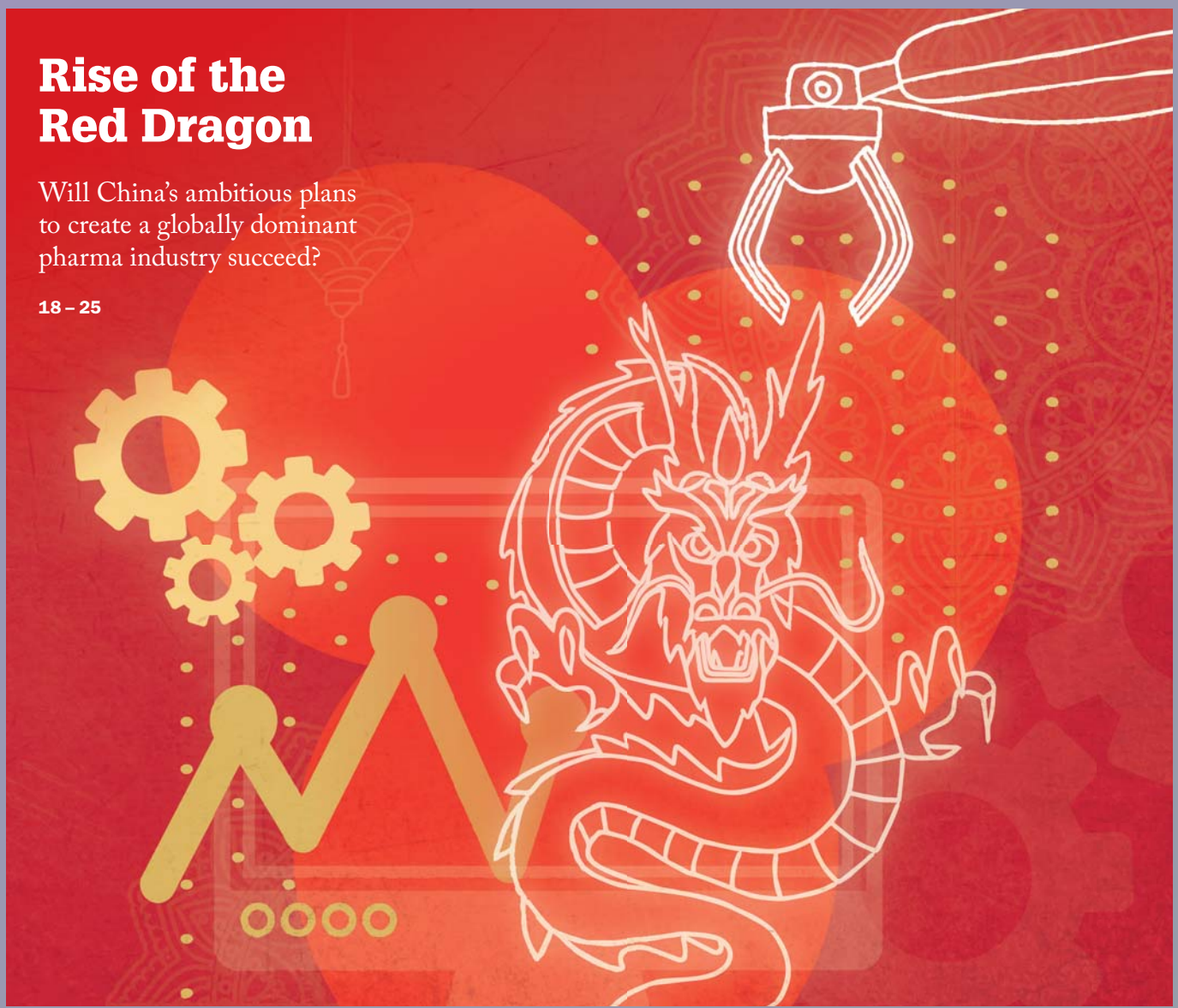
JULY 2018 # 43

the Medicine Maker™



Rise of the Red Dragon

Will China's ambitious plans to create a globally dominant pharma industry succeed?

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Online this Month

The Medicine Maker annual Innovation Awards are an opportunity for vendors to strut their stuff and showcase groundbreaking innovations that can really shake up the pharma industry. To be eligible, the product's launch date must be in 2018. The "product" can be equipment, software, instruments, technology, or even a service relating to any area of drug development, manufacture or formulation.

Who can nominate? Vendors are welcome to submit their latest innovations. We also welcome nominations from users – is there a piece of kit in your lab or manufacturing facility that you think deserves to be showcased? Let us know.

Nominations will close on November 2, 2018. The top fifteen innovations will be highlighted in the December 2018 issue of The Medicine Maker. The top three will be selected by a public vote and the winners will have the opportunity to share the story behind their innovations in a 2019 issue of The Medicine Maker. Due to the volume of nominations, we will only contact innovations shortlisted by the judging panel.

Questions? Email the editor: stephanie.sutton@texerepublishing.com
Nominations? Fill out the online form at http://tmm.txp.to/innovation-form2018

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The Power List 2019

Nominations for The Medicine Maker 2019 Power List are also open. Simply fill in the online form: http://tmm.txp.to/2019/powerlist

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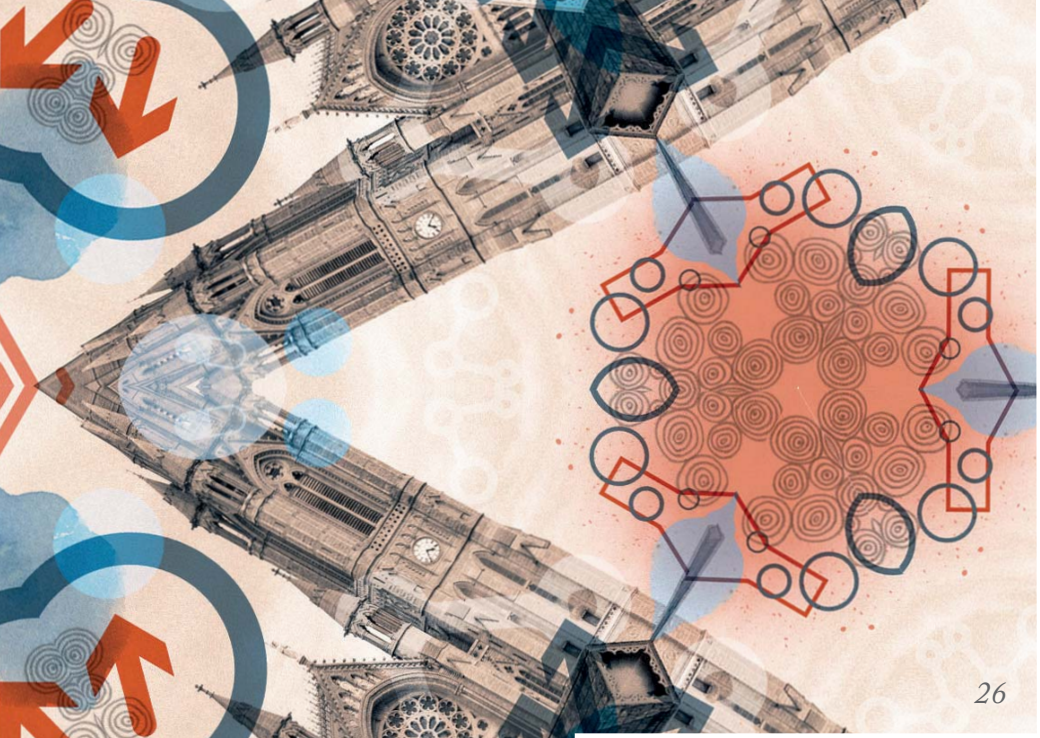

NextGen

Report

Profession

Sitting Down With

the **Medicine Maker**

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Editor - Stephanie Sutton
stephanie.sutton@texerepublishing.com

Deputy Editor - James Strachan
james.strachan@texerepublishing.com

Deputy Editor - Roisin McGuigan
roisin.mcguigan@texerepublishing.com

Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Publisher - Richard Hodson
richard.hodson@texerepublishing.com

Sales Manager - Helen Conyngham
helen.conyngham@texerepublishing.com

Business Development Executive - Sarah Griffith
sarah.griffith@texerepublishing.com

Head of Design - Marc Bird
marc.bird@texerepublishing.com

Designer - Hannah Ennis
hannah.ennis@texerepublishing.com

Junior Designer - Charlotte Brittain
charlotte.brittain@texerepublishing.com

Digital Team Lead - David Roberts
david.roberts@texerepublishing.com

Digital Producer Web/Email - Peter Bartley
peter.bartley@texerepublishing.com

Digital Producer Web/App - Abygail Bradley
abygail.bradley@texerepublishing.com

Audience Insight Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic & Audience Database Coordinator - Hayley Atiz
hayley.atiz@texerepublishing.com

Traffic and Audience Associate - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic and Audience Manager - Jody Fryett
jody.fryett@texerepublishing.com

Traffic Assistant - Dan Marr
dan.marr@texerepublishing.com

Events Manager - Alice Daniels-Wright
alice.danielswright@texerepublishing.com

Marketing Manager - Katy Pearson
katy.pearson@texerepublishing.com

Financial Controller - Phil Dale
phil.dale@texerepublishing.com

Accounts Assistant - Kerri Benson
kerri.benson@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Senior Vice President, North America - Fedra Pavlou
fedra.pavlou@texerepublishing.com

Change of address:
info@texerepublishing.com
Hayley Atiz, The Medicine Maker, Texere Publishing, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK

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

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Jurassic Medicine

No dinosaurs were harmed in the making of this vaccine.

Some of you may have spotted "big bad" pharma's cameo in the new Jurassic World: Fallen Kingdom movie. It's not central to the plot; just a one-line mention of a (shifty) biopharma CEO who wants to acquire a dinosaur to explore new bioactives. Unfortunately, the movie doesn't go into further details about how dinosaurs could influence modern medicine – or the many other burning questions I'm sure we all have. How does one perform tests on a dinosaur? Is a special facility required? Would the resulting "dinomab" be suitable for next generation bioprocessing techniques? Is there a disaster recovery plan in case the dinosaur rampages? (Of course not). And how on earth would regulators react to dinosaur-derived medicines?

Clearly, we shouldn't read too much into pharma's frequent portrayal as the fictional villain –any organization that performs experiments is juicy inspiration for a storyline. That said, Hollywood does like to tap into popular opinion and, right now, the general population has a low opinion of pharma. In the US, Edelman's annual Trust Barometer survey shows that pharma companies saw a notable drop in trust between 2016 and 2017 – from 51 percent to 38 percent. You can read more on page 13 in our Upfront section.

With trust in pharma falling, it's no surprise that the age-old anti-vaccination argument is also rearing its ugly head again. In the US, pockets of "intense anti-vaccine activity" are increasing. In Camas County, Idaho, more than a quarter of young children lack at least some vaccinations (1). The problem also affects other countries. At the start of June, the World Health Organization warned against an increasing anti-vaccination trend in Turkey, for example (2). In Australia, anti-vaxers recently erected a billboard that simply stated, "Do you know what's in a vaccine?" (Fortunately, it wasn't long before someone spray painted "Common sense" to the sign) (3).

It is 2018; dozens of studies have proven that vaccination is safe and highly beneficial. Whatever a pharma company's ultimate driver is – from altruism to corporate greed – there are regulations in place to protect us from badly designed vaccines and other therapeutics derived from unscrupulous sources (as exemplified by FDA's crackdown on stem-cell clinics (4).

What is in a vaccine? Proven science, common sense – and absolutely no dinosaurs (yet).

Stephanie Sutton
Editor

Stephanie Sutton

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1. *JJK Olive at al., "The state of the antivaccine movement in the United States: A focused examination of nonmedical exemptions in states and counties," PLOS Medicine, 15, 2018.*
2. *Hurriyet Daily News, "WHO warns against 'increasing anti-vaccination trend' in Turkey," (2018). Available at: https://bit.ly/2MF0IQD. Last accessed June 19, 2018.*
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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

There's Something in the Water

Drug emissions in UK rivers raise questions about long-term consequences for the environment

A recent study from the University of York, UK, found traces of 29 different drug compounds within two local rivers (1). The drugs detected included antidepressants, antibiotics, painkillers, and treatments for diabetes and epilepsy. The levels were in themselves low, but the team are concerned about the long-term impact of the emissions. How can the potential consequences for human (and environmental) health be better understood? And what can pharma do to help? We spoke to Alistair Boxall, Professor in Environmental Science at the University of York, about his quest to find out more.

Many studies have been done on pharmaceuticals emitted into the environment, but this one looked at emissions over time and in different locations. Why?

We know that pharmaceutical active ingredients occur in the environment, but our understanding of how concentrations vary in space and time is less developed. We need this understanding to allow us to properly assess the risks of these molecules to aquatic organisms. A key finding of our study is that concentrations of some active ingredients in rivers can be explained based on knowledge of what doctors in an area are prescribing at the time, and of river flows. We have also had some surprises; for example, in an earlier study looking at a wider range of pharmaceuticals, we detected some compounds that aren't prescribed in the UK; during periods of heavy rainfall we see elevated concentrations of compounds not usually detected, possibly due to inputs from combined sewer overflows which bypass wastewater treatment; and we detected some APIs in drinking water at similar concentrations to what we see in the river (although this data isn't published).

What sources are these drug traces likely to be coming from?

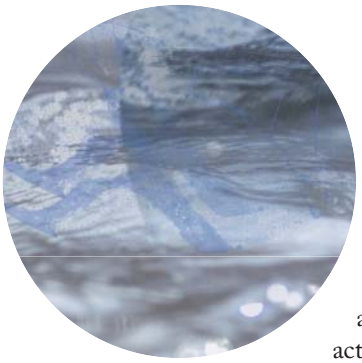
In York, we think the main source is from patient use, with a small amount arising from inappropriate disposal of medicines. In monitoring we are doing elsewhere, for example in Nigeria, manufacturing inputs appear to be a major contributor. Veterinary inputs are also possible – although in our work, few of the compounds we look for are used in veterinary medicine.

Is there anything pharma companies can do to help prevent these emissions?

Absolutely – some of the measures companies can take include introducing better treatments in their factories, or if obtaining actives from a supplier, they could ensure they only obtain materials from companies with good environmental standards. Longer term, they could move towards developing more environmentally benign medicines to replace the most environmentally risky molecules. Technological developments such as personalized medicine and nanomedicine, which will reduce patient doses, will also help reduce the environmental impact of medicine.

Do you think pharma companies also have a role to play in educating patients about safe disposal?

Yes. We recently ran a public survey in York and found that only about 16 percent of people know that we have a medicine take back scheme here in the UK. While better use of this scheme may not have a massive impact on the concentrations we detect, better awareness will mean that people become more mindful of the environmental



issues around the medicines we use.

What next steps would you like to see to tackle drug traces in the environment? Who needs to get involved?

In Europe and North America, I suspect that only a small proportion of the 1,500 or so active ingredients we use are causing environmental harm. We need to develop ways in which we can identify these molecules so that mitigation efforts can focus on the compounds that really matter. This will require better sharing of data by industry and academia, and the development of approaches for prioritizing active ingredients in terms of their environmental risk.

This is something we are already working on in the Innovative Medicines Initiative's Intelligence-led Assessment of Pharmaceuticals in the Environment (iPiE) project, which involves 13 pharmaceutical companies and ten research and regulatory organizations.

Elsewhere, such as areas of Asia and Africa, the problem of pharmaceuticals pollution will be more acute due to things like disease pressures, a lack of connectivity to the wastewater network, and poorer regulation. We need to understand the implications for human health and the environment, and then industry, governments, academics and the NGO community need to work together to solve the problem.

Reference

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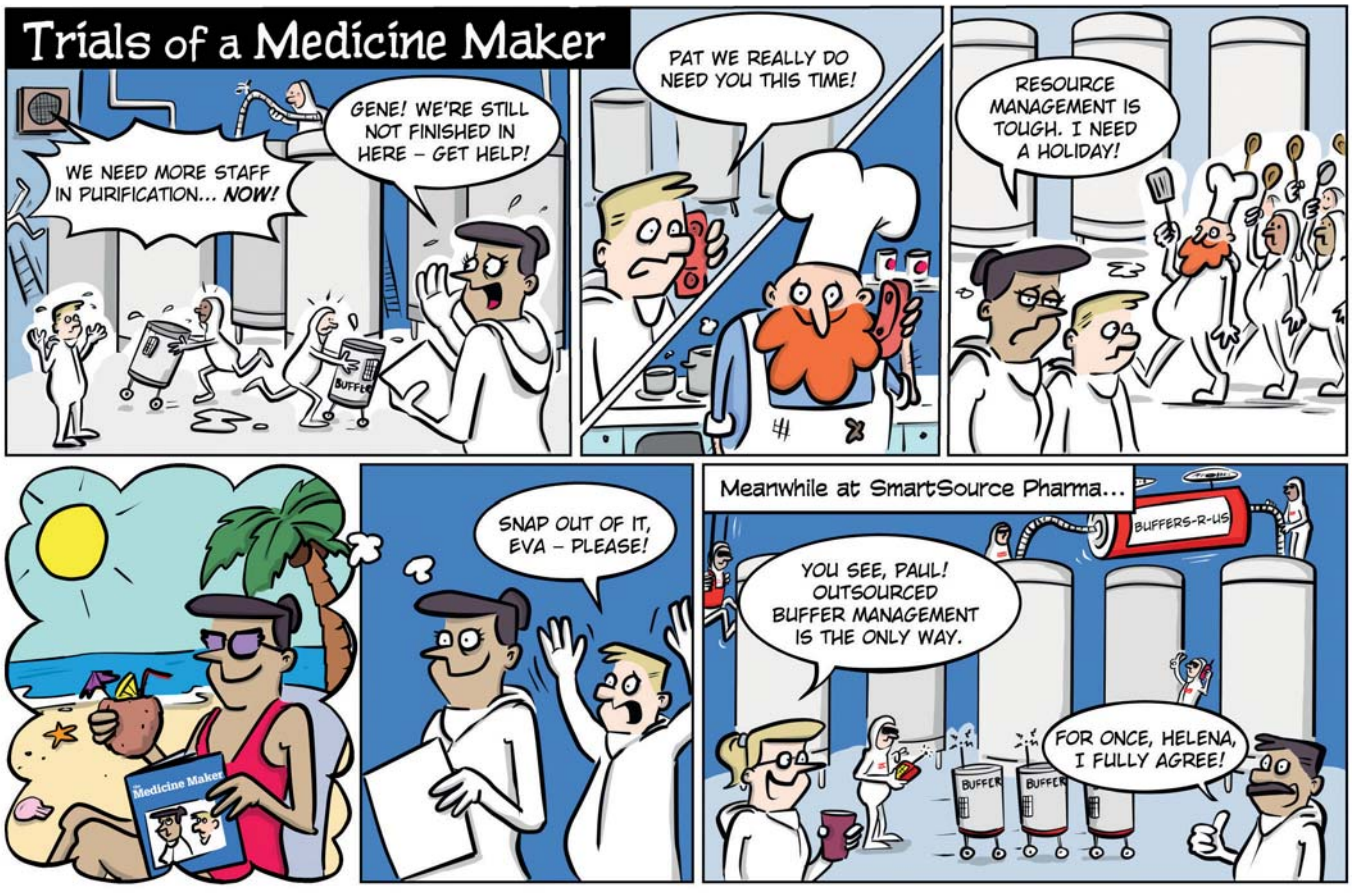
For more adventures featuring Gene and Eva check out our website: themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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A Nice Outsourcing View

What is the current state of pharma contract development and manufacturing?

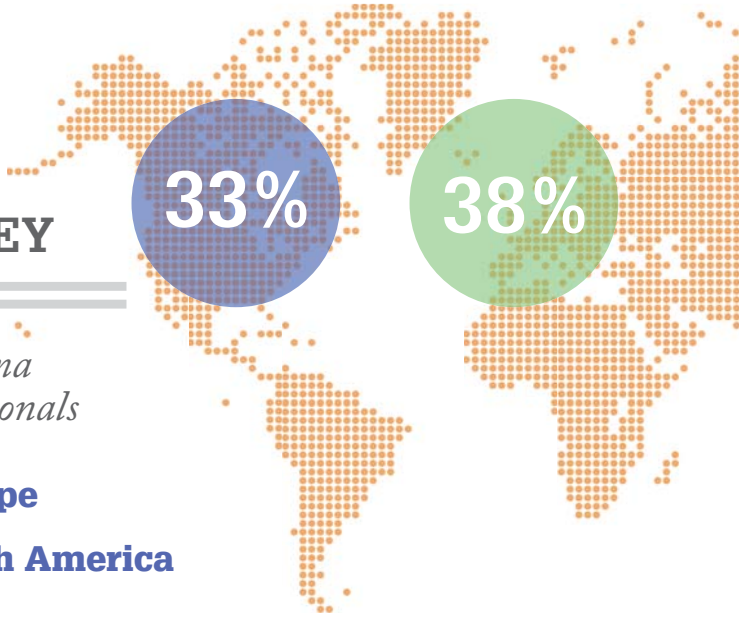
According to That's Nice, the health of the contract development and manufacturing market correlates directly with the health of the overall pharma industry – and the good news is that both sectors are fairing well. For CDMOs, however, competition in the marketplace is strong, and many sponsors (52 percent) are looking to decrease their outsourcing spend over the next five years.

Here, we present a snapshot of the outsourcing sector based on the 2017 Nice Insight Contract Development and Manufacturing Report (1). The report is based on a survey of over 700 pharma industry professionals.

Reference

1. *Nice Insight, Contract Development and Manufacturing Report (2017). Available to purchase at www.pharmasalmanac.com/industry-reports.*

THE SURVEY



Over 700 pharma industry professionals

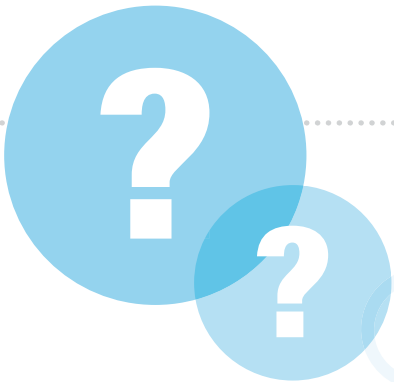
38% from Europe

33% from North America

29% from Asia

Over 75% of respondents were from big or midsized pharma and biotech companies.

USE OF CDMOS



Why outsource?

Access to specialized technologies

Improve quality

Gain expertise

Strategic plan

Reduce costs

Products outsourced by type

Small-molecule NCEs 25%

Large-molecule NBEs 21%

Large-molecule biosimilars 17%

OTC drugs 16%

29%

What service categories do respondents outsource?

Drug substance 59%

Drug product 58%

Specialized services 34%

Lab-based services 24%

Percentage of outsourced projects assigned to each region:

US & Canada 23%

Western Europe 14%

India 12%

China 11%

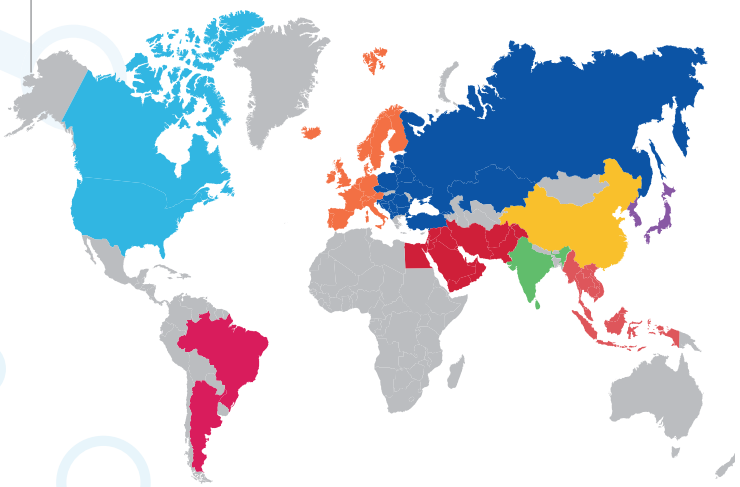
Argentina & Brazil 10%

Eastern Europe & Turkey 10%

Japan & Korea 8%

Singapore & South East Asia 7%

Middle East 7%



What makes for a good post-engagement relationship?

Good communication

On time delivery

Quality compliance

Responsiveness

Safety audits

Willingness to go above and beyond

Pure and Simple(r)

Making cancer drugs cheaper and more effective – with a paper "coffee" filter

The action of breast cancer drug tamoxifen is mediated not by the drug itself, but by its metabolite, Z-endoxifen. The body's ability to convert the drug varies between patients because of genetic differences in enzyme production. Administering Z-endoxifen directly would remove this variability, but, until now, synthesis of the drug has been prohibitively expensive. Now, researchers from Eindhoven University of Technology, Syncom BV, and the Antoni van Leeuwenhoek hospital in the Netherlands have found an inexpensive way to produce Z-endoxifen directly – using only a simple paper filter similar to those used for making coffee to isolate the pure drug.

The development has been some years in the making. "In 2011, Jos Beijnen (Netherlands Cancer Institute) asked if we would be willing to synthesize a gram of Z-endoxifen for his research group, which is looking into the pharmacology of different tamoxifen metabolites (among them Z-endoxifen). At the time, Z-endoxifen was hypothesized to be the active form of tamoxifen and its efficacy in clinical trials had not yet been shown," says Lech Milroy, Assistant Professor at Eindhoven University. "As part of her Bachelor's project, Daphne van Scheppingen and I produced milligram quantities of the Z-endoxifen as a 95/5 mixture of Z/E isomers using an optimized route."

Beijnen then contracted out the synthesis to coauthors Syncom (1), where further optimization work was performed by Bartjan Koning to increase the safety and scalability of the synthesis, ultimately enabling production of the drug on a multi-gram scale, in a single batch and with higher purity.

So how did they filter this special "brew"? By carefully controlling the work-up and purification conditions (including changing the pH of the separating medium) and replacing expensive preparative HPLC with trituration and paper filtration (see picture) at the last step, the Eindhoven team managed to simplify the separation of pure Z-endoxifen from the undesired E-alkene isomer.They also increased the stereoselectivity and further improved the reaction conditions and safety of the synthesis, allowing them to raise the overall yield of Z-endoxifen to 37 g in a single batch – a significant improvement on the 200 mg delivered after preparative reverse-phased HPLC reported in previous literature. "Our synthesis relieved a significant bottleneck in the process, enabling straightforward access to multi-gram – in other words, scalable – quantities," says Milroy.

TU/Eindhoven and Syncom's work has made Z-endoxifen more synthetically accessible to pharmacology groups. Says Milroy, "The mission now is to replace tamoxifen with Z-endoxifen in the clinic for the treatment of breast cancer."

Reference

1. *L-G Milroy et al., "A multi-gram-scale stereoselective synthesis of Z-endoxifen", Bioorganic Med Chem Lett, 28, 1352–1356 (2018).*

In Pharma We (Don't) Trust

Consumer trust in pharma nosedives because of the "blame game"

The 2018 Trust Barometer Survey from PR and marketing firm Edelman reports that trust in pharma in the US has seen the biggest drop yet in the five years since they started tracking it. Edelman assesses consumer trust in a variety of sectors, including the media, government, and healthcare, with pharma forming one sub-sector of the Health category. A 13-point drop in trust from 51 in 2017 to 38 in 2018 percent saw the pharma industry go from neutral into firmly distrusted territory – and pharma was also the least trusted sub-sector of healthcare in general. Internationally, consumer feeling towards pharma remained unchanged, at a neutral 55 percent – but across the globe, 80 percent of respondents reported that they felt that pharma companies placed profits ahead of patients, and 17 of 28 markets surveyed saw trust in healthcare overall decline (1).

It wasn't bad news in all markets – South Korea and Japan both saw significant increases in trust in pharmaceuticals, due to factors including adoption of anti-corruption regulations, new medicines becoming available, and marketing reforms.

Edelman offer two hypotheses for the significant drop in the US: the "blame game" surrounding the rising cost of healthcare, and the high cost of drugs – two areas in which the pharma industry is often apportioned considerable blame. The report authors also offer some advice to those in the healthcare industry looking to boost their credibility (2):

- Be your own publisher: only 53 percent of consumers trust health news, so using your own channels to share stories may be more effective.
- Focus on solutions: don't take part in the pricing blame game; instead, show your audience how you can play a role in the solution.
- Be the lab, not the sales force: focus on messaging around R&D, innovation and hard science versus profits, sales and marketing to avoid the "pricing outrage cycle".
- Treat the whole person: the Edelman data shows that people generally have positive feelings towards the future of health technology – and holistic wellness and disease management solutions matter as well as new treatments.
- Localize and humanize: tailor your communications to meet local standards and expectations. One size does not fit all.

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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

Ireland's Brexit Trump Card

Despite the Trump administration's tax cuts coming into force and Brexit on the horizon, Ireland's biopharmaceutical sector will continue to thrive.

By Tommy Fanning, Head of Biopharmaceuticals and Food at IDA Ireland.

Ireland's pharma story began just over 60 years ago, with Leo Laboratories making small molecule drugs out of Dublin. Today, Ireland hosts each of the world's top 10 biopharma companies, with biopharmaceuticals making up 55 percent of Irish goods exports – €67.8 billion in 2017. Sitting on the edge of Europe, Ireland has served as a springboard for European markets. But with the Trump administration's tax cuts coming into force and the UK's departure from the European Union on the horizon, some have questioned whether Ireland's biopharmaceutical sector can remain strong. I believe it can.

Major US companies are global corporations and will always require an international presence; and for companies looking to invest in the European market, Ireland will continue to be an attractive proposition. A series of investments made by US companies in Ireland since the legislation was announced – particularly on the biologics side – is evidence of this fact. In 2017, Merck Sharp & Dohme (MSD) invested in two sites (Cork & Carlow), Regeneron (Limerick) announced further expansion of their site, and Janssen (Cork), likewise, announced a major investment.

The first half of 2018 has noted some significant client investments including Chinese Biologics manufacturer Wuxi Biologics, which announced that it will locate its first manufacturing plant outside of China, in Dundalk (40 minutes north of Dublin Airport). Wuxi's plant will be the largest facility in the world using single-use bioreactors and will employ 400 people when fully operational. Edwards Lifesciences is to build a new plant to manufacture delivery components for its transcatheter heart valve therapies, investing €80 million and creating 600 jobs in the mid-west region, while MSD will invest in a major new drug substance facility in Dublin creating 350 jobs.

On the face of it, the Trump administration's recent reduction in the rate of corporate tax appears to pose a challenge to Ireland's favorable tax environment, with large US companies stating they intend to spend any spare money they have in the US. But these same companies are also pledging to invest in their international operations so I believe that the Trump Administration's tax reforms will also bring positive developments to the global life sciences market outside the US.

The truth is, the tax environment in Ireland is just the icing on the cake. A more significant pull-factor is the available skills base in Ireland. We've made sure we have people with the right skills for the biopharma sector; the National Institute for Bioprocessing Research and Training (NIBRT) has done a tremendous job in this regard.

The second key ingredient to Ireland's success is its strong regulatory and compliance culture. The Health Products Regulatory Authority (HPRA) is one of the leading regulatory agencies in

Europe, and works to make sure plants in Ireland remain in an acceptable state of GMP compliance. Though post-inspection GMP certification of Irish sites by the HPRA covers manufacture of medicines and active substances for all markets supplied, an important by-product of our strong regulatory environment is that, over the years, Irish sites have not received FDA warning letters. In short, all pharmaceutical quality systems have been thoroughly evaluated, and so companies can be confident that their innovative new product will be manufactured to globally acceptable standards of GMP. Without this vital infrastructure, it really doesn't matter how low your corporate tax rates are – companies will not invest.

Moreover, the mutual recognition agreement (MRA) on GMP inspection between the US and EU – an important step in regulatory convergence – means that the FDA will, following full implementation, be reliant on GMP certification provided by national regulators, such as the HPRA, for medicines and active substances supplied from the EU to the US. At that point, Ireland's strong regulatory and compliance culture will be even more attractive.

The UK's departure from the EU arguably throws up much greater challenges to the Irish economy, but for the biopharma sector, Brexit may bring new opportunities. At the time of writing, we still do not know what Ireland – and the EU's – relationship with the UK will look like. Will it be hard, soft, or somewhere in between? Time is ticking; and when companies have products in their pipelines destined for the European market they need answers soon.

Following the establishment of the single market in 1993, industry has developed supply chains on the assumption of frictionless trade between the UK and the rest of the EU. What often happens is that the drug substance and drug product is manufactured in Ireland, then shipped to the UK for packaging and qualified person certification, before launch into the European market. A harder Brexit would see Britain become a third country without the potential to carry out batch certification directly for the EU market – and that may force companies to validate new supply routes. For companies looking to relocate their supply chains, Ireland, as an established biopharma manufacturing base, makes sense from a logistical point of view. The HPRA is happy to talk to companies looking to relocate or to seek pragmatic solutions to issues that may result from Brexit.

We are already aware of some companies relocating their batch release activities for Europe to Ireland, and we are also seeing some sub-supply services companies and packagers putting jobs into Ireland. Pre-Brexit, IDA Ireland (responsible for attracting foreign investment in Ireland) had not been engaged with packagers to the same degree for a number of years.

Though Brexit is an unwelcome development that is not in Ireland's interest, it does represent an opportunity for the Irish economy and its biopharma industry in particular, which is well equipped to weather any storm and to capitalize on new opportunities.

The End of "Mini-Me" Medicine

Pediatric drug formulation has historically lagged behind the adult counterpart. Have government regulations had the right impact?

By Andrew Parker, Director of Project Integration at Juniper Pharma Services, UK.

Many a proud parent has affectionately proclaimed their child to be a "mini me," but within the field of pediatric drug development this affirmation is far from the truth. Children are not simply small adults – they need customized medicines to reflect their differing requirements. Unfortunately, the lack of tailored pediatric medicine on the market means physicians have to consider them as such, often going off-label by crushing up tablets designed for adults to create smaller dosages for someone proportionately smaller.

Compared with adult drug development, why has progress in pediatric medicine not kept pace? The unfortunate truth is that it all comes down to money. Market revenue is much lower for pediatric drugs because of the market size and the fact that fewer children fall ill compared with adults – a very unattractive investment prospect for pharma companies. Drug development is also costlier because of more complex pharmacokinetic processes caused by the size and weight differences that reflect a child's age. Drug absorption, metabolism and elimination are just a few of the factors that need to be tweaked.

Drug delivery is also more complex and ultimately expensive for pediatric medicine. If you have ever tried to feed a child vegetables, you will know that they have notoriously fussy taste buds. The upshot? The bitter flavor associated

with formulations may require masking to improve compliance. Swallowing can also be a problem in smaller children, requiring different formulations that may have a shorter shelf life but are more palatable, or alternative methods of delivery, such as sprays, with varying bioavailability.

To increase the number of pediatric medicines, some regions have introduced new regulations. One of the best examples is the European Union's Pediatric Regulation, introduced in 2006. The regulation requires formulation companies to screen every product developed for adults for potential use in children by devising an R&D plan, known as a Pediatric Investigation Plan (PIP), with the European Medicines Agency. The Pediatric Regulation has been an invaluable driving force in helping to meet the unmet medical needs of children – 58 percent of physicians stated they are increasingly prescribing medicines according to their licensed indication for children rather than going off-label (1).

Companies who ignore the Pediatric Regulation risk the respective adult drug authorization being blocked for launch. If that wasn't incentive enough, there are also other benefits offered for companies that comply, such as a six-month extension to the product's supplementary protection certificate. This extension will apply, not only to the product's pediatric indication, but to all indications of the product having the same active ingredient, free scientific advice, and two extra years of market exclusivity, if the formulation treats an orphan disease.

Over the past decade, the regulation has influenced children's medicine formulation in a significantly positive way. Between 2007 and 2016, over 260 new medicines for use in children were authorized, and there has been a clear upward trend in the number of PIPs being completed. Though pediatric research may still be regulatory-driven rather than company driven, legislation has forced an improvement in company expertise and resources for pediatric drug development.

A particular strength of the Pediatric Regulation is tackling disease areas where the needs of adult and pediatric patients overlap. There is significantly more market revenue available for formulating adult medicines, so if there is progress in the adult pipeline then pediatrics will directly benefit. Prime case studies are rheumatology and infectious diseases, which have seen a surge in completed PIPs and available treatments. However, progress has not been exclusively in these areas – oncology, endocrinology and metabolic diseases are other research fields with a high number of PIPs registered.

But is this regulation flawless? Certainly not – while marrying adult and pediatric pipelines benefits some diseases, it also leads to many being overlooked – in particular, orphan diseases. Cancer is the leading cause of death by disease past infancy in children, but rare pediatric cancer drug development continues to advance at a glacially slow pace. The slow progress is despite the EU's Orphan Regulation, which is having a positive affect on the development of treatments for rare cancers in adults.

An EU report evaluating the 10 years since the introduction of the Pediatric Regulation acknowledged this shortcoming, suggesting that both Regulations could be amended to work more synergistically when treating orphan diseases found in children. The report also stated a further evaluation would occur in 2019, when the Pediatric Regulation would be further finessed to ensure continued and improved advancement and acceleration.

Pediatric formulation has historically moved at a sluggish pace due to its more nuanced nature and decreased demand, but we, as an industry, should not accept this. We need medicines for children. As future pharma trends, such as personalized medicine and stratified development, make their way down the pharmaceutical value chain, it's important that the PIP process is updated to reflect these new changes.

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Faster, Cheaper, Better

Are catalysts being fully exploited in small molecule drug manufacture to reduce costs and boost process speed?

Maria Luisa Palacios-Alcolado is Technology and New Business Development Director at Johnson Matthey, UK.

Chemical synthesis can be summarized as the manipulation of chemical bonds. The process is essential to many manufacturing processes, but can present tough challenges. Catalyzed reactions offer one potential solution and broadly fall into two categories: heterogeneous and homogeneous. They differ in the phase of the catalyst and the reaction medium; heterogeneous

corresponds to different phases, homogenous corresponds to the same phase. Each type of catalysis has its own inherent advantages, and both can be used depending on the chemistry. To an organic chemist, it comes as no surprise that catalysis is important, offering the ability to shorten reaction times, often under more economically viable reaction conditions, while ensuring the formation of appropriate geometries. Typically, any non-catalyzed synthetic process is achieved by carrying out a reaction, followed by purification and isolation steps. The process is then repeated until the desired product is obtained. Catalysis has the potential to streamline the process by opening alternative reaction pathways or overcoming additional purification or isolation steps.

Because of its proven history in fine chemical applications, catalysis is being increasingly adopted in the pharma industry for the production of APIs. In my view, there are two notable reactions that have revolutionized the synthesis of small molecule pharmaceuticals. First, and perhaps the most significant, is the cross-coupling reaction, which allows new carbon-carbon bonds to be precisely forged. The most commonly used cross-coupling reactions are carried out with palladium-based transition metal complexes as catalysts, using the Nobel Prize winning Suzuki and Heck reaction cycles. These two catalyzed reaction cycles are similar in concept: a catalyst mediates the joining of two organic reagents to make new carbon-carbon bonds – typically a difficult but essential step in any synthetic process. Though there are several alternatives, the key differentiator of using cross-coupling reactions is the precise nature of carbon bond formation available.

Although cross coupling is used for a variety of reactions today, its scope was limited when it was first introduced. In the Suzuki reaction, for example, only aryl groups could be tolerated initially, which fundamentally limited the scope of potential pharmaceutical products. However, over the years, metallurgical research has resulted in the extension of tolerated functional groups through the broadening of our chemical understanding. Nowadays, the Suzuki reaction can be readily applied to aryl, alkenyl and alkynyl compounds (1) – a significant advance, as pharmaceutical synthesis involves many diverse functional groups.

"Catalysis has the potential to streamline the process by opening alternative reaction pathways."

The second example of where catalysis has revolutionized synthesis is ester hydrogenation – another essential chemical conversion process that splits an ester molecule into two alcohol products. Alcohol functional groups are common components of API materials, so ester hydrogenation is a viable route for drug component synthesis. However, prior conversions relied on metal hydride catalysts, which generate significant material waste and require time-consuming workup procedures, making them unfavorable for industrial applications.

To increase atom efficiency and achieve a more selective method of ester hydrogenation, Gusev catalysts are a good option. The Gusev catalyst, devised by Dmitry Gusev in 2013 (2), is a simple ruthenium metal complex (referred to as Ru-SNS) that is capable of selective conversion of esters into useful alcohol chemicals. The Gusev catalyst offers increased chemoselectivity (the selectivity for reacting at certain chemical sites), and is capable of achieving conversion rates of 90 percent for certain benchmarked esters (3).

Recent years have seen unprecedented levels of challenge and competition in the pharma marketplace. The industry must seek out ways to reduce the costs of R&D and manufacture. Currently, there is much focus on biologics and emerging cell therapies as the future of medicine. But small molecule drugs will always have a significant role to play, and the introduction of catalysts can help reduce manufacturing costs (4). Catalysis has the potential to streamline any chemical process and, when applied to the pharma industry, can help avoid the production of waste, while facilitating faster API synthesis.

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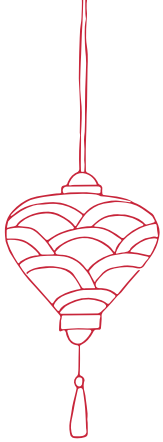


MAKE CHINA GREAT AGAIN

China is on course to reclaim its historical position as the world's largest economy by 2050. But the Chinese government, not satisfied with this trajectory, wants to modernize its economy and occupy the highest parts of global production chains – including pharma – much sooner. Will "Made in China 2025" succeed? We speak with industry insiders, consultants and academics to find out where The Red Dragon is headed – and what non-Chinese pharma companies need to know.

By James Strachan

Taking a long-view of history, China's current economic standing, relative to other countries, is an aberration. For most of recorded history, China has accounted for around 30 percent of the world population and 40 percent of world GDP. Indeed, as late as 1820, China's share of global GDP was greater than Western Europe, Eastern Europe, and the United States combined (1).

As Henry Kissinger notes in "On China," Western observers encountering China in the early-modern era were stunned by its material prosperity. In the 1760s, French political economist Francois Quesnay said, "[N]o one can deny this state is the most beautiful in the world, the most densely populated, and the most flourishing kingdom known" (1). As Kissinger points out, although China traded with foreigners and occasionally adopted ideas and inventions abroad, it often believed that the most valuable intellectual achievements were to be found within its borders. They had a point. For most of history, Chinese technological achievements matched their Western European, Indian and Arab counterparts, and prior to the industrial revolution, China was for centuries the world's most productive economy. But as Europe developed railroads, steamboats, mining and agriculture during the 18th and 19th century, China remained reluctant to embrace foreign innovations. A "Great Divergence" followed – along with a rapid decline of China's global share of GDP.

But on its current trajectory, China will reclaim its historical position as the world's largest economy by 2050 – accounting for around 20 percent of global GDP (2) and rivaling the combined economic might of the US and the EU27. Gone are the days when China looked upon Western technological and economic achievements with disdain. Today, the Chinese government seeks to emulate their successes – even copying foreign methods and institutions.

Made in China 2025

Made in China 2025 is the Chinese government's plan to create a "modern," more globally competitive economy. The idea is to transition away from "dated" industries, such as coal and steel, to make way for higher value industries, focused on science and innovation. Labor productivity is several times lower in China than in industrial countries and even some developing countries (2). Moreover, Chinese enterprises use an average of just 19 industrial robots per 10,000 industry employees, compared to 531 in South Korea, 301 in Germany and 176 in the United States (2). China seeks to change this by making use of production lines and management processes based on modern information technology and highly automated machines.

"The scope and the effort put into the strategy is quite remarkable. **Although the top down industrial policy is nothing new to China, the complexity has greatly increased."**

"Singapore, Japan, Korea, the US, Germany and Britain have all implemented similar strategies in the past," says Diana Tan, General Manager of Kantar Health China, a global healthcare consulting and research firm. Miao Wei, Minister of Industry and Information technology (MITT) in the Chinese government adds, "By 2025 [...] China will basically realize industrialization nearly equal to the manufacturing abilities of Germany and Japan at their early stages of industrialization," (3). According to Tan, Made in China is widely seen as being modelled on German Industry 4.0 and other countries' similar plans or blueprints. It will focus on:

- improving manufacturing innovation
- integrating technology and industry
- strengthening the industrial base
- fostering Chinese brands
- enforcing green manufacturing
- promoting breakthroughs in "10 key sectors"
- advancing restructuring of the manufacturing sector
- promoting service-oriented manufacturing and manufacturing-related service industries
- internationalizing manufacturing.

"The scope and the effort put into the strategy is quite remarkable," says Max Zenglein, researcher at the Mercator Institute for China Studies. "Although the top down industrial policy is nothing new to China, the complexity has greatly increased. To reach its targets, the government is employing a wide set of tools, including setting up massive funds and supporting the build-up of a new environment for innovation and industrial clusters. There are efforts to learn from past failed experiences and attempts to reduce inefficiencies in resources. In part, the effort also includes integrating successful private companies to complement efforts by state-owned companies."

The state will play a significant role in Made in China 2025, providing an overall framework, as well as financial and fiscal tools, through the creation of manufacturing innovation centers (15 by 2020 and 40 by 2025). "China is and will be for the foreseeable future a state controlled economy," says Mark Wareing, Minister-Counsellor and Director, Advanced Manufacturing, Innovation, Technology and Transport at the UK Department for International Trade. "There will be restructuring of old industries and investment in modern industrial parks with incentives offered for foreign investment, plus relaxation of company ownership laws. This is already happening, not only in the Tier 1 cities, but also in other, poorer areas. There is also the proposed Greater Bay Area initiative, which will link the areas of the Pearl River Delta with the entrepreneurial heartland of Shenzhen and the financial might and logistics portal of Hong Kong."

One of the "10 key sectors" targeted by the Chinese government is pharma and medical devices. China currently has the second largest pharmaceutical market in world – only the US is bigger. A clear goal is to make Chinese biopharma companies more competitive, and to have Chinese firms move up the value-added chain in production.

The Chinese pharma industry has seen rapid growth over the past decade, with sales increasing from $26.2 billion in 2007 to $107.1 billion in 2015 (4) – something that Fadia Gadar, VP Global Business Development at SGS, has witnessed first-hand. "When I first visited China over a decade ago, I would never have thought things could get to where they are now," she says. "Over the past three years, things have begun to really change. For example, just a few years ago you would barely see any foreign cars, now you see Hondas, Toyotas, and, more recently, BMWs and Mercedes. And on the business side, when you look at the qualifications of the people we hire, in terms of their knowledge and ideas – it's very impressive."

However, though pharmaceutical sales have rapidly increased in China, research and development remains relatively low: the ratio of R&D to sales was around 2.7 percent for most Chinese pharmaceutical companies in 2012 – significantly lower than that of US counterparts (ranging from 15–20 percent). Most Chinese firms, therefore, engage in low-value-added activities, such as manufacturing, formulating, packaging and distributing generic products. The sector also struggles with overproduction of certain drugs. For example, in 2012 there were 1272 applications of generic drugs, each of which was submitted by different sponsors more than 20 times, accounting for 60.7 percent of the total. And in 2014, the China Food and Drug Administration

(CFDA) released the first list of overproduced drugs (more than 500): 34 categories of drugs were manufactured by more than 500 pharmaceutical companies in China, such as aspirin, ibuprofen, metronidazole and norfloxacin. Overproduction has become a serious problem for the Chinese pharmaceutical industry: manufacturers rarely exceeded a single-digit profit margin, often failing to make a profit entirely (5).

But the Chinese government is keen for things to change. One big challenge is that R&D costs money – and most generics companies in China's fragmented market can't afford to invest. As of 2012, there were around 4500 domestic pharmaceutical manufacturers and 14,000 domestic pharmaceutical distributors in China, and more than 70 percent of pharmaceutical manufacturers were small-scale enterprises with less than 300 employees and revenues of less than $3 million (5).

A regulatory revolution

To remedy the situation, the Chinese government will need to promote stricter standards, which should price out smaller companies, leading to consolidation and, thus, greater economies of scale – which it is doing, largely based on the US FDA model.

"They are following the FDA by the book – to show the rest of the world that they are trustworthy," says Gadar. Carolina Ung, lecturer at the University of Macau, and co-author of a paper looking at the obstacles and opportunities in Chinese pharmaceutical innovation, cited above (5), believes that the current reform of China's regulatory system is a multifaceted undertaking. "From the waves of new and revised policies and regulations seen in the past years to the recent major historical structural reforms of the regulatory system, it is obvious that China is aiming to improve regulation efficiency and consistency," she says.

Frederick Abbott, Professor of International Law at Florida State University, USA, and author of a WHO report on Chinese policies to promote local production of pharmaceutical products (6), believes China is making substantial strides in improving the quality and safety of the medicines it produces. "There has been a great deal of attention on good manufacturing practices, new mechanisms for medicines approvals (including allowing transfers of marketing approvals between researcher-applicants and third-party producers), environmental controls, recognition of foreign approvals, foreign investment controls, competition law, IP, and so on."

As Abbott's report for the WHO shows, China's pharmaceutical industry developed when the country was relatively isolated from international trade – and while the economy was closed, regulation was not a priority. "This left the regulatory framework with a lot of need for improvement," says Abbott. "But a lot has already been accomplished."

A big change came with the 2010 revised edition of Good Manufacturing Practice for Pharmaceutical Products. According to the WHO report, "It was widely anticipated that these strengthened GMP regulations would raise compliance costs to the point where smaller and less well-capitalized manufacturers would cease doing business." In fact, Pharma China estimated that over 1000 Chinese pharmaceutical companies would be pushed out of business, while Chinese experts predicted that compliance with the 2011 standards would raise the cost of drug products by 30 percent (6).

Tan argues that regulations are rapidly evolving in other areas. "One area is Generic Consistency Evaluation (GCE), which has recently set higher standards for ingredients and manufacturing processes," she says. "Generic drugs will need to show therapeutic equivalence in efficacy and safety to their innovator counterparts, through bioequivalence testing. Companies that comply with the new policy will benefit from a lower tax burden of 15 percent (versus 25 percent). What is essentially a quality initiative will also have an impact on affordability and lowering the cost of healthcare in China (premium pricing for off-patent drugs will be difficult to justify ."

China is also making significant improvements to its regulation of clinical trials. "We see more clinical trial centers – from specific clinical sites accredited with GCP (Good Clinical Practice) to all qualified hospitals, improvement in Ethics Committee processes, a greater number of drug reviewers hired, as well as self-inspection of clinical trial data," says Tan.

China's decision to join the International Conference on Harmonisation of Technical Requirements for Registration of

WARNING LEADER

China is in the process of overhauling its regulatory system to bring its standards closer to those in the US and Europe, but there is still a long way to go. Data published by the FDA on inspections, warning letters and red lists (import alerts) across the world gives an insight into the scale of the challenge.

From 2016 onwards, China received the greatest number of warning letters and red lists (refusing an inspection or gross misconduct), of any country in the world (see Figure 1). This may be a reflection of the dramatic pace at which the Chinese pharmaceutical market has grown over the past five years, as well as a decline in compliance. The figures also demonstrate how globalization is forcing the FDA to spend an increasing amount of time abroad. In fact, as of 2017, the FDA is inspecting foreign and domestic drug facilities in equal number (see Figure 3).

The figures also revealed that 88-100 percent of all foreign drug manufacturing sites added to the FDA red list during the five-year period (2013-2017), remained there as of June 2018 (see Figure 4). This suggests that is takes a significant amount of time and effort to "de-list" and the vast majority of firms are not managing it. Of those 191 sites still on the red list, 88 were in China and 54 in India, collectively contributing 74 percent of the total import alerts.

Overall, these findings suggest that Chinese (and Indian) pharmaceutical producers still have a long way to go, with more stringent quality controls, more rigorous monitoring and documentation needed.

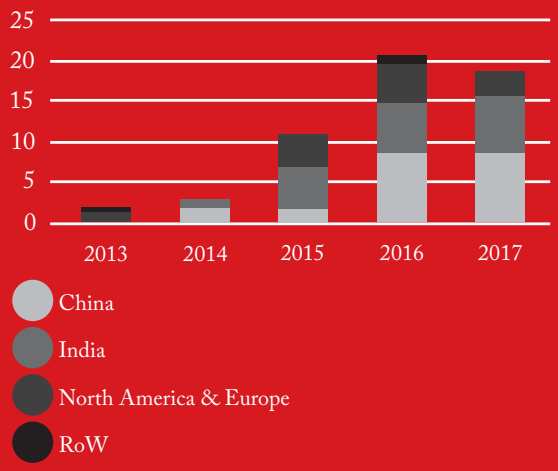


Figure 1. API cGMP Warning Letters by country/region.

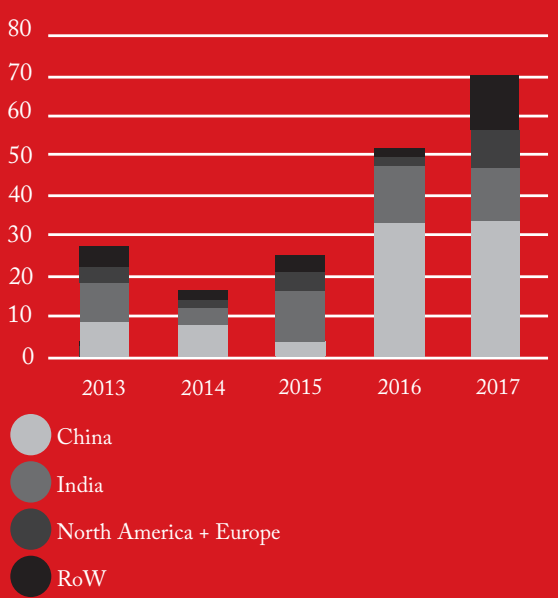
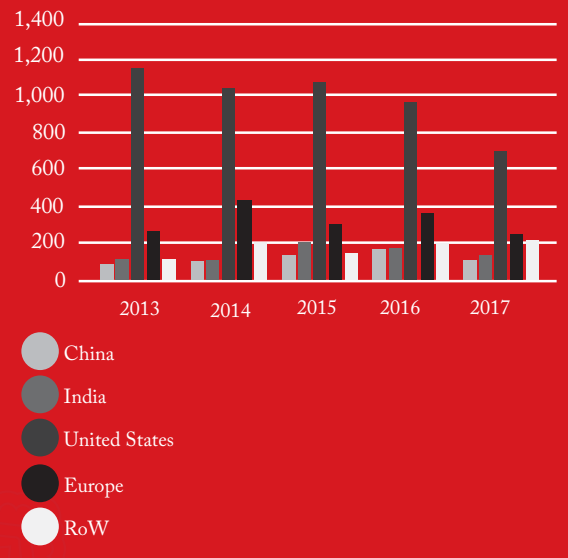


Figure 2. FDA Red List by country/region.



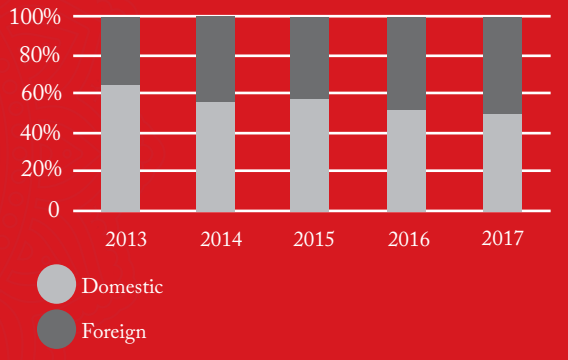


Figure 3. FDA GMP inspections of registered domestic and foreign drug establishment by region.

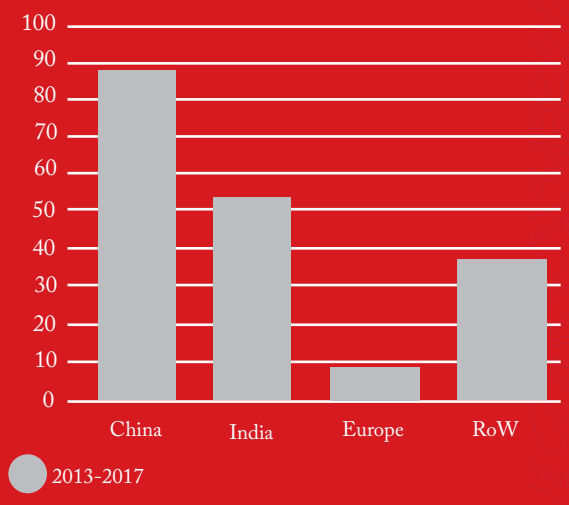


Figure 4. Drug manufacturing sites added to the FDA Redlist from (2014-2017) that are still on the Redlist (as of June, 2018).

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Pharmaceuticals for Human Use (ICH) is another step towards higher standards as part of the country's regulatory reforms. To join the ICH, new members must implement a basic set of regulatory requirements for the manufacture of pharmaceuticals, for the conduct of clinical trials, and for stability testing of pharmaceutical products. But many smaller companies still struggle to meet ICH standards. Abbott points out that, as with India, "There are substantial differences between the quality controls in place among the major producers with international presence and smaller producers addressing only the national/local market."

"When you look at our client portfolio at SGS, the vast majority are local companies," says Gadar. "We find that the regulations are still quite loose for the smaller companies, in local markets, whereas the larger firms will closely monitor quality. Once we had the FDA approval in our laboratory in Shanghai, we started to see an increase in business with the large, multi-national companies, suggesting that that for those companies, CFDA approvals are not enough to satisfy their outsourcing requirements and strategies." (However, quality concerns are not limited to small firms selling into the domestic market, as our sidebar, "Warning Leaders," shows.)

China also faces the problem of competing with private industry for individuals well-trained in regulation, making it difficult to retain staff. "I would not underestimate language as a barrier to training of personnel," says Abbott. "There are not many pharmaceutical specialists from the OECD who are fluent in Chinese and available to conduct training programs."

A protectionist plan?

With China joining the ICH and bringing its standards in line with the rest of the world, as well as implementing policies to

"There are around 100,000 State Owned Enterprises of Some form or another and China has massive resources, particularly in finance. If it is the intention to achieve the ambitions of Made in China 2025, then it will be done."

encourage foreign investment, some have seen Made in China as a move towards globalization. And yet, the central goal of Made in China 2025 is to occupy the highest parts of global production chains – which some commentors have described as "protectionist." Indeed, the plan identifies the goal of raising domestic content of core components and materials to 40 percent by 2020 and 70 percent by 2025. Hitting this goal would represent a serious threat to manufacturing industries across the developed world. Max Zenglein and his team found that the Czech Republic, Germany, Italy, Hungary, Japan and South Korea are most vulnerable – "due to the importance of manufacturing in the targeted industries in the relevant countries," says Zenglein. As for pharma, Zenglein's team found that within the EU economies, the pharmaceutical sector would be the sixth most affected industry. "Based on the relevant importance of the sector in their country, Belgium, Ireland and Denmark are potentially most at risk," he says.

That said, Zenglein believes China offers significant opportunities for foreign companies – at least for now. "China is still in dire need of key technology, which provides great opportunities for foreign companies," he says. "But companies will also need to be aware that China is changing as an economic partner. It is a market with great potential but also one in which the government is heavily supporting Chinese companies. One of the aims of Made in China 2025 is to increase the market share of Chinese companies in the targeted sectors not only within China but globally. Companies will need to balance their short-term business interests with the long-term risks."

Jin Zhang, pharmaceutical business strategist and the editor of The Pharmaceutical Consultant offers some advice for foreign companies looking to invest in China. "First, you must recognize that the product is very important – focus on companies with innovative products," she says. "Second, look for a team with experience in the Chinese market. Third, recognize that the Chinese market has different needs from other countries. And fourth, play by China's rules – what works in the US and the EU might not work in China."

Foreign companies in China must also deal with further so-called protectionist practices around intellectual property enforcement. Daniel Chow, Ohio State University College of Law, wrote a paper on the three major problems threatening multinational pharma companies in China (7). "I first encountered the problems working for Procter & Gamble in China," he says. "I was in charge of protecting P&G's brands and discovered that there was a major counterfeiting problem with various products, including pharmaceuticals." Chow argues that competition law authorities use heavy-handed tactics, such as dawn raids to intimidate multinational companies (MNCs) in China. "PRC authorities also charge MNCs with price fixing, use aggressive tactics to pressure MNCs to lower their prices, and also accuse MNCs of engaging in bribery of PRC officials to obtain business," says Chow. "Chinese companies that engage in far more egregious practices often have not been prosecuted."

Chow also argues that China has a web of policies that force companies to transfer their pharmaceutical patents to Chinese companies. "The lower level of protection in China means that patent rights become available to the public more rapidly than in the US or EU," he says. "For example, pharmaceutical companies will first apply for a patent before they seek regulatory approval in China for the drug. The US and EU provide a period of marketing exclusivity for the drug after the end of the patent to compensate for the loss of the patent term during the approval process. China does not, effectively reducing the life of the patent by 40 percent."

MNCs have also complained for years about forced technology transfers in exchange for market access in China. Gadar believes that foreign companies can't do much about this problem. "The issue is always the same – it's trust," she says. "There may be things you can do, but at the end of the day, you're dealing with humans. The most important – and difficult – thing is to find people you can trust."

Mark Wareing believes there is a need in China to standardize enforcement and raise penalties for IP infringement. "Otherwise, the desire to innovate (and hence develop IP) will not be achieved," he says. "But you can expect to see loosening of ownership structures (already announced by President Xi) and tightening of IP laws – in fact, over 95 percent of IP cases in the courts are now Chinese on Chinese. Also, several of the New Technology Parks and Zones specifically reference local support for IP enforcement to assuage foreign fears." Wareing believes foreign investors must

pick their locations and their partner organizations carefully and take good, impartial, local advice. "Embassies are particularly supportive here," he says.

Abbott also believes that China has undergone a transition in the field of IP protection. "On their face, China's IP laws are consistent with the TRIPS Agreement, and the Chinese government has been encouraging domestic filing of patent applications, and the rate of patenting in China is increasingly comparable with major OECD countries," he says. "Countries in the process of development go through a transition between predominance of appropriation and innovation. Enforcement is likely to be weak during the appropriation/catch-up phase and to grow stronger as the country becomes an innovator. Enforcement of IP in China has improved substantially in recent years. As the Chinese government is now focused on biopharma innovation, patent enforcement is likely to be a more substantial priority. Paradoxically, I expect that, within the next decade, OECD industry will be as or more concerned by Chinese over-enforcement of IP rights than under-enforcement."

Chow disagrees. "My own view is that China under Xi Jinping is moving in the opposite direction and will become even more protectionist and nationalistic in the near future without effective intervention by the US and possibly other allies," he says. "The US government might be able to change this course – and I know that the Trump Administration is trying to do so with aggressive trade practices, such as increased tariffs, directed against China. But this is a dangerous, risky tactic that might backfire. It remains to be seen what will happen."

Will China dominate?

The world has already seen how the US and the EU – because of their large markets and preference for strict consumer and environmental regulations – have effectively been able to export their regulatory standards to the rest of the world. Could China replace the EU and the US as a source of de facto global standards? The answer will hinge upon the success or failure of China's ambitious plans to create globally dominant hi-tech industries, such as pharma, as the country attempts to reclaim its historical position as the world's largest economy.

"There are around 100,000 State Owned Enterprises of some form or another and China has massive resources, particularly in finance," says Wareing. "If it is the intention to achieve the ambitions of Made in China 2025, then it will be done."

Zenglein isn't so sure. "China certainly is an economic force to reckon with and is quickly emerging as an increasingly competitive and capable global player in more sophisticated industries," he says. "But it is doubtful that all of the targets will be reached within the set timeframe by 2049."

"China is providing incentives for talented expatriates to return to China to pursue research," says Abbott. "It is training large numbers of PhD scientists; it is providing R&D subsidies, including R&D parks; it is making it easier to move products from laboratory to marketing authorization and production; it has improved its patent system; it is encouraging foreign investment in R&D centers. China appears quite serious about becoming one of the major biologicals R&D and production centers."

The Chinese market will maintain its strong growth in the next decade, according to Zhang. "The majority of Chinese pharmas will focus on improving the quality of generic drugs and expand their territories in China," he says. "However, some leading pharmas will definitely begin to enter overseas markets and begin to play a more important role in the global stage."

So far, China's regulatory capacity and the willingness to elevate the protection of consumers and the environment has not kept pace with its economic growth. And as Anu Bradford argues in her paper on the "Brussels Effect," though China may soon be the largest consumer market, GDP per capita is a better prediction of a country's regulatory propensity (8). "I think it's a culture – mindset – thing," says Gadar. "Many in China have now been exposed to the Western world but many are still driven by the local. I think, in time, China will move towards a compliance culture."

Gadar also points out that China is only one of the world's rapidly developing economies. "Malaysia, Indonesia, India – the whole East Asia Pacific region is growing," she says. China may well create a globally competitive pharma industry in the coming decades, but several other countries will not be far behind.

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All Eyes on Biopharma Trends

What are the hot topics in biopharma manufacture? What are the challenges? And where do we need to go? We provide hard data, expert insight, and thoughts for the future in a three part series. Here, we present Part 1.

By Roisin McGuigan and Stephanie Sutton

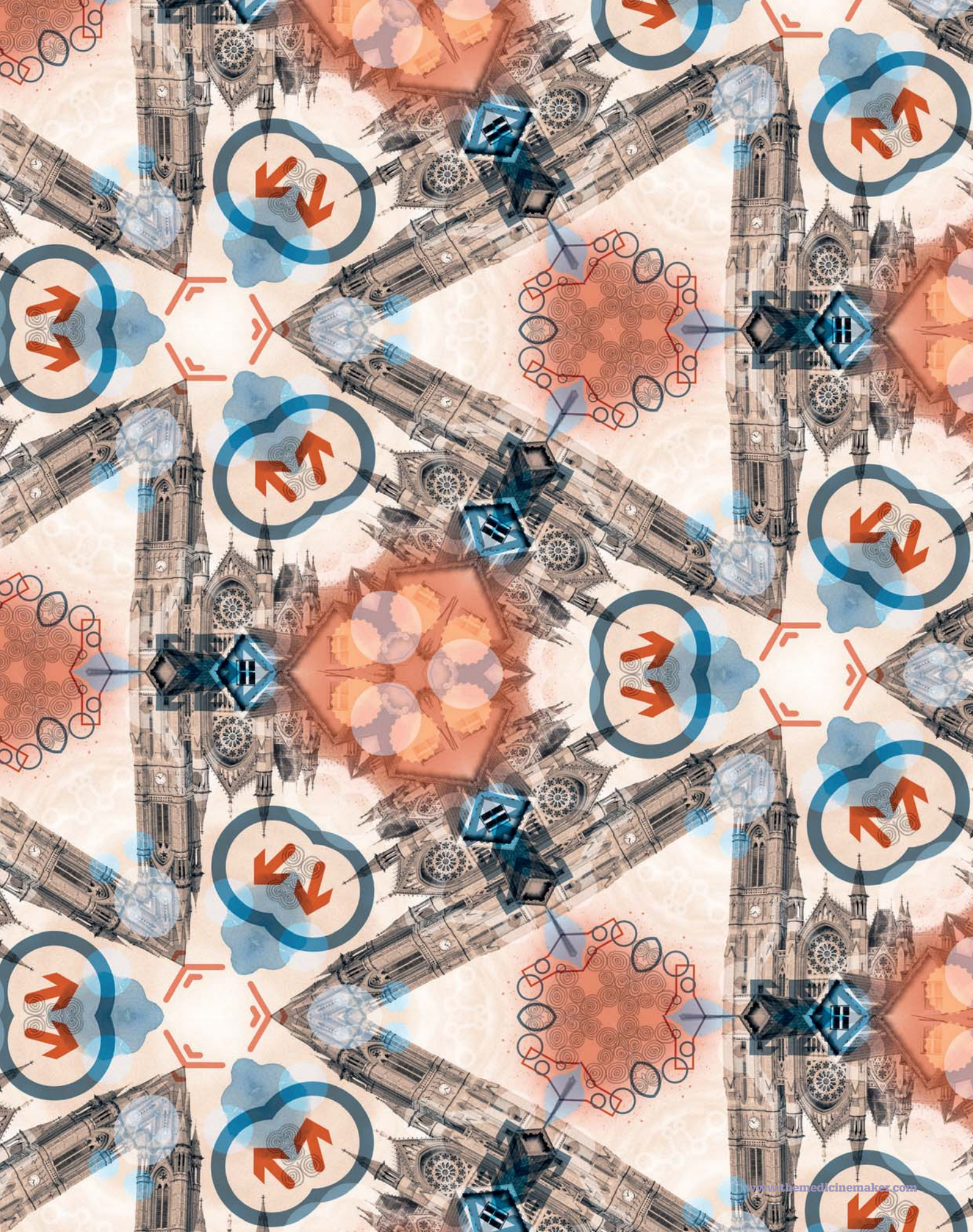
The Medicine Maker and Ireland's National Institute for Bioprocessing Research and Training (NIBRT) have collaborated on numerous occasions – perhaps you recall our cover feature from 2016 (http://bit.ly/2axat4a). More recently, The Medicine Maker and NIBRT teamed up to learn more about current manufacturing practices and trends in the biopharma industry, and where the field is heading next, by conducting a survey of industry professionals. You can download the full survey report – for free – here: https://bit.ly/2lDuHwl (1).

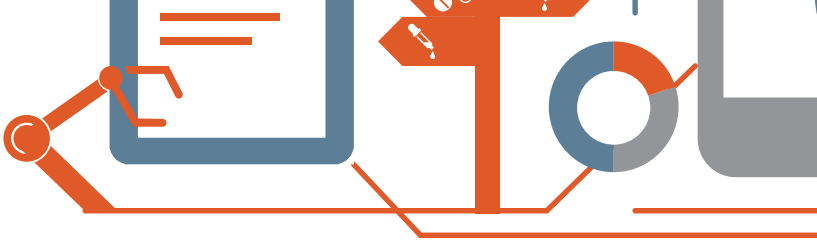
Our goal? To help inform – dare we say, advance – the biopharma industry by looking at current issues, incoming trends, and exciting innovations. In the next few issues of The Medicine Maker, we'll be sharing what we've learned from the survey, and what some of the esteemed members of our 2018 Power List have to say about the results. In Part 1, we take a look at biopharma therapeutics, now and in the future…

The current state of play

When survey respondents were asked to select the most commercially important biopharma therapeutics available right now, the top answer was monoclonal antibodies (73 percent) – see Figure 1.

"The results align with my own thoughts, as both mAbs and vaccines are growing in significance – especially as the greatest contributors to human longevity continue to be access to clean water, antibiotics, and vaccinations," says Steve Arlington, President of The Pistoia Alliance. "In the future, their importance to biopharma will depend on the discovery of therapies to treat unmet medical needs, and, in particular, dementias, such as Alzheimer's, which are becoming more prevalent as our life expectancy increases. We are seeing mAbs, both when used as single therapies or in combination therapies, revolutionize survival rates in many areas of oncology. People also need to realize that mAbs must be used in conjunction with other procedures, such as diagnostics and scanning. The use of mAbs alone will not be enough."





"I'm very interested in continuous process manufacturing and the use of manufacturing intelligence, such as big data, virtual reality, artificial intelligence, robotics and full automation."

John Bournas, President and CEO of The International Society for Pharmaceutical Engineering (ISPE), also agreed that mAbs would be important as potential treatments for Alzheimer's. "mAbs formed the foundation of the industry and will continue to be financially important, even while cost pressures drive firms to seek manufacturing efficiencies," he says. "Many potential Alzheimer's treatments are mAbs, and one or more successes in this space would make mAbs production technology and capacity critical for years to come."

Vaccines were ranked by survey respondents as the second most commercially important biopharma therapeutics. "Vaccines have always been one of the most important class of products for battling infectious diseases – and we should continue to put effort into these to improve quality of life in developing countries. However, their promise for preventing more complicated diseases, such as cancer, is in its infancy, and may not be as broadly applicable as we would hope," says Marc Bisschops, Director Continuous Bioprocessing at Pall Biotech. "For the immediate future, I definitely agree that mAbs (and mAb derived therapies) will remain the most important class of biopharmaceuticals."

Therapies of the future

When asking survey respondents what the most commercially important biopharma therapeutics in the next 5–10 years were likely to be, mAbs remained the top answer (56 percent) – as predicted by our experts above – but cell and gene therapies also ranked very high (Figure 2). Bournas says, "Which therapies are most 'commercially important' depends on the definition of importance – for the commercial market, mAbs will be important; however, cell and gene therapies will play an important role in the development of new products."

It's clear that these cell and gene therapies offer much hype – and so far clinical results are justifying the excitement. However, the Power List members we spoke with, while acknowledging the great potential of these therapies, believe there is still work to be done. In particular, they say it may very well take longer than 10 years for real transformation to be seen.

"The development of cell therapies and gene therapies will move very fast, but personally I think it is unlikely that they will be as important as mAbs in the next 5 to 10 years. It may take a bit longer than that because of the more complicated method of action, as well as manufacturing and administration challenges," explains Bisschops.

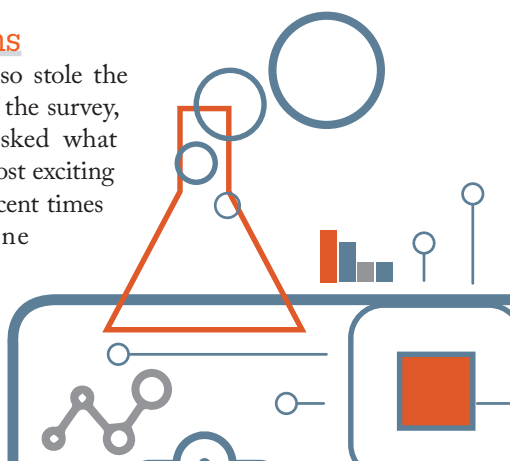
Hal Baseman, Chief Operating Officer of Valsource, also agrees that the cell and gene therapy field may come with teething issues. "In my opinion, advanced therapy medicinal products, such as cell and gene therapies, definitely come with processing challenges. They represent a significant shift from large-scale to small-scale manufacturing methods, and changes in validation, testing, and regulation. Despite this, the field provides opportunities for new companies, facilities, and manufacturing approaches. To what extent this results in a significant increase in product doses remains to be seen."

Another challenge is commercialization. Arlington says, "At the moment, regardless of whether a breakthrough is on the horizon, pharmaceutical companies can't work out how to make money from the treatment. Many challenges exist in the process of developing cell and gene therapy treatments, with the additional concern over how a company would deliver and successfully commercialize such a product. The current structures within healthcare providers make it difficult to see attractive delivery models to make these therapies cost effective and commercially viable. We believe this can be overcome, but probably not within the next decade."

All of this said, such therapies should have a significant impact on human health, in the long term. Bisschops adds, "These therapies could easily become as important as mAbs in the future. Contrary to mAbs, these therapies should – in principle – allow a more sustainable cure for very complicated diseases, such as cancer and auto-immune diseases."

Ideas and innovations

Cell and gene therapies also stole the spotlight in another part of the survey, when respondents were asked what they considered to be the most exciting therapeutic innovation in recent times (Figure 3). Cell and gene therapy made the top spot by a large margin



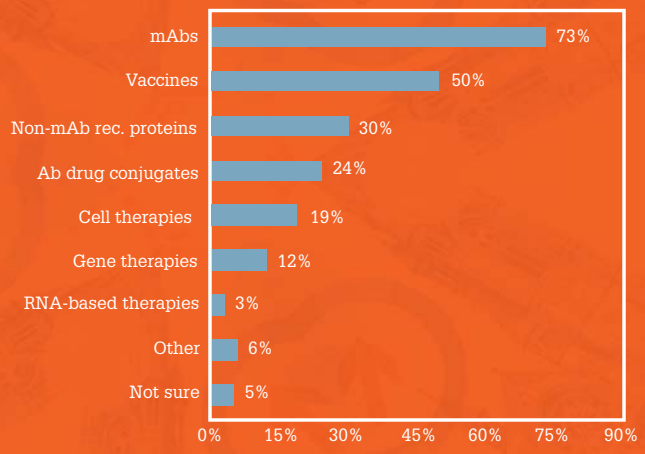


Figure 1. Most commercially important biopharma therapeutic products currently available.

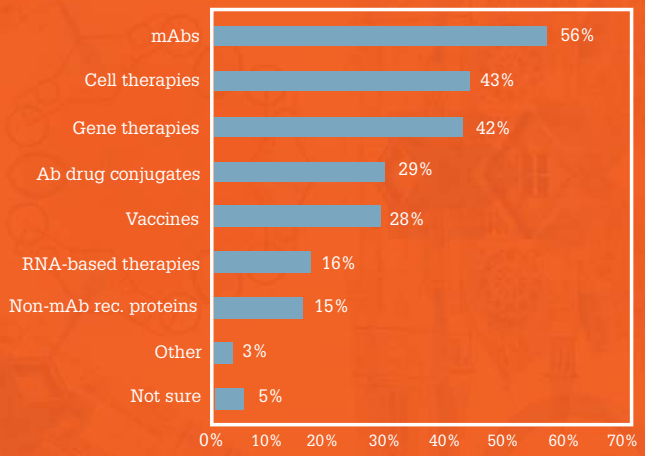


Figure 2. Most commercially important biopharma therapeutic products in the next 5 to 10 years.

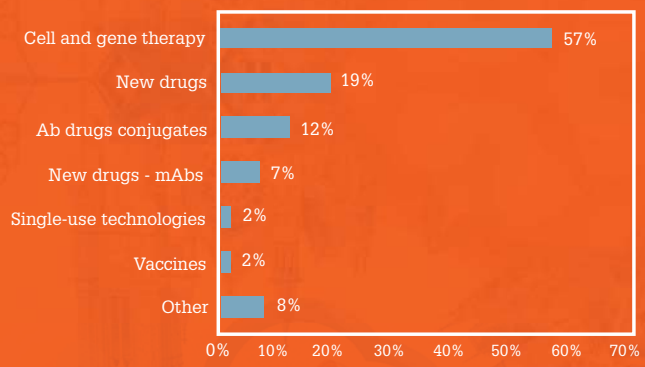


Figure 3. The most exciting therapeutic innovation in recent times.

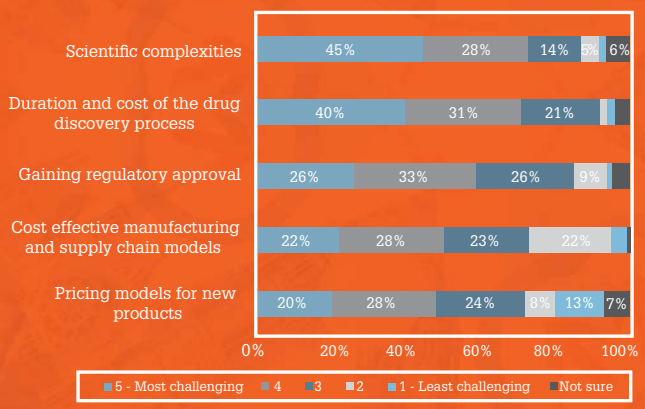


Figure 4. Issues Issues with bringing new biopharma therapies to market: level of challenge.

A View From NIBRT

What recent therapeutic innovation has excited NIBRT in the biopharma space?
The FDA approval in 2017 of the first two chimeric antigen receptor (CAR) T-cell therapies: Novartis' Kymriah and Kite/Gilead's Yescarta, was certainly a key landmark. But while these therapies provide very promising clinical results, many challenges remain to manufacture such therapies at scale and in a cost-effective manner.

Does NIBRT think mAbs are a hot area at the moment and will they live up to expectations?
Yes, we agree that mAbs will continue to be the most commercially important biologic therapy in the foreseeable future. We're seeing increasing diversification in the complexity of mAbs, including ADCs, bispecifics, and antibody fragments coming through approvals which require ever more sophisticated manufacturing and supply chain solutions.

What are the institute's thoughts on the potential of cell and gene therapies? Do you think they'll be more important than mAbs in the next 5-10 years?
There is certainly very significant potential for these therapies and we're beginning to see the first investments in commercial scale manufacturing facilities. Despite this progress, there are many scientific, manufacturing and supply chain issues to be addressed if cell and gene therapies are to reach their full potential. We're really only at the start of this journey.

What issues are most challenging with regard to bringing new biopharma therapies to market?
Key challenges include developing efficient manufacturing and supply chain models that can deliver these therapies to patients in a cost effective manner while maintain the highest levels of quality. This challenge is enhanced by the global shortage of workforces with the required biopharma manufacturing skills and experience.

What do you think industry can do to ease these challenges?
As experts in this article state, collaboration is key. We are beginning to see effective consortia focus on addressing common issues in biopharma manufacturing, although there is a long way to go on this. From a skills perspective, we need to ensure that there is a continued global supply of highly motivated and trained individuals developing their careers in biopharma. Again, there are some excellent initiatives in this area but it requires a constant and ongoing drive.

(57 percent). For the most part, experts from our Power List agree. Bournas says, "Cell and gene therapies are very exciting – the approval of the first product brought us closer to advancing personalized medicine. RNA therapies are another exciting and innovative area of advancement. These therapies have attacked brutal diseases with great success, and that is what makes them so cutting edge."

"From a therapeutic perspective, personalized medicine and advanced therapy medicinal products are exciting," says Baseman, "but they and other therapies will also provide the opportunity to develop and advance innovative sterile product manufacturing and process control approaches. From a manufacturing perspective, I'm very interested in continuous process manufacturing and the use of manufacturing intelligence, such as big data, virtual reality, artificial intelligence, robotics and full automation."

Other new drugs are also emerging too, and Bisschops says we should not overlook other science. "The first approvals of cell therapy have definitely been exciting," he agrees. "But I'd also like to add that all of the work on existing biological therapies has resulted in a great accumulation of knowledge and fantastic science that helps us understand complicated diseases and the biology of the human body much better. This should enhance our ability to cure these diseases."

Arlington, however, adds that true innovation takes time. "Though there is a lot of great science occurring, I would say there haven't been any innovative breakthroughs related to specific

"From a therapeutic perspective, personalized medicine and advanced therapy medicinal products are exciting."

therapies that have excited me recently," he says. "The innovations that we're seeing today have been in the works for many years. This is not unusual, and it takes considerable time to reach the proof of concept stage. There are promising leads yet to be confirmed in the oncology field and in non-alcoholic steatohepatitis. Right now, there are certain areas that are gathering speed, such as companion diagnostics, which show great promise and will help to make precision medicine a reality. But despite their potential, the likes of FDA and EMA still need to work out how best to regulate the area before companion diagnostics can be speedily adopted."

The challenges of scientific progress were also acknowledged by survey respondents. Respondents were asked for their thoughts on the most challenging issues that arise when bringing new biopharma therapies to the market (Figure 4). The issues that respondents felt would be most challenging were the scientific complexities in discovering effective therapies for unmet medical needs and the duration and cost of the drug discovery process. A number of respondents also pointed to the challenges of manufacturing, which Baseman is also concerned about.

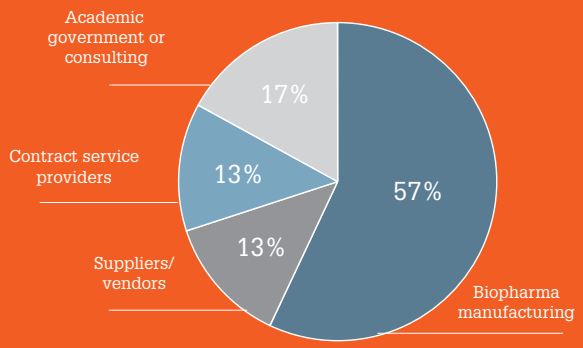
"Trying to fit existing manufacturing approaches, regulatory expectations and guidance to the manufacturing methods needed for new therapies is a challenge," he says. "Traditional approaches to manufacturing, testing and process control may not necessarily align with new therapy manufacturing methods. Trying to force fit these methods may not be the best way to proceed."

Meanwhile, Bisschops is particularly concerned about the manufacturing hurdles of cell and gene therapies. "For recombinant proteins, vaccines and mAbs, processes are well understood by regulators and biopharma companies, but it is different for newer therapies. Recent successes have demonstrated that there are approaches that work for cell and gene therapies, but it is yet unclear how this will eventually work out. To make it an affordable and scalable process, adequate strategies for manufacturing need to be developed. For instance for cell therapy, the current strategy seems to be to harvest cells from the patient and have them sent to a

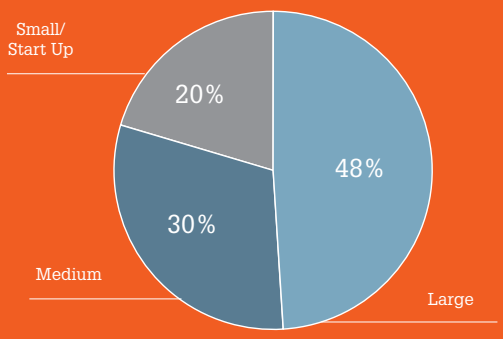
Who Did We Ask?

The survey was fielded from 30 October to 22 November 2017, with over 200 surveys collected. Respondents were based in Europe (45 percent), North America (35 percent), and Asia (16 percent). Four percent came from other regions.

Job Sector of Respondents



Company Size



"Workforce availability is a challenge right now – does the industry have the workforce with the right skills to handle the new technologies being developed?"

specialized facility for applying the cell therapy. Once the cells are treated (tested and released), they are sent back to the patient for administration. There may be room for improving the logistics of this treatment, reducing patient risks, inconvenience and costs."

Come together to succeed

Finally, we asked our Power Listers for their advice on what biopharma needs to focus on to rise to the challenges that lay ahead for the field. The key theme is collaboration; the industry must work together to overcome the issues facing the industry.

Arlington: "It is becoming more difficult for individual biopharma companies to come up with answers to industry challenges by themselves. More collaboration is needed at all stages of the R&D process – and regulators and HTAs need to be involved much earlier. Coming together and releasing pre-competitive information will allow the industry to share best practice, enjoy increased efficiency, and reduce costs across the board. As one example, The Pistoia Alliance is involved in a project to increase knowledge of antibody structures – which determine their specific interactions with antigens – in the public domain."

Baseman: "Scientific and risk-based critical thinking is needed to challenge existing methods and develop innovative and more effective manufacture and process control approaches. A partnership of manufacturers, technology suppliers and regulatory health authorities is the key. Sharing of information between these groups, and across these groups, would reduce the uncertainty and risk of new technologies and approaches. Modernization of manufacturing facilities and processes, and easing of restrictive and burdensome global post-approval change requirements are also important to reduce barriers to innovation."

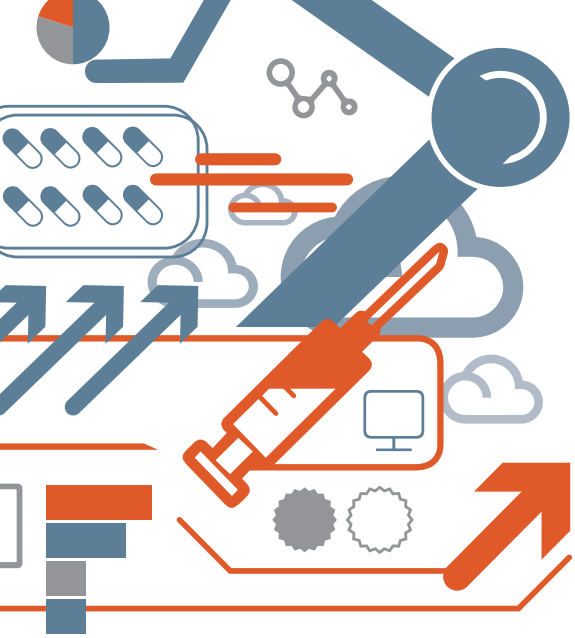
Bisschops: "I agree; the biopharma community must work together. We all need to realize that we are serving the health of our society – a truly noble goal. A collaborative approach between sponsors, patient organizations, regulatory agencies and suppliers will result in strategies and solutions that eventually provide the most added value to society as a whole – and therefore benefit all partners in the biopharmaceutical community."

Bournas: "The collaboration of industry and regulatory bodies will pave the way to mastering the new manufacturing paradigm. This is the core of my work at ISPE – the society aims to bring industry and regulators together to work through industry challenges with an open mind to new approaches. Preparing the workforce of the future is also an important initiative for the industry. Workforce availability is a challenge right now – does the industry have the workforce with the right skills to handle the new technologies being developed and the new ways of manufacturing? The Global Pharmaceutical Manufacturing Leadership Forum (GPMLF), in collaboration with ISPE, is taking a close look at industry workforce challenges, and working with industry and academia to identify the skills and training needed by students and young professionals coming into the workforce. They are the future of our industry."

Indeed, skillsets and training are imperative for the future of the industry – and we'll be tackling this topic in the second article of this series, which will be published in the August issue of The Medicine Maker.

Reference

1. *NIBRT & The Medicine Maker, "Biopharma Trends: Trends in Biopharma Manufacturing Survey Report" (2017). Available at https://bit.ly/2lDuHwl.*



A Corking Conference

Want to learn more about the future of biopharma, and hear from international experts within the field?

Inspired by the conclusions from our joint research into industry trends, The Medicine Maker and NIBRT are collaborating on an exciting new conference series focusing on global trends in biopharma and the future of the industry. The inaugural event – Biopharma Trends 2018: Towards Industry 4.0 – will be held on November 13 and 14, 2018, in the Clayton Hotel Silver Springs in Cork, Ireland.

The event will bring together industry leaders to discuss and debate the feasibility of Industry 4.0 and its application to biopharma, covering all the 4.0 building blocks – from cloud computing to big data to smart technology and integrated systems.

Attendees can look forward to unique insights during presentations from renowned presenters, and practical workshops hosted by NIBRT. Speakers include Martin Van Trieste (Parenteral Drug Association), Bernhardt Trout (Novartis and MIT), Jonas Bostrom (EduChem VR and AstraZeneca) and Jim Breen (Janssen).

Industry 4.0 represents the adoption of intelligent, data-driven approaches, and is already bringing tangible benefits to other sectors. But which elements can benefit biopharmaceutical manufacturing, both now and in the future? Is the revolution all empowering – or simply all hype? Join us at Biopharma Trends 2018 to find solutions to the latest issues facing biopharma, and to ask questions of your own. Industry 4.0 is the fourth industrial revolution, and it's already making its mark on biopharma manufacturing – don't miss this chance to be part of the conversation!

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Meet the Experts

Steve Arlington

President, The Pistoia Alliance

Steve is a Champion of Change on our 2018 Power List because of his work with the Pistoia Alliance. He is passionate about greater collaboration within and between industry, the regulator, the payer, and the provider. Previously, he was Global Lead Partner, Pharmaceuticals and Life Sciences consulting, at PricewaterhouseCoopers.

John Bournas

President and Chief Executive Officer, ISPE

John has been a member of the Power List since 2017. He is responsible for developing ISPE's global initiatives and business operations, and also leads the organizational efforts in solidifying working relationships with international regulators. Like Steve, he is passionate about collaboration, as well as training the workforce of the future.

Marc Bisschops

Director Continuous Bioprocessing, Pall Biotech

Marc's work with continuous chromatography and continuous downstream processing earned him a place on the 2018 Power List. He is listed as an inventor on various patents related to continuous process technologies. He hopes to help the biopharma industry become more efficient and agile.

Harold (Hal) Baseman

Chief Operating Officer, ValSource

Hal has over 39 years of experience in the pharma industry and has also been very active in the Parenteral Drug Association, including a stint as Chair. He has been a leader, author, editor and contributor to numerous technical reports, articles, books, and presentations. He is an Industry Influencer on our 2018 Power List.

Read the full Power List at
https://themedicinemaker.com/power-list/2018/

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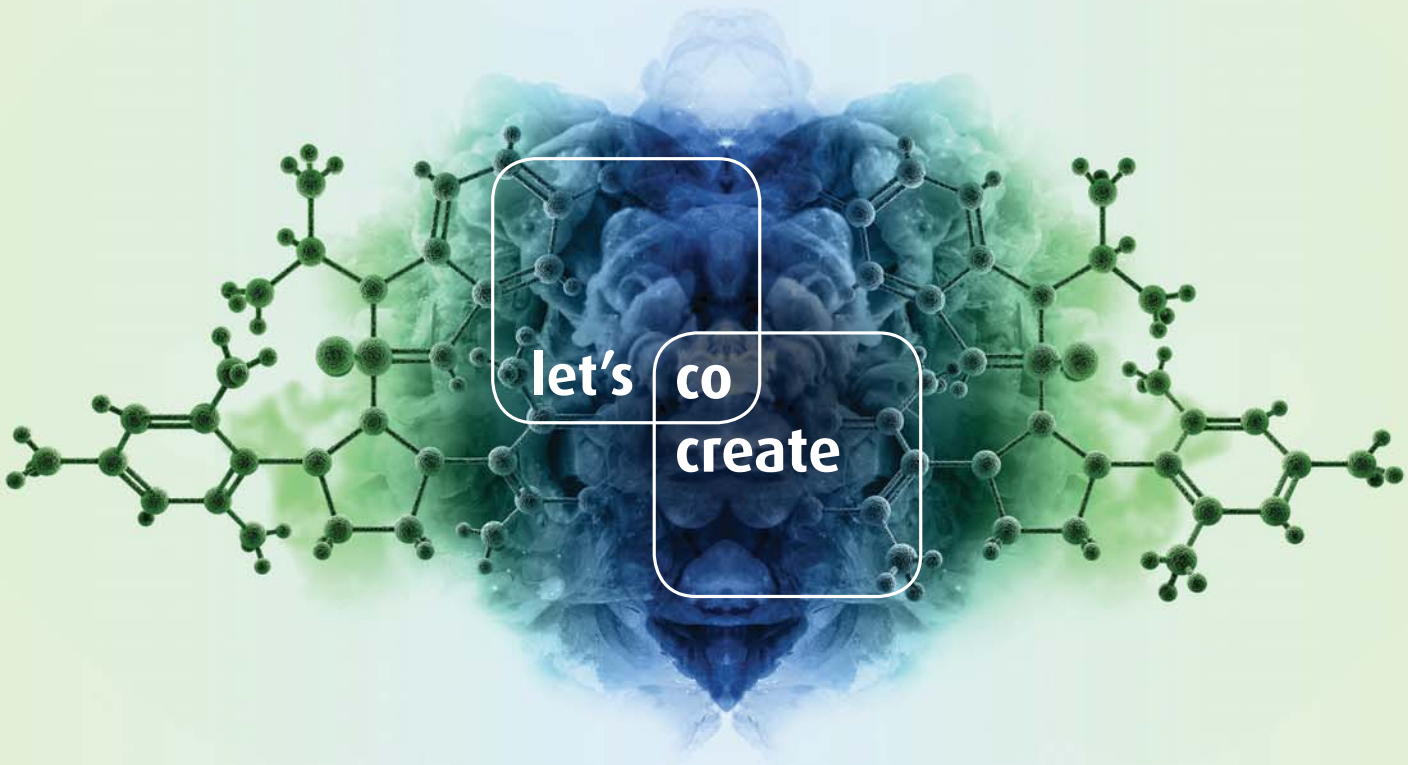

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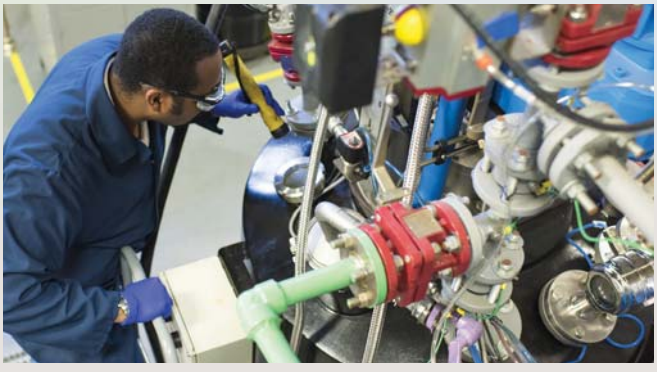

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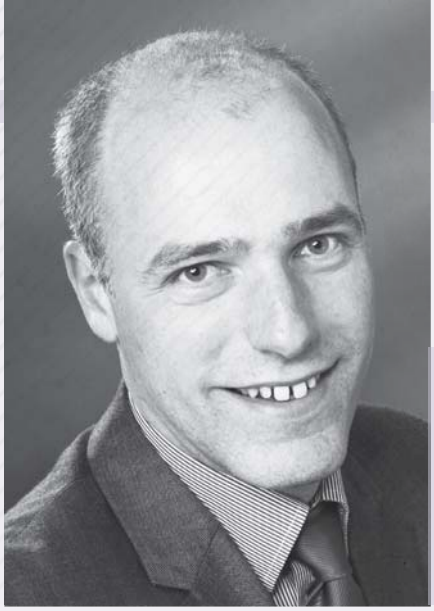
Maintaining the Analytical Edge

Working across life sciences, performance materials and healthcare divisions, Site Management Analytics is Merck's internal solutions provider for tough analytical challenges. Here, we learn more from Christoph Saal, Director, Site-Management Analytics Healthcare, and Saskia Haehn, Manager, E&L and Packaging Materials.



Christoph, could you give us a potted history of Site Management Analytics?

So in some ways, the history of Site Management Analytics goes back to the beginning of Merck's 350 years in business! Back then, Merck guaranteed customers that purchased chemicals were subject to quality control for the first time. Of course, it would be virtually impossible to list all the changes and milestones since then – but it's been a road of continual improvement and innovation, founded in quality. In my 18 years at Merck, the role of Site Management Analytics has moved away from routine quality control towards more closely supporting our research and development teams with advanced – and still high quality – analytical capabilities. Today, analytics is an integral part of R&D at Merck; indeed, the border between the two is much less defined than it was even 10 years ago.

Today, we do remember our roots with some specialized quality control – for example, when less common techniques, such as NMR or X-ray diffraction, are needed. Merck's business units – performance materials, life sciences and healthcare – are all subject to different regulations as the sectors deal with different products ranging from, for example, liquid crystals for displays to pharmaceutics, so they all have their own respective quality management system. On the other hand, the business is driven by a stronger need for analytics for R&D, which has led Site Management Analytics to focus on R&D activities.

The shift has also been driven by trends in miniaturization and automation. To give an example; as you bring a small molecule candidate through clinical development, you need to gain information for crystal form selection, so we do a significant amount of solid-state characterization work. Fifteen years ago, you'd perform different crystallization experiments under different conditions at perhaps a 5 g scale and then send samples to our lab for analysis. Today, the same task is done at a much smaller scale – more like 10 mg and using much more experiments. From these, we gain much more information about the behavior of a compound. The crystallization experiments and analysis of such a higher number of samples are conducted in the same laboratory to maximize efficiency and leverage automation.

How does Site Management Analytics help its internal customers?

Our work spans three core areas across Merck R&D – routine analytical support, project support and innovation, with the latter two taking on the prominent role in recent years. When it comes to routine support, we're responsible for making relatively simple measurements, but we use sophisticated tools, such as NMR. Here, turnaround times, cost and quality are the three drivers.

In project work, we will be tasked with solving more complex problems, which not only involves closer collaboration with our customer – the R&D team – but also other laboratories across Site Management Analytics. As an example, selecting the right crystal form of an active pharmaceutical ingredient is key when entering clinical development. Therefore, many labs doing crystallization experiments and characterizing the crystals using a broad range of analytical techniques, such as X-ray diffraction, differential scanning calorimetry, thermogravimetry, dynamic vapor sorption, measuring solubility and dissolution rate, particle size and shape, nuclear magnetic resonance, infra-red, Raman, and mass-spec, are brought together. The work is done in Site-Management Analytics involving a team of medicinal chemists, people from drug metabolism and pharmacokinetics, process development, regulatory affairs and pharmaceutical development. The answer we deliver is which crystal form should move into clinical development based on scientific consideration.

Finally, by "innovation" we really mean technology scouting and the need to consider what our customers may request or need in the years ahead. In other words, to ensure that our R&D continues to exist at the forefront, our analytical support must also be at the cutting edge. And so over the years, we've needed to add capability to support work in emerging areas – proteomics, crystal design, gene editing, for example.

I have to say that, when it comes to analytical science, remaining competitive means building, developing and maintaining an external network; going to conferences, reading journals, making contact with external biotech companies, CROs, and universities are all key to us offering the best analytical support possible for Merck. It matters that we are an integral part of the scientific society.

Saskia, how would you describe Site Management Analytics?

I'd probably describe us as an internal specialist CRO. We have about 230 people, including 30 PhDs and 40 engineers, with vast expertise in every aspect of analytical science, including chromatography, mass spectrometry, spectroscopy, and microscopy… everything you can imagine! We use that knowledge to support all three of Merck's business units – life sciences, performance materials and healthcare. We are located in the headquarters in Darmstadt, but we act globally.

Could you share an example project from your lab?

Over the last 10 years, there has been growing concern about extractables and leachables (E&L) in the pharma field, and we've been involved in a number of development projects on primary packaging or process materials. I'd like to highlight one special project in my laboratory, which I think is not only of interest for Merck's business, but also for other pharma businesses. Merck Life Science is a global player in providing single-use systems and has a catalogue of more than 400 consumables. Recognizing the importance of E&L, Merck launched the Emprove® program for consumables. The program collects data on the nature and concentration of extractables, in turn, helping customers with risk assessment and process design. Essentially, alongside our portfolio of single-use technologies, we offer comprehensive E&L reports, making Merck's offerings unique. Now that we've laid the groundwork in providing this information, our customers can save time and money, because they no longer need to perform their own E&L studies.

What is the origin of the report? Well, you can probably guess that all data are generated by our experts in Site Management Analytics!

"You can probably guess that all data are generated by our experts in Site Management Analytics!"

Can you offer an overview of frequently used analytical techniques?

We rely heavily on chromatography-mass spectrometry – both normal and headspace GC-MS as well as LC-MS. Both are essential for the separation and identification of inorganic extractables and the different techniques are used to cover volatile, semi-volatile and non-volatile compounds. But because of the nature of the challenge in E&L work, we have to use a number of other techniques to cover all possible entities like ion chromatography for anions and ICP-MS for elemental impurities. Invariably, more sophisticated technologies are required for the complex task of structure elucidation – which is also the most time consuming part of a project! The nature of the material also has a significant impact on the techniques required and the complexity of the task. For example, if you do an extraction of a Teflon material, the extracts will be very clean; you may only have one or two peaks to identify and quantify. But if you extract a rubber stopper? You'll get more than 50 peaks – and I'm sure you can imagine how much more time is needed…

What other challenges do you encounter in this deep analytical work?

Sample preparation is typically challenging because we have to keep the scope as wide as possible, as we do not always know what we should find in the extract. Any sample preparation task we perform can have a possible effect on the substances that are included in the extract. Moreover, we can't easily perform recovery studies because we do not know which compounds are included – and so we try to keep sample preparation to a minimum to reduce any losses of compounds of interest that may occur. Some of the compounds we are looking for require high sensitivity, which can be another challenge, demanding the best methods and instrumentation.

Finally, as guidelines for extractables testing are somewhat in development, we have to set the bar as high as we can. And that's why I'm proud of the Emprove® program – the results of which I hope will contribute to an improved regulatory landscape in some way.

What are the most rewarding aspects of your role?

The most rewarding aspect for me is knowing that I contribute to safer products for our customers – and, in turn, safer end products for their customers. I think that will always give me a good feeling! It's also very rewarding to see how much our group has grown over the years – and how much our work is appreciated.

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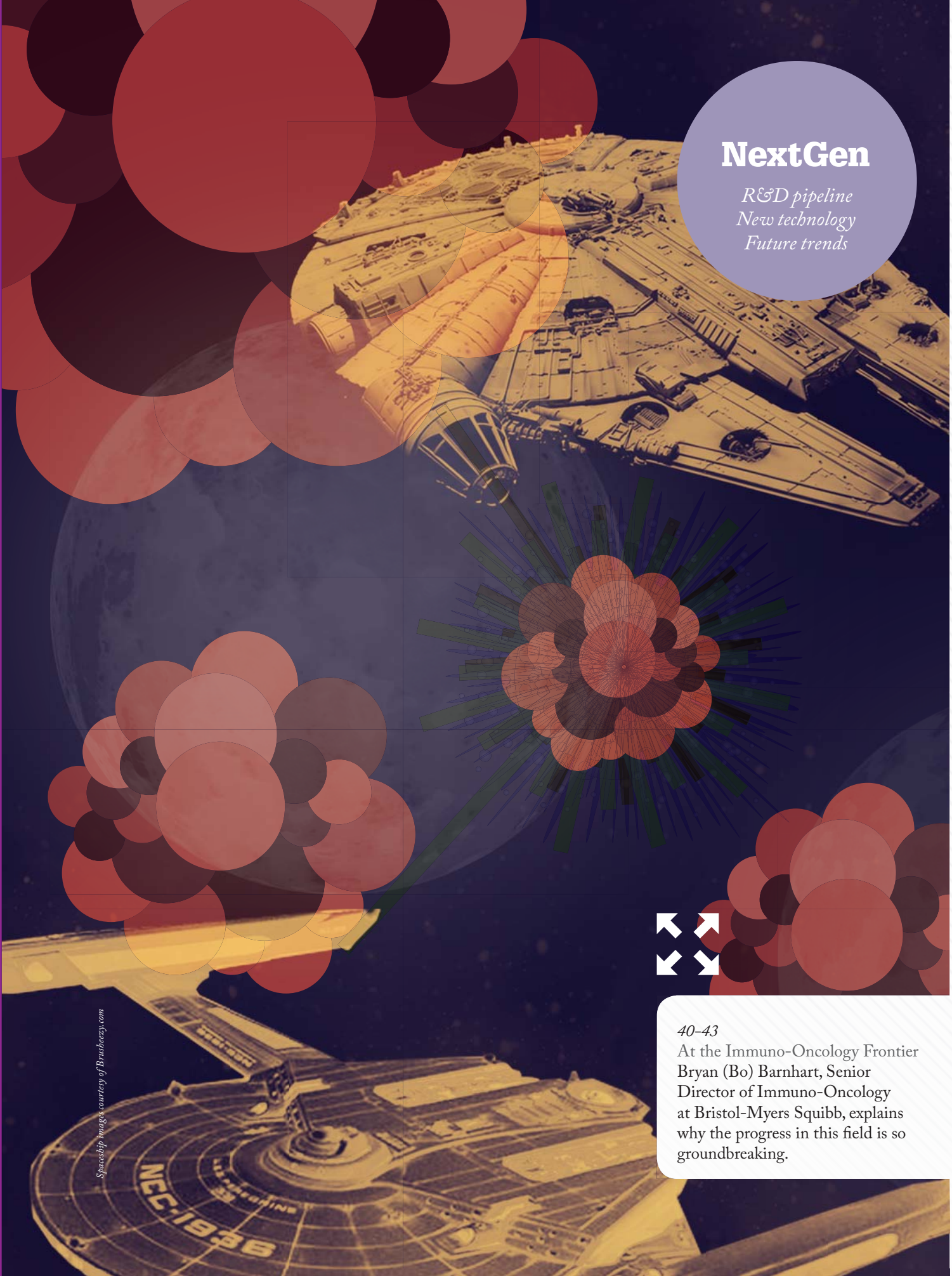

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At the Immuno-Oncology Frontier

The use of the body's own immune system to fight cancer – immuno-oncology – has seen great progress over the last decade, with a number of big pharma companies working to further advance the field in the next ten years. Here, we learn more from Bryan (Bo) Barnhart, Senior Director of Immuno-Oncology at Bristol-Myers Squibb.

How is the immuno-oncology field changing – and what new research is emerging?

It's not even been ten years since the first approvals emerged for immuno-oncology drugs, but the impact has been remarkable. Over the next ten years, the industry will uncover new research and hopefully increase the number of patients that are able to respond to treatment.

Right now, there is a lot of fascinating science emerging from microbiome research, both in academia and industry. This is an area that has largely been untapped for oncology, but our understanding has expanded significantly over the last few years. In a short space of time, we've learned not only how the microbiome affects the immune system with regards to cancer, but also how it can have a potent effect on other aspects of health. I am really interested in how the microbiome interacts and enhances immune responses. There is likely scope to better understand an individual's microbiome and take advantage of its interaction with the immune system; indeed, BMS is driving some excellent collaborations in this area, with a view to enhancing immune response to cancer.

Another emerging area that has large potential is increasing our understanding of how innate immunity affects anticancer responses. New research is looking at turning on the immune system in places where it is not very active, or enhancing it where it's suboptimal for anticancer therapy.

When developing these therapies, what are the challenges with side effects?

There can be side effects if the immune system is hyper activated – this is something we look at very carefully. There are many really smart people dedicated to understanding how the immune system responds, as well as the similarities between autoimmune disease and immuno-oncology (although obviously they are going in two different directions). There are important, and sometimes subtle, nuances and differences between those effects, and turning off one pathway in autoimmunity is not equivalent to turning it on for cancer therapy. At BMS, we spend a great deal of time trying to understand how things differ and how we can walk the line of activating what we want to and where

"A decade ago, melanoma had very different treatment paradigms and response rates than it does today."

Meet Bo Barnhart

You studied English literature and biology; why combine the two?

Some have told me that it seems an unusual combination, but it made sense to me. I'd always had an interest in literature, but I had an aptitude for science. The decision turned out to be a very good one because the ability to use language and communicate effectively is incredibly important in science. These skills can often be overlooked and don't always come naturally to scientists. Combining science and English means that I can think and write in different ways – analytically and in terms of language.

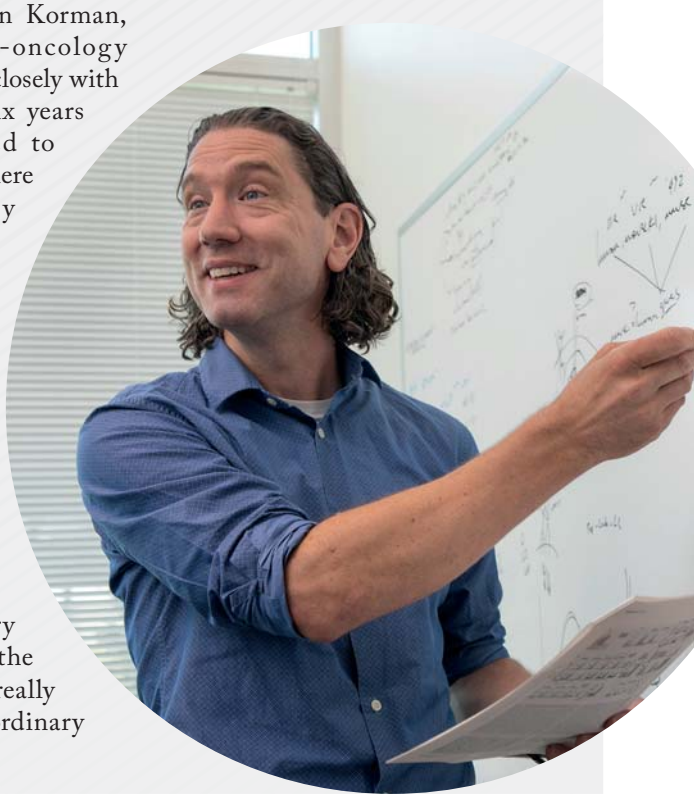
Being able to communicate well is a crucial foundation for effective collaboration. The first professor I ever had for immunology once told my class that immunology is, in many ways, a language first; before you can move on and grasp the most complex ideas and concepts, you have to be able to work within the language of immunology. She was right – it really is a separate language, with different types of cells, different processes, and other aspects that accumulate to build the immune system. Throughout my career, whether mentoring or working with collaborators, I've found that it is important to use common but engaging language.

How did you get started in industry?

Following graduation from Rutgers University, I stayed on at a laboratory where I'd worked as an undergraduate, which gave me an opportunity to really build a foundation for research. I did a lot of work with basic immunology and I was also given the opportunity to lead work and have projects of my own, which isn't very common for a new graduate!

I went on to do a PhD in immunology in Chicago and then moved on to a cancer biology laboratory in Philadelphia at the University of Pennsylvania. In time, I had the opportunity to apply to the oncology department at BMS. I was really keen to move into industry to get involved with real drug development and I was so impressed by the oncologists there during the interview. I worked for a number of years in BMS's oncology group in Princeton, New Jersey. As the years went on, immuno-oncology really started to arise as an exciting new way to treat cancer. We had some collaborations in place at the time, but the field was so new that most companies didn't have specialized immuno-oncology departments. BMS eventually acquired Medarex, led by Nils Lonberg and Alan Korman, pioneers in immuno-oncology research. I worked very closely with them and then after six years in Princeton, I moved to Northern California where the immuno-oncology group was centered. I've worked here ever since. Immuno-oncology was a really good fit with my background, having done research both in immunology and cancer biology.

Working with Nils and Alan was an absolutely incredible opportunity. These two scientists were very senior people within the organization, but they really understood – in extraordinary detail – the fundamental science that leads to complex immune interactions and responses. It really encouraged and energized me to spend a lot of time working on more effectively understanding the biology behind what we work on. And it was wonderful to see that such senior members of an organization can still be very tapped into science and research. Alan and Nils' extreme perseverance and persistence in following good science was another valuable and broadly applicable lesson. Science can be a very frustrating field at times and you need to work to have your ideas accepted. They talked about the history of the field and how, not even ten years ago, many experts believed that immunotherapy would never be effective. Today, we know that it holds significant potential.



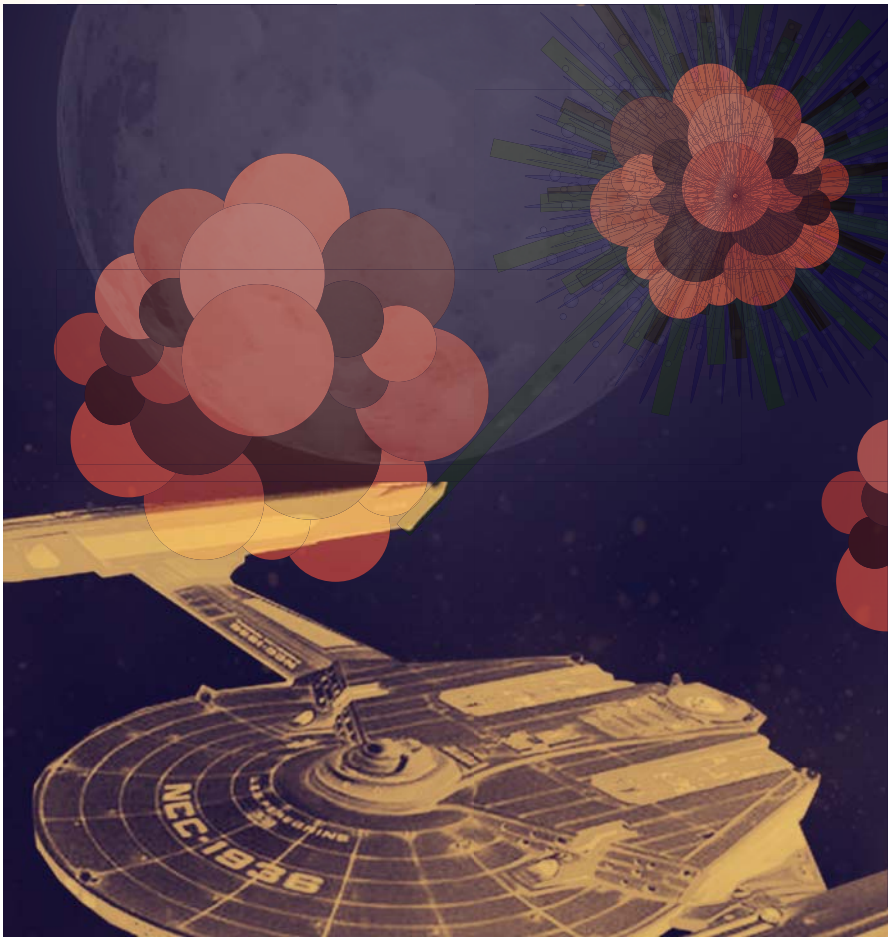
we want, without triggering an overactive response elsewhere. We also put a lot of effort into identifying targets that are as tumor-specific as possible.

We are now seeing fantastic scientific data and clinical success, but certainly not every patient or cancer type is responsive. It will be a significant challenge to reach the point where we really understand – on a molecular and cellular level – what is happening within an individual patient's tumor; how is the tumor avoiding destruction by the immune system? Why does the tumor continue to grow in the face of what should be a fairly effective response? Picking apart tumor resistance mechanisms will allow us to combine the right approaches to get the best possible responses in each patient.

What is BMS focusing on?

We have a large focus on understanding the mechanisms behind how the immune system attacks a tumor and how best to turn on the immune system in a productive way. The immune system has many layers of regulation so there are several potential ways that we can activate the immune system by removing certain suppressive effects. Right now, there is much attention on what combinations most effectively enhance the immune response. Many companies, academic groups and clinical studies are showing that hitting multiple pathways in combination can enhance responses in many cases. I think that makes a lot of sense immunologically.

We're also spending a lot of time looking at the tumor itself as well as its environment. It is very well recognized that the tumor itself is a very suppressive and stressful environment. A tumor can establish its own extreme suppression of the immune system and we're learning year over year that the number of ways that the tumor can do this is extraordinary. Different tumors appear to use different mechanisms, so we're putting a lot of time into understanding how the tumor sets up a suppressive environment – whether it be the tumor cells themselves, other cells that the tumor recruits, or the way the tumor sets up its blockade to prevent immune cells from even getting to and recognizing the tumor.



Another very important area that we are looking at is a better understanding of particular patient populations, including indication-specific resistance mechanisms or mechanisms to enhance immune responses within particular types of cancer.

Central to all of our work is collaboration – both internally (across different sites) and externally. Collaboration is essential for good science as different perspectives can bring new ways of tackling problems.

What have been the most exciting or rewarding moments of your work?

When I transitioned from New Jersey to California, I was involved in screening antibodies. It's pretty dry work, but one of the antibodies had a bit of an odd profile so we decided to follow that up. Interestingly, it had a truly unique biological feature. It was one of those "aha" moments! When you are doing labwork and screening, it is very methodical, so this moment really stood out. I remember the moment we saw the activity. There were a lot of exciting discussions in the lab. I also still have the old data figure showing these kind of odd, first observations. Ultimately it not only became a therapeutic that we could pursue, but also a unique biology.

Another rewarding aspect is the fact that we are working for patients. BMS

actually does a really good job bringing us into contact with patients and we have frequent visits from patients who have benefited from our medicines, whether it be oncology, autoimmune disease or any of the other therapeutic areas that we're working in. Every time we see or hear from a patient, whether they're in the room with us or by video feed, I think it really does bring the importance of what we do home. We can spend a lot of time in a sterile lab environment and it is rewarding to think about the impact that each of your experiments can have on patient lives. One very personal example stands out: my father died last year, and at his memorial service, one of the people who stopped by specifically came up and thanked me for the work that BMS did on Opdivo (nivolumab). He was a patient. Such moments really help me realize just how important our work is.

What would you do to change the field?

We are at a remarkable point. I think we'll one day look back on immuno-oncology's genesis in the last decade as a turning point for the way we think about and treat cancer, and the way patients respond when they have a diagnosis. We're not there yet, but we're definitely moving in the right direction

One area where we can perhaps do better as a field is in educating the public. Immuno-oncology is a new field and I quite frequently see surveys that show how few people even know what immunotherapy is. We have to acknowledge the fact that this field is not terribly accessible. If we can better educate people then it will go a long way towards helping patients understand what treatment opportunities are out there.

With our growing understanding of immuno-oncology, I really hope we will see more cancer types begin to respond. A decade ago, melanoma had very different treatment paradigms and response rates than it does today. Immuno-oncology has transformed treatment for patients – but only some patients. I mentioned my father earlier. He died seven and a half months after being diagnosed with pancreatic cancer. It was a very rapid decline and his quality of life was poor from his diagnosis onwards. It is very difficult to treat resistant forms of cancer. Even with immunotherapies, we simply don't have enough good, long-lasting treatments for many tumor types. I believe we will increase response rates in the future. And we have to, if we are to say that we have truly been successful in this field.

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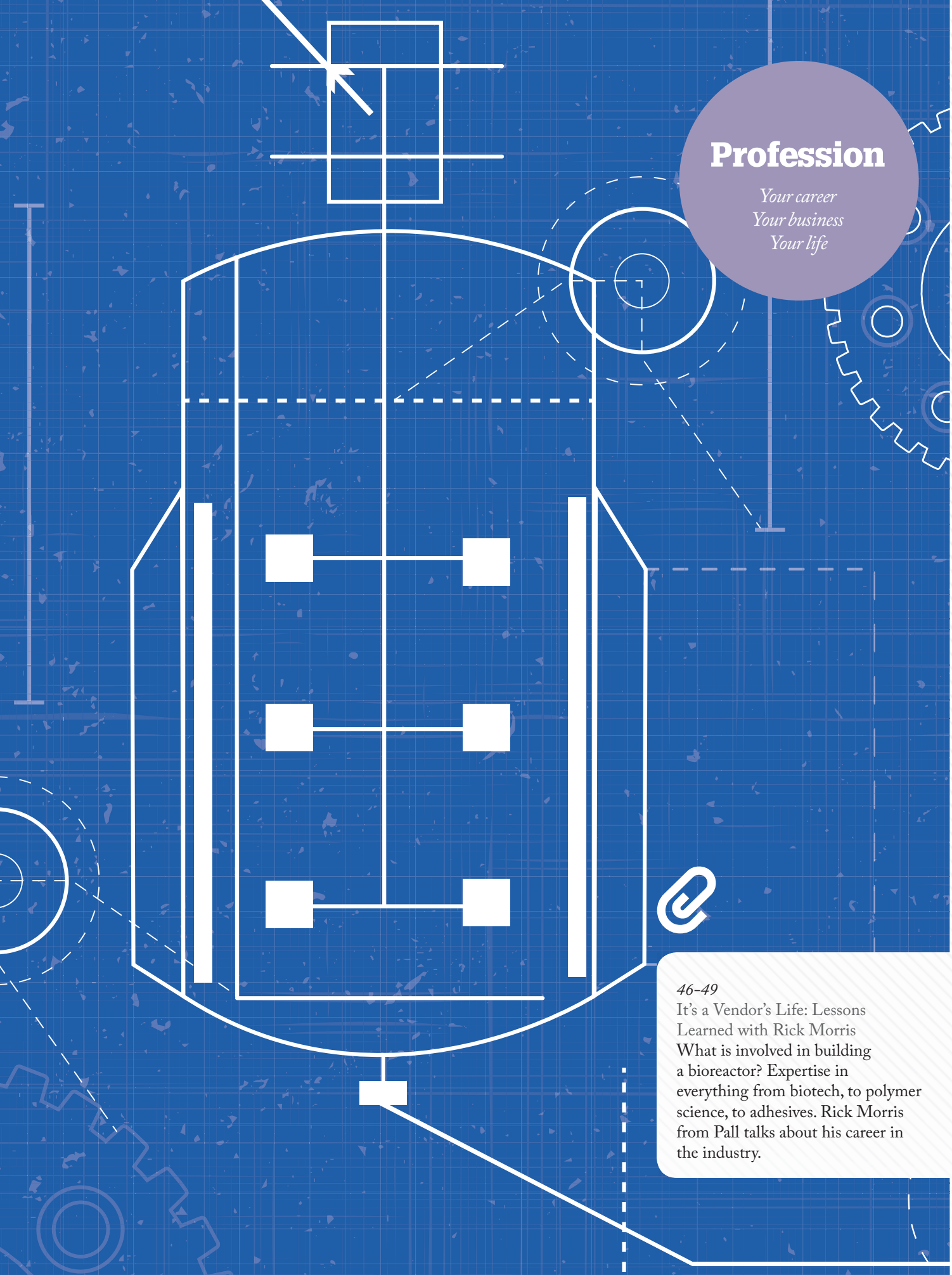


It's a Vendor's Life: Lessons Learned with Rick Morris

Despite initially envisioning a career in the polymer and textiles industry, Rick Morris now builds equipment for biopharma manufacturers – and he loves it.

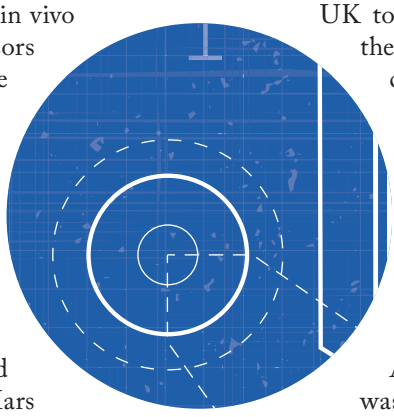
Higher education helps you on your way into senior roles

When I was at school, I wondered if I should go to university. No one had ever gone to university from our family, so for me there were many questions about how exactly you go to university and what you should study. I spoke with careers advisors at school, and my science teachers, particularly my chemistry teacher (Mr Lawrence), were a big influence. I looked into sponsorship opportunities and I applied to various companies, including a local company called Courtaulds, which focused on textiles and chemistry. Ultimately, I was accepted by Courtaulds. First, I did a year in industry where I was involved in making different manmade fibers and weaving processes, and then I went to Leeds University and studied chemistry, polymers and textiles.

Unfortunately, during the time of my degree in the 1980s, the textile industry and the polymer industry in the UK went through a big downturn. When it came to returning to Courtaulds, they could no longer guarantee a job so they released me from my contract. I decided to do a PhD – it was something I'd wanted to do anyway because I'd noted that all of the senior staff at Courtaulds seemed to have a PhD. Higher education is very important, if you want to go far in life. As my career progressed, I also learned that those even higher up had an MBA. In time, I achieved this too and it has definitely helped my career! At the time, these higher qualifications seem unobtainable, but when you finally obtain them it doesn't seem like a big deal. But it is. It is a sign that can stretch yourself and that you're capable of handling more advanced research projects.

Gain broad experience and grab new opportunities

How did I get into biotech? During the third year of my degree, I focused on enzyme and antibody immobilization on radiation grafted copolymers, which was a forerunner for chromatography. I learned about RNA, DNA, amino acids, proteins, and so on, and it was interesting so I did my PhD on a similar theme. My first foray into the industry was at a company that later became MediSense. The focus was on electrochemical sensors for personalized diagnostics. Initially, I worked on in vivo electro-chemical sensors that monitored glucose for diabetics. My job was to make hollow fiber membranes. (I remember when we needed to test these diagnostics and everyone in the team spent at least one night in Oxford Infirmary being fed Mars bars, measuring glucose going up and down!) We decided not to push out an in vivo test as a start-up because it involves many regulatory hurdles. But we later developed an in vitro test.



From there, I joined another company as a developmental scientist and ended up running a pilot plant for about a year

"Many people in industry may not truly appreciate the work that goes into building a high-tech biopharma system."

that made various sensors. And then one day, some guys who had previously sponsored projects at MediSense asked me out to dinner. They were forming a start up in Sydney, Australia. And asked if I wanted to join them… in Sydney.

Looking back over my career, I have traveled and moved around a lot but the hardest move was that jump from the UK to Australia. Although the language is similar, the culture is not the same and the distances are huge. At one point I travelled from Sydney to the national university in Canberra. It's not that far in the grand scheme of things in Australia, but to me it was like going half way across the UK. I remember panicking, thinking that I'd end up stranded in the desert. I packed the car up with water and supplies in case I broke down or got lost. But it was suburbia all the way!

Be a change agent

I was in Australia for about three years,

Rick Morris is Senior Vice President of R&D at Pall Biotech, Pall Corporation.

working in different areas from water filtration, to cell separation and biotech projects, before being asked to run a plant in San Diego. I ended up being the general manager, which was interesting because, as well as running the plant, I was also doing direct sales. Jumping from being a scientist to sales for some people can be difficult, but I didn't seem to have any trouble with the transition. When I was around 13 years old, I used to help out in our family's post office/general store, which, looking back, got me used to working and interacting with people! Because it was technical sales, I enjoyed talking about the intricate details of a product. But today, sales people often speak with procurement folks, who only care about price. It takes a lot to get past the "gatekeeper", but the best salespeople are those who can network.

All in all, I've worked at a lot of different companies over my career and been through many acquisitions. I've always added to my skillset along the way, and built up a distinct ability to be flexible! The biggest piece of career advice I can offer is: always be open to change. Don't fight new changes coming in. Try and be flexible and work well in different situations. And don't stay pigeonholed – you don't want to be the expert in just one area.

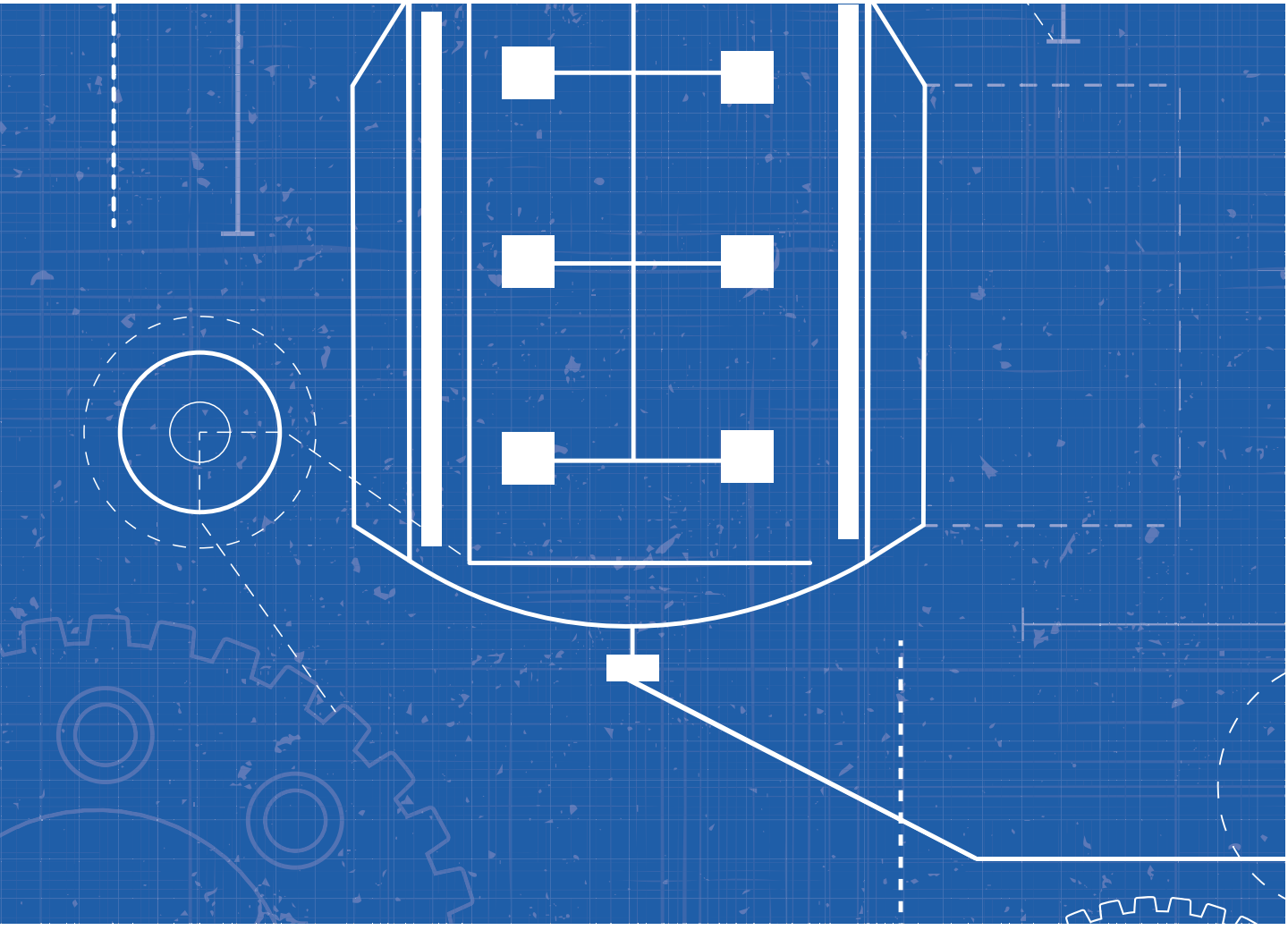
Being involved in equipment R&D draws on my many experiences – which makes it truly satisfying

Having experience in many different areas – polymers, filtration and biotech (even inkjet printing at one point) has really helped me at Pall, where I work today. For some, working with equipment may not evoke the same excitement as actually developing new medicines, but I find it very rewarding. I've always loved technology and making things, and I now get involved in many different areas – from polymer science to adhesive technologies. My previous work with sensors has also been hugely important; bioreactor users often want to measure glycosylation, which makes use of electrochemical sensors. In some cases, what's needed in the biotech industry is the ability to approach all technologies and get the best out of everything. I have to work with plastic bags, tanks, sensors, fix things to other things, measure data, analyze data… There are a lot of interesting people to work with!

It's incredible that our technologies lead to new therapies that can treat people. With the new cell and gene therapies coming through pipelines, there could be some fantastic differences made to patient lives. I'm really glad to be involved in this business.

Usability is king

Today, I am the senior vice president of biotech R&D at Pall and my team focuses on creating new systems. Many people in industry may not truly appreciate the work that goes into building a high-tech biopharma system, such as a bioreactor, or even the work that goes into just making a high-quality single-use bag; you need to select the right film, the side seals need to be just right to reduce the chance of



"Over the years, the idea of user-friendly equipment has become increasingly important."

it splitting, the integrity test needs to be performed in an exact manner, and you need aseptic connectors that fit perfectly. It's completely unacceptable to produce a substandard product that will leak after two days.

Over the years, the idea of user-friendly equipment has become increasingly important. For years, many people in the biopharma equipment industry didn't seem to give it much thought. You'd make a system – perhaps a fantastic system – and put it out on the market, but it wouldn't be user friendly. Today, we have a whole department that works on usability and it feeds into every part of the design. Rather than having square-shaped equipment, many systems today are more rounded – it's a small touch that makes a system look more user friendly. It's also easy to connect different components and you don't break your hands trying to get things together. The work that goes into making sure systems connect smoothly should not be underestimated. I've seen people in other divisions develop fantastic filters that were so large they were taller than a person. How do you get that into a

"Vendors today are partners in the industry and we really do put a lot of work into our role in industry."

tank? It's nigh on impossible for most people to take the filter up the stairs or through a lift and then install it. It had to be redesigned. Having something that works is one thing. Make it work and be user friendly, and then you'll really resonate with the people you are selling to.

We must collaborate – and advance together

When you work for a vendor, there is a danger that you are always seen as "selling" something. Vendors today are partners in the industry and we really do put a lot of work into our role in industry. We partner with academia and regulatory authorities – and this is essential to advance the field. Right now, we're looking to advance the continuous bioprocessing field. We can't do this without collaborating with other experts.

It is well accepted that the costs of biopharma manufacturing need to come down because the final drugs are simply too expensive. To lower costs, other industries have adopted continuous processing. Biopharma and biotech is one of the last industries to go to continuous, which is very strange because it has some of the most eminent scientists in the world working in it! But from a process and manufacturing point of view, progress has been very conservative. Regulators cannot endorse our technologies but they are encouraging the industry to look at continuous bioprocessing. I was at a recent event where the FDA's Scott Gottlieb said that he wants continuous processing to be used across the industry – not just for monoclonal antibodies, but for cell and gene therapies too. He sees these processes evolving a great deal. People in industry always say that regulation is a hurdle, but the FDA is definitely leading us to the water. Whether we all drink from the pond is up to us.

The Successful Experiment

Sitting Down With… Mike Thompson, Chief Executive, Association of the British Pharmaceutical Industry (ABPI), UK.

Did you always want to work in pharma?
Well, I'm not a doctor or a scientist. I actually started my career as a marketing trainee with Unilever – where I worked for 14 years. I was then hired by Glaxo as an "experiment" after they were persuaded by a consultancy that the NHS was changing and that they needed to bring in someone with different skills. It was unusual at the time and I was, in fact, the first non-pharma person they brought in. I quickly came to appreciate just how worthwhile the mission statement of our industry is – and 20 years went by in a flash!

What are some of the biggest challenges you're currently facing?
I have to say that during my interview for the ABPI job, the words "Brexit" and "industrial strategy" were not mentioned! But I think too often people see things as problems and fail to appreciate the opportunities. I entered the industry because I believe it needed to change, and the UK needed to change to get the best out of the industry. Sometimes you need to shake things up to spur on change – and it just so happens that the shaking has been done for me! It is a fantastic time to be in the industry right now because everybody has recognized both the potential and need for new thinking in the UK.

So you think that Brexit will be a catalyst for change?
I absolutely think it will. In a sense, we became comfortable with the UK being a gateway to Europe. Regardless of the Brexit outcome, this is likely to change. We must, therefore, stand on our own two feet and recognize that we're a market worth just 2.3 percent of the global marketplace. To attract global companies, we're going to have to be the best. I believe we will look back in 10 years and say, "Gosh. That was a difficult time to go through, but it was a catalyst in getting us to address some of the things we've always needed to address, and we've come out of it much stronger."

And are you optimistic about the Brexit negotiations?
There is a scenario that will present real challenges in supplying our medicines to patients across Europe. But I believe that politicians have great skill in going to the precipice and then turning back – and finding a way out. I do not believe that we will get into that situation (even if it is the one thing causing me sleepless nights at the moment). We have been abundantly clear to politicians about the risk involved, and I feel pretty certain that we will get results – though I don't know how or when…

"It is a fantastic time to be in the industry right now because everybody has recognized both the potential and need for new thinking in the UK."

What most excites you about the future?
We haven't even begun to understand the impact of the genomics revolution. And I'm pleased to see the UK government investing in biobank and the 100,000 genomes project – those projects are putting the UK at the forefront of understanding the potential of the genomics revolution. I think in 20 or 30 years, people will look back at the completion of the human genome and realize that it was truly an incredible moment in human history. It's taken us some time to see some of that work translate into new medicines, but I think we're eventually going to be able to cure certain incurable diseases. We're only at the beginning and it's enormously exciting to be a part of it – it's almost like a space race.

What are your thoughts on the potential of cell therapies?
Keith Thompson from the UK Cell and Gene Therapy Catapult played a video of CAR-T therapies in action at the ABPI's recent annual conference. The last time I saw anything like that, I was playing Pac-Man in the 1970s! Seeing cancer cells being gobbled up brought to life the power of these new therapies. The question now: how do we get these groundbreaking therapies to patients? Simon Stevens, CEO of the UK's National Health Service (NHS), has said that he understands the importance of these therapies and is already changing the way the NHS is configured to allow these medicines to be delivered to patients. On the pharma side, we're going to have to change our supply chains, but these changes are also happening.

What is the most memorable moment of your career?
Early on in my career, I was responsible for the HIV portfolio at GSK. I remember speaking with a leading clinician about the impact our medicines were having on him and his patients. He said the introduction of triple therapy meant that patients who had come to his hospital to die were, in a short period of time, now able to go home – and even back to work. Those sorts of stories are so powerful that they never leave you.

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