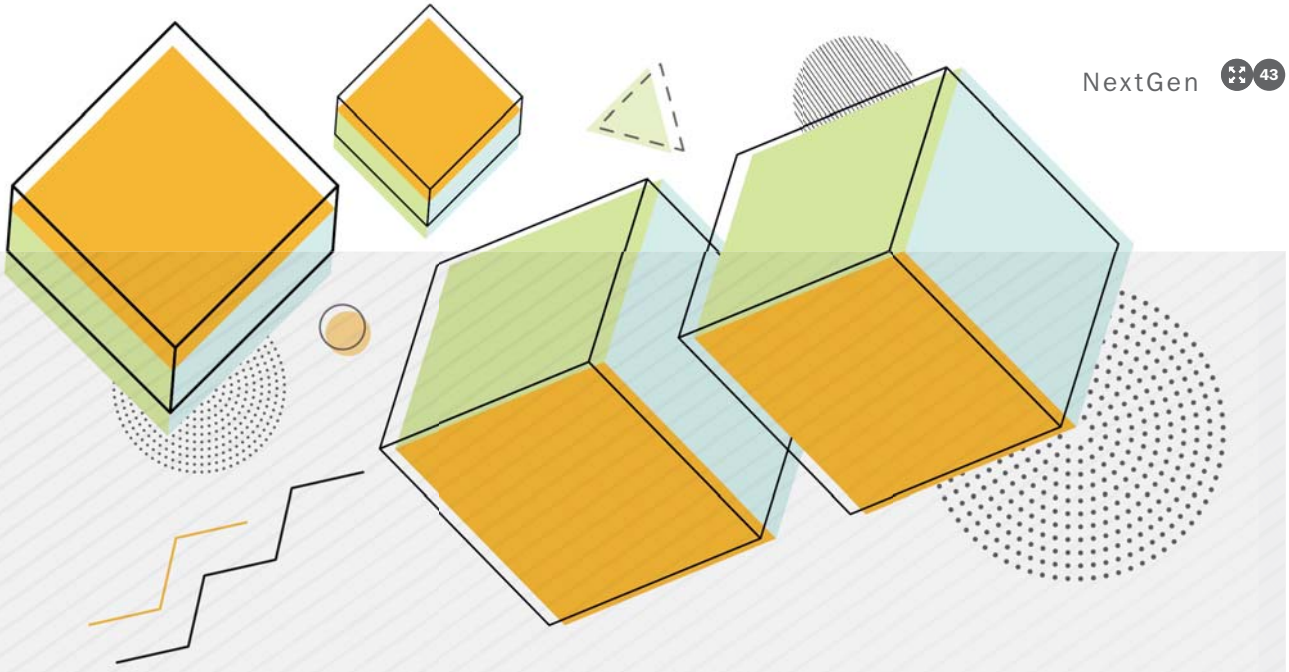
Verification Router Services (VRS) have been recommended to the industry as options for dealing with the demands of the Saleable Returns Act. These interoperable systems are used by companies to manage myriad requests to and responses for acceptance, formatting and delivery. In other words, VRS are like directories where GTIN is used to broker requests between appropriate parties. But some in the industry view blockchain as the best long-term solution for VRS, not considering the long-term challenges that will have to be overcome for the ledger technology to have the impact that is needed.

There are many established product information management systems and partner collaboration platforms that allow for the quick distribution and consumption of product master data, as well as the opportunity for downstream trading between industry partners. These proven systems and platforms are not inhibited by issues of performance, governance or personal data handling. I think there is little sense in moving to the uncertainty that implementing myriad blockchain solutions can introduce, especially in the use case of saleable returns.

However, in other areas, there are potential benefits, especially for less developed pharmaceutical markets in creating large scale serialization and traceability ecosystems. While blockchain has yet to demonstrate its disruptive capacity in advanced markets, its potential to add value to the supply chains of emerging economies is high. As many countries that fall into this bracket lack their own serialization and traceability ecosystems and models, there is huge potential for them to adopt existing ecosystem models like the EU's EMVS (European Medicines Verification System) or the US' DSCSA. Government coordinated blockchain could be an alternative means to facilitate the adoption of these large scale serialization and traceability models and give them the competitive lever to help transform their markets' structures and improve supply chain integrity thus increasing patient safety. In doing so, emerging economies could enforce one blockchain standard verification and traceability platform, cut their implementation times, improve the solution outreach and reporting capabilities and also accelerate their compliance with global standards.

Blockchain is a huge buzzword right now because it promises a fascinating and novel solution for complex problems – and certainly there are some advantages – but I do not believe it is a best of breed solution to the serialization and traceability issues faced by the pharmaceutical industry at large. In many cases, existing cloud-based systems are more than adequate to meet the needs of FMD and DSCSA. When thinking of applying blockchain, ask first if blockchain really delivers any tangible advantages over existing solutions, and if so, what are the tradeoffs you will be facing in implementing and maintaining it in the long run.

Pasi Kemppainen is Management Advisor, Global Serialization and Traceability at Santen Pharmaceutical.



Serialization Under the Lens

Compliance with serialization legislature has become an industry imperative with pharmaceutical companies in both developed and emerging economies keen to create and adopt serialization models to keep counterfeiters at bay and better protect patients. But while serialization is often talked about in relation to preventing drug counterfeiting, it is certainly more than a case of slapping barcodes on drug products to protect against fakes. Rather, it is a means for improving the end-to-end visibility of the supply chain; breaking down the obstacles that prevent the easy recall of products; and facilitating the development of superior data-driven tools that are capable of predicting patient behaviour.

US DSCSA

First enacted in 2013, DSCSA outlines how interoperable systems should be developed to track and trace the distribution of Rx drugs in the US. By complying with the Act, the entire pharmaceutical supply chain will help support the FDA in protecting patients against counterfeit, contaminated and otherwise harmful drug products. By January of 2015, manufacturers were expected to have printed lot numbers for their prescription drug products in line with the first major deadline of the legislation.

Manufacturers were then expected to have all prescription drug products serialized and compliant with the FDA's "Standardized Numerical Identification" guidance by November 2017. The guidance suggests that serial information is available in human and machine readable formats. Some, however, have struggled to comply with these standards; a general feeling of unpreparedness and a lack of qualified vendors have been significant stumbling blocks to progress.

Subsequent deadlines have seen repackagers called to serialize repackaged medicines and, over the course of the next four years, drug products will also need to be authenticated and verified by wholesalers (November 2019) and dispensers (November 2020). In 2023, the whole supply chain will be expected to achieve traceability and make use of interoperable systems.

EU FMD

The Falsified Medicines Directive was first introduced in July 2011 by the European Council and European Parliament. The legal framework aims to protect European citizens against the threat of counterfeit medicines and assure that drug products have been checked and verified for quality safety and efficacy.

In the years since it was first introduced, professionals throughout the supply chain have adopted new practices to comply with the directive. In June of 2013 EU member states were expected to ensure that all active substances imported from outside of the EU were accompanied by a written confirmation from the country of origin. By June 2014, online retailers were expected to begin using an obligatory logo introduced by the Directive, indicating their legitimacy as a legally operating pharmacy or retailer. Members were given until June 2015 to prepare for its application.

In February 2019, marketing authorized holders had to place a 2D barcode and an anti-tampering device on the majority of prescription medications and some over-the-counter products.

The Phoenix of Process Innovation

Out of the ashes of the UK's former largest chemical manufacturer, a not-for-profit company dedicated to de-risking innovation has risen. This is the story behind CPI.

By James Strachan and Stephanie Sutton

Imperial Chemical Industries (ICI) once employed as many as 30,000 people in Teesside in the North East of England. The company's history dated back to the 1920s and the demolition of its three 100 m cooling towers in 2012 signaled the end of an era for a region – and a community – defined by their industrial heritage.

Similar stories can be seen the world over. From the US "Rust Belt" to the industrial heartlands of Southern Ontario, Canada, to Bergslagen, Sweden, globalization has led to industrial decline, which can, in turn, influence social and economic issues.

Globalization is arguably one of the defining political issues of our time, with governments across the developed world thinking about how to reduce geographic inequality and create stable jobs in former industrial regions. One big hope for advanced economies is creating jobs in high value, high productivity industries, such as pharmaceutical manufacturing. The big stumbling block? The inherent risk of innovation.

Waste into worth

In the UK, CPI is an example of how older industrial sites can be given a new lease of life, benefiting the local economy, the country, innovation and, ultimately, patients worldwide. Since its establishment, CPI has worked on a number of pharma-related projects, including the BioStreamline project to optimize the development of novel biotherapeutics, and PROSPECT CP (Prove Real-world Scalable Predictive Tools/Technologies for Complex Particles) project, which involves the creation of a facility for continuous wet granulation.

CPI was born in Teesside out of different parts of ICI. "At one time, ICI at Wilton was the epicenter of the world's chemical industry," explains Graeme Cruickshank, CPI's Chief Technology and Innovation Officer. "When ICI was broken up and sold to various other companies, there was a question of what the best opportunity was for some of the existing infrastructure in Wilton. At the time, people said that if the scale-up reactors were closed, we'd never break the problem of turning waste into worth because they can't be reopened."

One NorthEast, the regional development agency for North East England, stepped in to keep parts of the facility open and CPI was established in 2004 as a not-for-profit focusing on process innovation. It received an initial £0.6 million in UK government funding and then in 2011 became a founding member of the government's network of High Value Manufacturing Catapult centers. These centers are designed to aid the future growth and success of manufacturing in the UK.

According to Cruickshank, CPI's goal is to act as a "catalyst" that brings together academia, businesses, government and investors to "translate bright ideas and research into the marketplace," and provide access to the right experts, equipment, facilities, networks, and funding. "While we are mainly located in the North East of England and have contributed significantly to regenerating local industry in this region, we also provide innovation services to multi-national companies, as well as companies across the whole of the UK," he adds.

Today, CPI works across a number of high-value markets, including pharmaceuticals (small molecules, biopharmaceuticals and complex medicines), medtech, speciality chemicals and materials, electronics,

automotive and more. It operates seven facilities – many of which target the pharma industry (see sidebar: Innovation Network).

The valley of death

According to Cruickshank, many good inventions are not successfully commercialized because there are several steps in between inventing something and selling it – all of which require investment in money, people and time. "This is called the 'valley of death.' The width of the valley is how long it takes to make the decision and the depth is the capital required. Our role is to help people make decisions faster by spending less money," says Cruickshank. "One of our unique selling points is that we allow companies to test out ideas without interfering with current production lines or having to invest in new infrastructure."

As scientists often focus on the product without considering the manufacturing scale required once commercialized, cost of goods evaluation is a useful

Case in Point

Examples of how CPI works with companies in the pharma space.

Continuous and nanomedicine manufacturing

- A UK-based consortium including CPI has developed a unique continuous processing reactor and modelling control techniques for the continuous production of high value pharmaceuticals. The project developed three demonstration-scale systems; a flow reactor system at CPI and two continuous crystallisers at the University of Strathclyde. In addition to the reactors, the project has also established novel control design and analytical techniques to complement the reactors (1).
- CPI is part of a European project titled "Nanofacturing," which is focusing on the development and scale up of nanopharmaceutical production. Coordinated by Midatech Biogune, part of the UK-based Midatech Pharma, the project focused on the manufacture of insulin coated gold nanoparticles, which are being used in Midatech`s insulin delivery patch. The delivery patch is a non-invasive, needle free, drug delivery mechanism which allows nanopharmaceuticals to be administered to the patient via a polymer strip which is applied inside the mouth (2).

Formulation and aggregation

- CPI has collaborated with Arecor to investigate ways to enhance the compatibility of biologic medicines with drug product containers and thereby potentially improve stability and shelf life throughout transportation and storage. Using a range of methods for characterising protein aggregation, CPI and Arecor have investigated the effect of silicone oil on the stability of a number of proteins and the effect of formulation on mitigating any negative effects observed. They demonstrated improved stability of the test proteins in the presence of silicone oil, with substantial aggregation occurring. Subsequently the team were then able to demonstrate stabilisation and almost complete inhibition of aggregation using specific excipient combinations (3).
- CPI, Arecor and Fujifilm Diosynth Biotechnologies UK are collaborating on a two-year project titled "Improved Downstream Operation through Formulation Innovation," which has been supported by grant funding from Innovate UK's Industrial Biotechnology Catalyst (IBC) scheme. The project's aim was to achieve a step-change in biopharmaceutical yield and quality by improving product stability. To achieve this, the partners focused on developing novel formulation platforms capable of being applied to routine biopharmaceutical manufacturing to deliver significant improvements in performance (4).

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technique to help prioritize practical work. "One thing CPI often asks first is 'how much product do you need to make?' I've had some interesting answers to that question!" says Harvey Branton, Biologics Chief Technologist at CPI. He adds that some companies have estimated they'll need to manufacture tons of product going beyond the scale of most CMOs, once current process yields are taken into account. "This highlights that people don't always understand how commercial manufacturing works and what is required for successful scale up! Manufacturing volumes can vary wildly from project to project and we advise accordingly. For example, even though the manufacturing methods are similar, the approach to support a vaccine (where 20 litres may represent a year's supply) is very different to a commodity product requiring tons of product annually. Final manufacturing processes need to be robust and additional experiments may be required to ensure that the product can be cost effectively manufactured."

According to Nick Johnson, Commercial Director at CPI, there are two main kinds of innovation CPI is poised to help with: incremental and disruptive. "Incremental innovation is quite routine for large organizations. A big pharma company might have

"One thing CPI often asks first is 'how much product do you need to make?' I've had some interesting answers to that question!"

an existing manufacturing practice and be interested in how they can make incremental improvements, for example, and some companies also ask us how we can augment their R&D capabilities," he explains. "Disruptive innovations are more the preserve of small companies and SMEs often come to CPI with a great idea, but without the R&D infrastructure, nor the technical expertise, to make it a reality. We can help them optimize their innovation and get it to the market. We also do a lot of work with universities looking to spin out their technologies."

CPI can also advise companies on how to access government funding. "There are all kinds of government support programs available to help with innovation," says Johnson. "And getting the right funds at the right time can be absolutely critical for SMEs. We have a group that looks at the funding landscape and engages with industry around how to apply and secure those funds. "Increasingly, we are speaking with the investor space to help marry up people with funds they wish to distribute with the right companies and organizations."

Innovation reborn

CPI has been involved in a number of ground-breaking pharma projects. "Cell-free expression is just one example of how we can contribute. This

Innovation Network

Including the headquarters in Wilton, CPI has seven centers:

- The National Printable Electronics Centre
- The National Formulation Centre
- The National Industrial Biotechnology Facility
- The National Biologics Manufacturing Centre
- The Medicines Manufacturing Innovation Centre
- The National Healthcare Photonics Centre
- The Graphene Application Centre

The newest centres are the National Healthcare Photonics Centre and the Medicines Manufacturing Centre.

The National Healthcare Photonics Centre provides open-access facilities to help companies develop photonics-based technologies for healthcare. Phase Photonics is currently working with the centre and the Centre for Oral Health Research at Newcastle University to develop an optical biosensor for the diagnoses of oral diseases. LightOx is also collaborating with the centre on freely-moving probes that readily incorporate into cells, or with a range of flexible linkers, to give specificity to unique applications. The small molecules enable cell imaging, detection, tracking and tagging of bioactive molecules, and the technology results in cell death without damage to healthy cells. To drive forward their innovation, LightOx has used CPI's imaging equipment to analyze chemicals, as well as expertise in device design and support with approaching the healthcare market.

The Medicines Manufacturing Innovation Centre is the newest addition to the CPI family. The centre will be located in Renfrewshire, Scotland, and aims to be an international beacon for innovation in small molecule medicines manufacturing. Users will be able to evaluate, test and prototype processes using an array of advanced Industry 4.0 manufacturing technologies including continuous, digital and autonomous manufacturing.

CPI employs over 400 people and has completed more than 1100 projects at a value approaching half a billion pounds. However their success or failure is judged by the UK government, who assess the impact of their work based on whether the organizations they've worked with employ more people or secure further funding, or ultimately make investments to develop successful business within the UK.

isn't something that's widely used yet, but we have customers with processes that could really benefit from this emerging technology," says Branton. CPI are actively involved in a range of special interest groups which regularly bring academics and industry together to discuss disruptive manufacturing approaches. Some of these include novel expression platforms, directed evolution and automated approaches.

More recently, CPI has been involved with PROSPECT CP in collaboration with AstraZeneca and GlaxoSmithKline. The continuous wet granulation facility is due to be completed in Q3 2020 and will be available as a national, open access center for contract development. "Continuous granulation is receiving enormous attention from pharma manufacturers. Solid oral dosage forms are still the most prevalent delivery method, so innovations have a correspondingly significant effect. Wet granulation was chosen as inherently it is a unit operation used to deliver tablets, particularly those for drug substances with challenging processing properties," says Jacquin Wilford-Brown, a Principal Scientist at CPI involved in PROSPECT CP. "Some molecules are simply not amenable to direct compression approaches (e.g., products containing high doses of APIs), so delivering a solution to help the challenging molecules in a portfolio has a substantial impact."

This capability also compliments the newest CPI center, the recently-announced Medicines Manufacturing Innovation Centre, which will be located in Scotland and is a collaboration between CPI, AstraZeneca, GlaxoSmithKline, the University of Strathclyde, Innovate UK and Scottish Enterprise. The facility aims to help with the development

"Old facilities can be given a new lease of life to benefit local communities and economies."

of next generation pharmaceutical manufacturing technologies.

The shutdown of manufacturing facilities often fills media headlines, but the history of CPI shows that old facilities can be given a new lease of life to benefit local communities and economies. "As a direct result from working with CPI, a number of companies have gone on to invest in assets and innovation within the Tees Valley in the North East region of England. Fifteen companies have also co-located with CPI's innovation and incubation facilities at NETPark and Newton Aycliffe," says Johnson. "This allows companies access to our facilities, whilst attracting skills to the local area. CPI employs over 430 highly skilled members of staff. Over 40 percent hold a PhD or equivalent and 90 percent of CPI staff live in the North East of England."

And reinvigorating local manufacturing hubs can have a huge impact on a country. The North East of England, for example, currently produces around a third of the UK's GDP in terms of pharmaceutical manufacturing, and the International Monetary Fund found that a 40 percent increase in R&D spending by the private sector could increase GDP by around five percent in the long term in advanced economies such as the UK (1).

"This year, we are celebrating the 15th birthday of CPI! We've come a long way!" says Cruickshank. "The really funny thing about our work is that when we do our job well, our customers go away! If I help a company to be successful then they may not need us anymore! And that's a really rewarding thing to see."

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Sitting Down With…
Adrian Woolfson,
Executive Vice President of Research and Development, Sangamo Therapeutics, Brisbane, California, USA.

The Interface Between Art and Science

What influenced your early career?

As a young scientist, I had the pleasure of meeting and learning from industry heavyweights. I applied to do my doctoral research at the MRC Laboratory of Molecular Biology (LMB) in Cambridge, UK, but they were reluctant to take me on because as a student with training in psychology, what could I possibly know about molecular biology and its applications? I believed that my psychology training and medical background set me apart and allowed me to see things from a different, fresher perspective. They must have thought so too, because they took me on!

At the time, I didn't realize how privileged I was. On my first day, I had tea with three Nobel Prize winners, Max Perutz, César Milstein and Fred Sanger. And over the course of my time there, I came to know several others, including Sydney Brenner and Aaron Klug. LMB was filled with men and women who had and were revolutionizing the field. It was surreal. Everywhere I turned, I found a new source of inspiration. It pushed me to strive for the best throughout my career.

What's the best advice you've received?

My doctoral thesis focused on the natural and artificial forms of Cluster of Differentiation (CD-1). My supervisor, César Milstein, was the creator of monoclonal antibodies. During my time working under him, we were able to demonstrate that the aggregation of proteins in the cells of patients with Huntington's disease contributed to its disease pathology; we patented a method for protein folding and ended up making the first CD-1 tetramers.

These were massive achievements for me, but Milstein sought out the most inconspicuous and minute aspects of our investigation. I had a tendency to fixate on the obvious, but he would remind me to look at the total picture – interrogating the areas of uncertainty in our work that would help bring about the best outcomes for us. That mental process made me approach my work differently and led to the discovery of soluble cluster differentiation antigens.

We measured soluble CD antigens in the blood and showed that different diseases had different soluble signatures of these antigens. We were years ahead of the biomarker field as the technology to quantify our discovery hadn't yet been developed.

How did you find the transition to industry?

The work I was doing with Milstein and his idea that the state of the immune system predicted the disease state helped us anticipate the explosion of the immuno-oncology field. In 2003, we founded ProteinLogic. ProteinLogic uses ImmiPrint, a diagnostic platform inspired by our discovery, to perform diagnostic testing for personalized medicine.

I was excited by the cut and thrust of the biotech space, but I was limited in how much I interacted with industry and I wanted to learn more. By chance, my brother's friend, who was a headhunter, told me about a position at Bristol-Myers Squibb. They were looking for an oncology specialist to join their operations. I thought it would be fun to go along and speak to them. Soon after, I found myself accepting the job and launching their chronic myelogenous leukemia (CML) program in the UK. Before long, I was transferred to their European team and then onto global operations.

It was a completely different environment than medicine. In a hospital, I would be rushed off my feet trying to do my best to see patients. By contrast, working in industry meant that much of my time was spent sitting behind a desk, but by no means was it boring! I was constantly meeting interesting people and was fortunate to learn from brilliant marketers.

At the time, we were focused on tyrosine kinase inhibitor therapies for CML. It was the first cancer where you could directly and causally show chromosomal abnormalities, so it was a great grounding experience and helped me settle into the industry.

Why move to Sangamo?

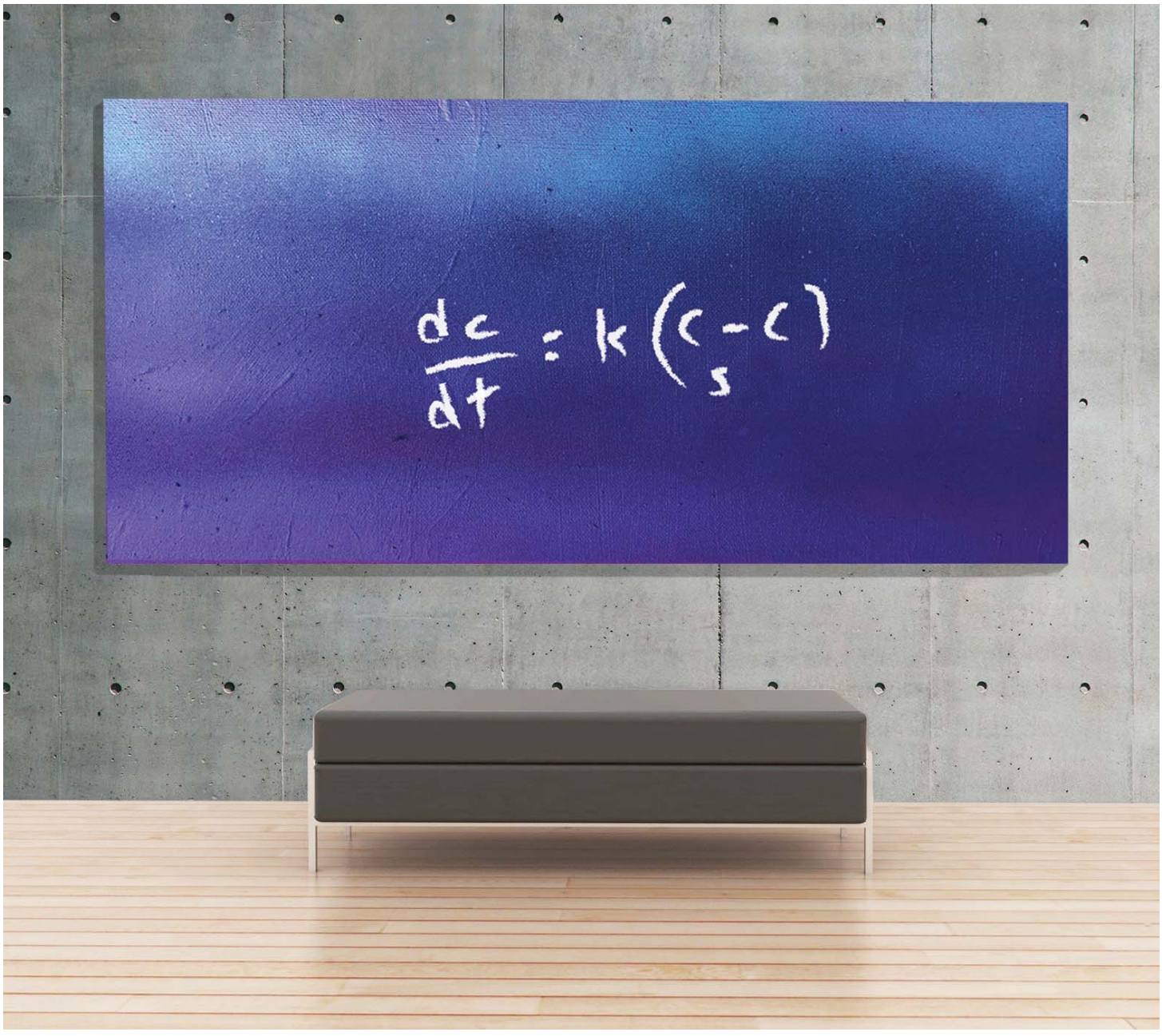
Before joining Sangamo, I spent 10 years in big pharma. I accepted a position at Pfizer in 2013 as the global head of immuno-oncology and haematology. The experience was great, but I had a desire to get back into gene editing. I knew about the work Sangamo was doing and had followed them quite closely. They were the first in the world to edit human cells and to conduct clinical trials on gene-edited T cells.

Out of the blue, I learned about a position with the company and it turned out to be my dream job! It was particularly interesting because it combined clinical development and science. I felt like a kid in a toy shop – Sangamo's pipeline has lots of diversity and optionality – and honestly, it's exciting! Sandy Macrae, our CEO, has an incredible vision for the company – his ambition and high-energy personality were motivators for me.

What are your current goals?

I want to help Sandy to keep pushing the boundaries of science and biotechnology, while simultaneously maintaining a portfolio of safe projects that have a high likelihood of technical success, like ex vivo genome editing. Juggling the old and the new is something I love doing; it plays into my creative side and helps us to stay forward-thinking.

Our zinc finger platform is proving to be effective in the treatment of disease by engaging with target sites without eliciting off-target effects. People are realizing CRISPR isn't synonymous with genome editing, and seeing the promise of zinc finger. The applications of the technology are vast and I am interested to see how we will be able to progress our products through the trial stages and into the market.



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