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the Medicine Maker

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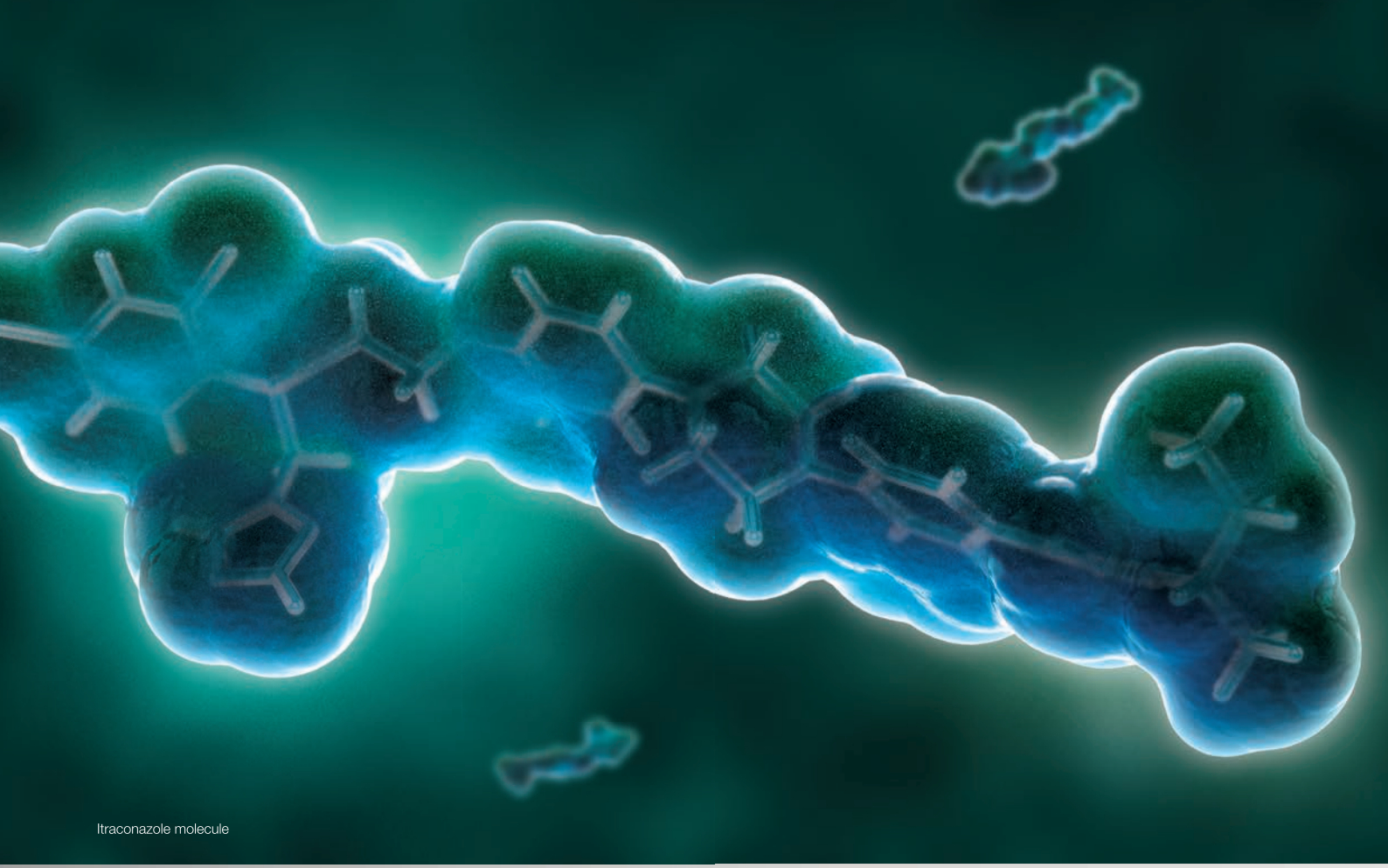

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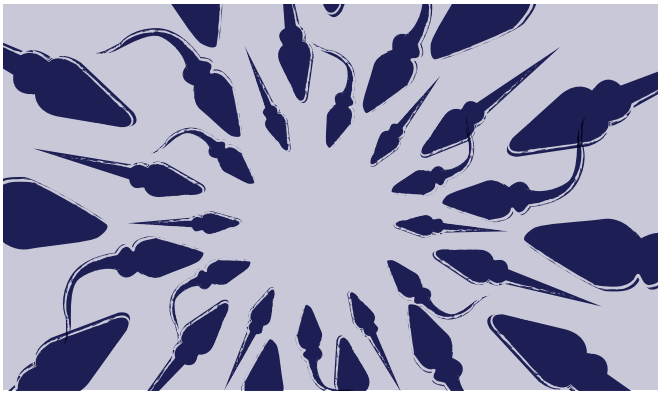
Online this Month

The Power List 2017

Did you miss out on the April 2017 print issue of The Medicine Maker, which included our annual Power List of the top one hundred professionals in drug development? You can read the full list online at: *https://themedicinemaker.com/power-list/2017/*



Prepare for the Mecha-Sperm!

Our feature on page 20 showcases a number of innovative drug delivery projects, but there's more innovation on our website too, where we catch up with researchers in Germany, who are investigating a very unconventional drug delivery method: human sperm. Learn more at: *http://tmm.txp.to/0517/sperm*

Future or Science Fiction?

What will medicine look like in 2050? Bertalan Mesko's job is all about looking at which technologies could transform our lives – and healthcare. We find out more about his career at: *http://tmm.txp.to/0517/Mesko*

The Medicine Maker Innovation Awards 2017

The Innovation Awards are back for 2017. In the December 2017 issue of The Medicine Maker, we will showcase the most exciting drug development and manufacturing technologies released over the course of the year. Nominations are now open. Visit our website for more details: *http://tmm.txp.to/0517/innovationawards*

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the **Medicine Maker**

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The Worst of Side Effects

Is growing awareness of unwanted drug effects good or bad for patients?

Not all drugs are fully understood, which is why unanticipated side effects can occur. In recent years, there has been growing acknowledgement of a severe – and even more counterintuitive – drug effect: suicide, with a number of drugs, particularly antidepressants, under scrutiny. GlaxoSmithKline, for example, has faced a number of lawsuits regarding Paxil. And in a landmark case in April, GSK was even ordered to pay $3 million in damages to the family of a suicide victim who had been taking a generic version of Paxil (1). Clearly, there is a discussion to be had over whether the innovator drug community should be broadly liable for generic versions of its drugs, but that is a topic for another time…

Quantifying suicidal behavior is difficult, particularly in depressed or psychotic patients (over 90 percent of suicide victims suffer from clinical depression or other mental health disorders), but studies have shown a link between suicide ideation and some prescription drugs, particularly in children and adolescents. A number of antidepressants in the US have had a black box label since 2004, and a study conducted in 2016 even claimed that antidepressants could double the risk of suicidal and aggressive behavior in young people (2). Not all suicides can be attributed to drug effects – but the pharma industry is certainly a big (and perhaps easy) target at a very difficult time for grief-stricken friends and family.

It also doesn't help that the media often accuses drug companies of downplaying the risks of suicide ideation and other severe drug effects. In the previously mentioned GSK case, for example, attorneys for the suicide victim's family allege that GSK failed to adequately warn the suicide victim's doctor about the risks of Paxil (GSK, on the other hand, points out that label did provide warnings and that the wording is FDA approved).

It is very important that companies do not try to hide any side effects in studies, but there is also danger in over-emphasizing the risk of side effects – especially when it results in patients who refuse to take life-saving or life-changing medicines.

A thought-provoking study published in May followed patients before and after learning they were taking statins (rather than the placebo) – and highlighted the so-called "nocebo" effect (3), which describes side-effect reporting that is more common when a patient is aware of taking a given medication. Unfortunately, the study was funded by a statin manufacturer further fueling the pharma fire... Nevertheless, it does raise some questions: how strong is the nocebo effect with other medicines – and how is it affecting patient compliance in the short and long term?

Stephanie Sutton
Editor

Stephanie Sutton

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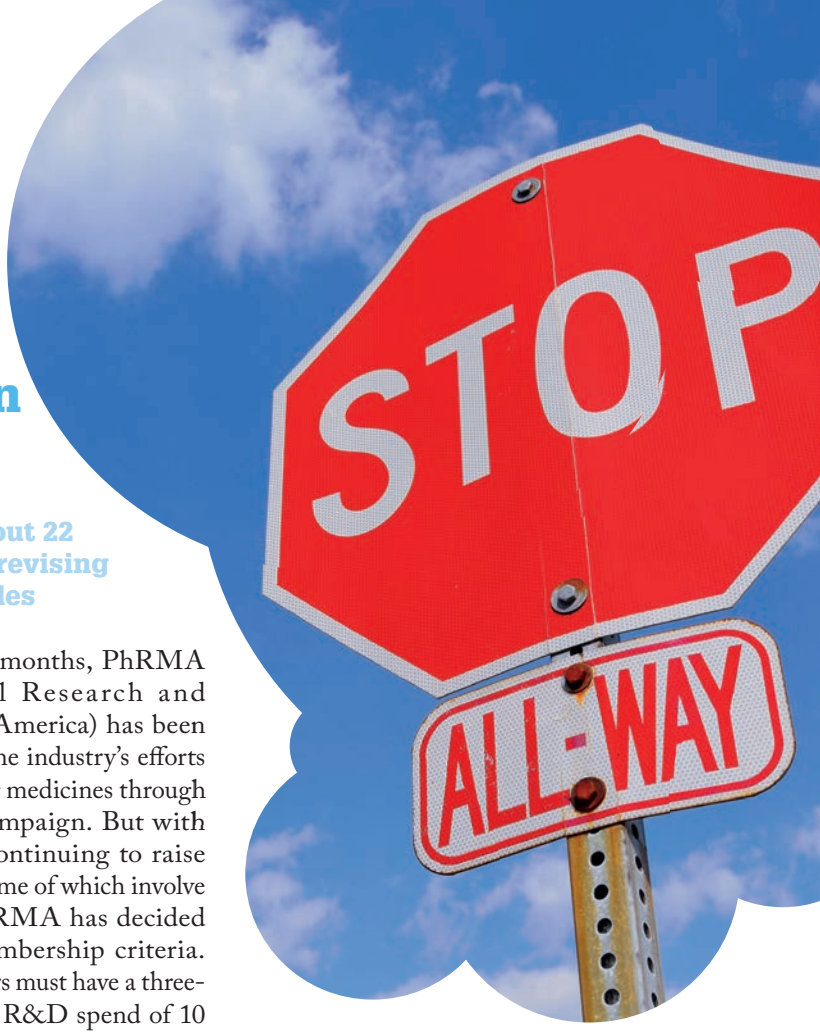
2. *T Sharma et al., "Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports", BMJ, 352 (2016). PMID: 26819231*
3. *A Gupta et al., "Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase", The Lancet, S0140-6736 (2017).*

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



It's Just Been Revoked

PhRMA weeds out 22 members after revising membership rules

Over the past few months, PhRMA (Pharmaceutical Research and Manufacturers of America) has been trying to promote the industry's efforts to develop lifesaving medicines through its "Go Boldly" campaign. But with pricing scandals continuing to raise their ugly heads – some of which involve its members – PhRMA has decided to shakeup its membership criteria. Henceforth, members must have a three-year average global R&D spend of 10 percent of sales or greater, and a three-year average global R&D spend of at least $200 million per year (1). Moreover, the "research associate" category of membership – which allowed smaller companies to join for reduced fees – has been eliminated entirely, meaning those 15 companies are no longer members.

Seven full PhRMA members also didn't make the cut, having failed on one or both of the criteria:

- AMAG Pharmaceuticals, Leadiant Biosciences, Orexigen Therapeutics and The Medicines Company all had an R&D/sales ratio greater than 10 percent, but did not spend more than the minimum of $200 million per year on R&D.
- Mallinckrodt Pharmaceuticals met the minimum $200 million spend, but were below the 10 percent R&D to sales ratio.
- Horizon Pharma and Jazz Pharma didn't meet either one of the new criteria.

Mallinckrodt actually resigned from PhRMA in April – though apparently not in anticipation of the new rules. Instead, the company claimed that the financial and time commitment required as a full PhRMA member outweighs its value to Mallinckrodt (2). Mallinckrodt has been involved in a number of pricing scandals – most recently, it was fined $100 million over a monopoly on a specialty drug (Athar) used to treat infantile spasms. The company is also facing a DEA investigation into some of its opioid sales practices.

One of the 15 associate members to be pushed out of PhRMA was Marathon pharmaceuticals, which recently drew congressional criticism after charging $89,000 for Emflaza. Marathon CEO, Jeff Aronin, sat on PhRMA's board before the recent revision of the membership rules.

"By putting in place new membership criteria, the board is sending a clear

message that being a member of PhRMA means being committed to doing the time-intensive, scientifically sound research it takes to bring bold new advances in treatments and cures to patients," said Joaquin Duato, PhRMA Board Chairman and Worldwide Chairman, Pharmaceuticals, Johnson & Johnson, in a statement (1).

PhRMA also pointed out that most of its members invest significantly more in R&D than required by the new criteria. "On average, PhRMA members invest 20 percent of their revenue in R&D, and the biopharmaceutical sector as a whole accounts for 17 percent of all domestic R&D funded by US businesses – far more than the software (13 percent), automobile (5 percent) and aerospace (4 percent) industries." *JS*

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Hidden Fungi Treasures

Does Penicillium contain a treasure trove of undiscovered secondary metabolites?

Over the years, bacteria have served science well as a source of pharmaceuticals. Because of their amenability in the lab and their simple cellular architecture, scientists know a great deal about bacterial genetics – and their potential for producing secondary metabolites. But with the majority of the low-hanging fruit picked, it may be time to turn to another source of secondary metabolites: fungi.

It's well known that Penicillium fungi are able to produce important pharmaceutical compounds such as antibiotics, cholesterol lowering medicines and immunosuppressant drugs. And though some consider Penicillium to be an exhausted source of therapeutics, others think there are treasures waiting to be discovered. To settle the argument, a team of researchers from Chalmers University of Technology, Sweden, set out on a new research project.

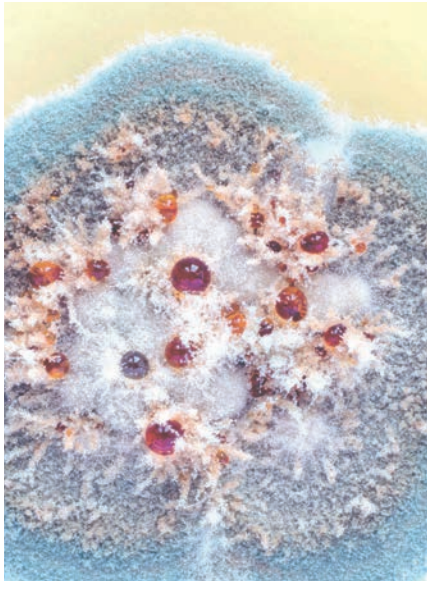
"One can cultivate fungi and isolate the compounds they produce, but most bioactive compounds are not being produced under standard laboratory conditions," says Jens Christian Nielsen, co-author of the study. The authors, therefore, decided to apply a genome mining strategy to fully assess the genetic potential for the production of bioactive compounds by the Penicillium genus.

The researchers sequenced the genomes of nine Penicillium species and, together with 15 published genomes, investigated the secondary metabolism of Penicillium (1); the authors said they were able to identify "an immense, unexploited potential for producing secondary metabolites..."

"Even though the species analyzed are from the same genus, we could see that they are able to produce a very diverse selection of secondary metabolites, with only a tiny fraction of the identified metabolic pathways being previously known," says Nielsen. "This means that we have an untapped resource in our hands that could fuel the pharma industry with new drug leads."

Nielsen suggests that providing the pharma industry with an overview of metabolic capabilities of different species will speed up the screening process for new antibiotics and hence lower the costs of development. "We were able to identify new variations of known antibiotics and new producers of known drugs, which might be more efficient for production. We may also be able to identify species that can produce completely novel compounds."

Filamentous fungi (like Penicillium) tend to produce secondary metabolites in small quantities, so the goal for the



research team now is to figure out how to produce the bioactive compounds efficiently. Says Nielsen, "We are working on transferring the secondary metabolite pathways from Penicillium species to yeast. The idea is to engineer yeast cell factories for efficient production of secondary metabolites, both to study their specific activities and, to create economically viable production processes." *JS*

Reference

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European RAPSody

With big regulatory changes on the horizon, RAPS invests in Europe. Executive Director Paul Brooks tells us more

Who?

The Regulatory Affairs Professionals Society (RAPS) is a global organization for regulatory professionals in the healthcare, medical device, biologic and pharmaceutical sectors.

What?

RAPS is increasing its investment in Europe. Over the last 12 months, we have seen our existing European member base grow by approximately 19 percent – to more than 1,500 members across 29 countries. In addition, important regulatory developments in Europe, such as the imminent introduction of the Medical Device Regulation (MDR) and the Falsified Medicines Directive (FMD), are creating the need for greater support for regulatory professionals in this sector.

Why?

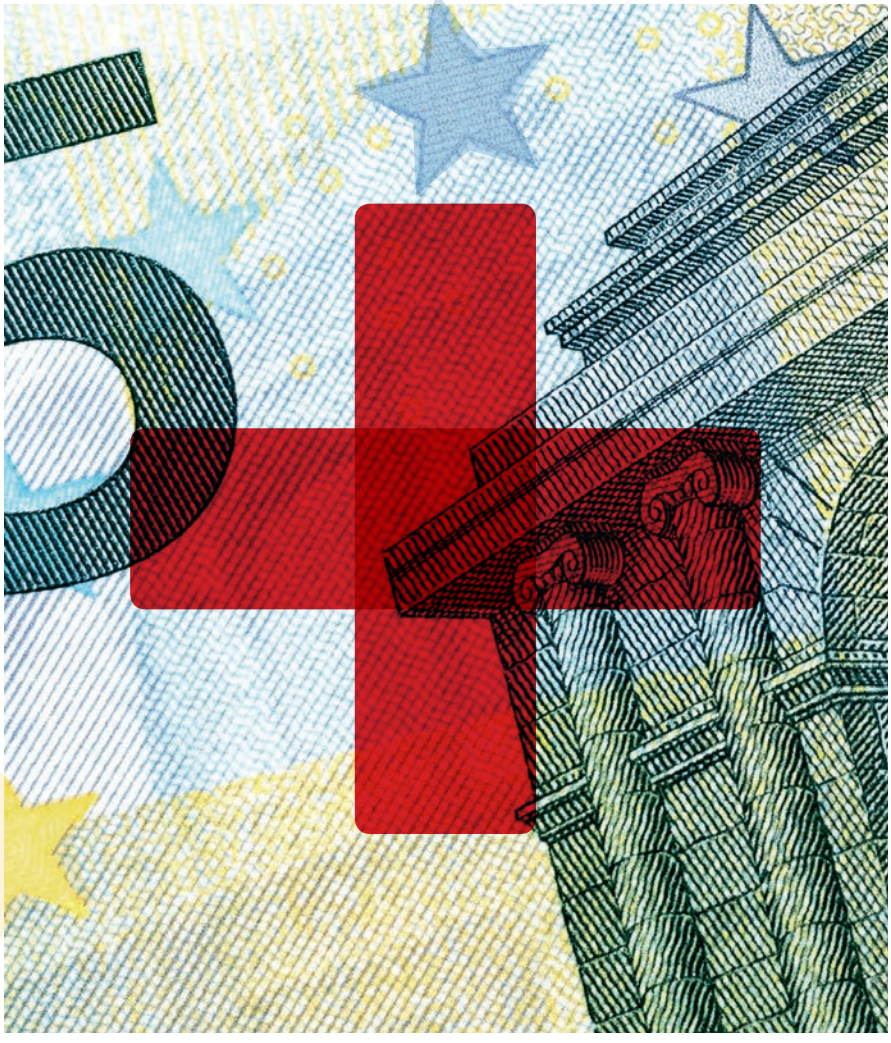
Changes to medical device regulations in Europe present a huge challenge to manufacturers. The MDR is high on the industry's agenda as we move towards the 2020 deadline and is a major source of discussion and resource for our members. We strive to keep our members abreast of these regulations and the implications they bring with regular updates and events.

Similarly, the pharmaceutical supply chain is currently faced with the huge task of preparing for the introduction of the European FMD, which comes into effect in 2019. New track-and-trace requirements are also being introduced in the US as part of the Drug Supply Chain Security Act in 2017. There are, therefore, lessons that can be transferred across geographies and it is our goal to connect regulatory professionals in different markets, allowing for knowledge sharing and the adoption of best practice.

The increasing use of electronic common technical documents (eCTDs) in the industry is also proving a challenge for many, and it is our goal to assist our members with this transition by providing training and guidance.

How?

RAPS will invest more than €2 million over three years to implement its growth plan in Europe, which includes the opening of its first European office. The office, which will be the European HQ, will be a base for activity across the entire European regulatory community. In addition, RAPS has announced a series of European events including a RAPS Roadshow. The next event takes places in July in Brussels: "EU Regulatory Essentials, Medical Device and In Vitro Diagnostics: Transitioning from Current Directives to New Regulations". *JS*



WHO Wants Cancer Biosimilars

Will a pilot project to prequalify "generic" biologics improve safe access to medicines?

Improving access to medicines in middle- and low-income countries is dependent on effective regulatory oversight but, in many cases, medicines regulatory authorities (MRAs) in the developing world are unable to adequately carry out all functions (1). In the past, this approach lead to reliance on stringent regulators in developed countries, which is problematic because it puts the decisions in the hands of regulators who aren't accountable for the needs and safety of the target patients.

The World Health Organization (WHO) championed an alternative approach with their prequalification program; a team of assessors, which includes WHO staff and experts from national regulatory authorities, evaluates data presented by medicine makers. And a team of inspectors verifies that the manufacturing sites for the finished pharmaceutical product and its active pharmaceutical ingredient(s) comply with WHO good manufacturing practices. Once a decision is made, the medicine appears on the WHO's list of prequalified medicines and can be purchased by international procurement agencies – such as UNICEF, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and UNITAID – for distribution in resource-limited countries.

Traditionally, WHO prequalification focused on only a few diseases (in particular, HIV, malaria, and TB), with the majority of approved products being generic HIV drugs. However, the WHO has now launched a new pilot project for prequalifying biosimilar medicines (2). In September, drug manufacturers will be able to submit applications for prequalification of biosimilar versions of two products in the WHO Essential Medicines List: rituximab and trastuzumab. The WHO is also reportedly planning to explore options for prequalifying insulin (3).

"Biosimilars could be game-changers for access to medicines for certain complex conditions," said Dr Suzanne Hill, WHO's Director of Essential Medicines and Health Products, in a press release. "But they need to be regulated appropriately to ensure therapeutic value and patient safety."

The WHO says it will also review the 2009 Guidelines on the evaluation of similar biotherapeutic products to "ensure that WHO's guidance to national regulatory authorities reflects recent evidence and experience." *JS*

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ABPI Sets Out Its Stall

The Association of the British Pharmaceutical Industry releases a manifesto for the UK's upcoming election

Any election gives political parties – as well as stakeholders in particular policy areas – a chance to outline their views and positions on the next five to ten years of government. And with the UK at a critical juncture, the Association of the British Pharmaceutical Industry (ABPI) has decided to set out its stall on the future of the National Health Service (NHS), the future of pharmaceutical research, development, manufacturing and investment in Britain, and the impact of the UK's future relationship with the European Union (1). We caught up with a spokesperson for the ABPI to find out more.

How important is the UK pharma industry to the UK economy?

The pharmaceutical sector is a major contributor to employment, taxes and GDP – providing high skilled and highly productive jobs across the UK. The UK Life Sciences sector contributed £30.4 billion to the economy in 2015, providing an estimated tax contribution of £8.6 billion to the exchequer. Each life sciences job supports 2.5 jobs elsewhere in the UK economy, meaning the sector supports a total of 482,000 jobs. The average productivity of UK Life Sciences employees, expressed as Gross Value Added (GVA), is £104,000 compared to the UK GVA average of £49,000. And jobs are distributed throughout the UK, with every region containing a UK head office of a life sciences firm.

How do you think the UK can improve patient access to medicines?

Government analysis shows that, on average, for every 100 patients in comparable countries who get access to a new medicine in its first year of launch,

just 18 patients in the UK receive the same. Reforming the NHS to embrace new treatments is crucial to providing quality care to more patients within a sustainable budget.

In an ideal world, how would you like to see the NHS and the pharma industry better collaborate?

As we look at the future of medicine and new ways of treating cancer, Alzheimer's, and many other diseases and chronic conditions, we want to work more closely with the NHS to revolutionize the way healthcare is provided and improve patient outcomes a result. One example is how we collaborate on "real world evidence" and healthcare data collection. Building on the success of a long-term NHS/pharmaceutical company partnership that tracked the treatment of asthma in Salford (known as the Salford Lung Study), the Greater Manchester Health and Social Care Partnership has recently kicked-off a diabetes program with a number of pharmaceutical companies. This work tracks, monitors and reviews care in "real world" settings. More partnerships like this will give us the best chance of creating the most appropriate and cost-effective medicines for patients throughout the UK.

What are the main priorities for UK pharma companies as the UK negotiates its exit from the EU?

The negotiations that determine Britain's new relationship with the EU will be critical to how medicines are delivered to patients in the UK and in Europe, and the future success of the pharmaceutical industry. For a sector that plans a decade ahead, it is critical to secure a new relationship with the EU that prioritizes patients and public health. This means securing co-operation with the EU on the regulation of medicines, securing the ability to freely trade and move medicines and pharmaceutical supplies across borders, securing access to the best talent, and securing predictable access to funding and collaboration for scientific research.

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Single Use – Your Way

Disposable technologies are expected to see even greater demand in the future – and that puts pressure on suppliers to up their game in terms of lead times.

By Karen Green

Single-use systems are well established in the industry. The first single-use technologies to emerge were very simple; for example, single-use tanks and mixers. In time, the first single-use bioreactor was launched (the WAVE bioreactor) and stirred bioreactors are commonplace today. Now, we are also seeing increasing uptake of more complex, sophisticated single-use systems, such as chromatography and final-fill systems. Many vendors are actively innovating in this area – including Merck KGaA.

The advantages of single use are well known – especially, ease of use. Pre-packed columns and ready-to-use filtration assemblies have made a huge difference to many companies' bioprocessing operations because they are so easy and fast to set up; single-use parts are pre-eradiated, sterilized, and ready to use as soon as they are removed from the packaging. With stainless steel, on the other hand, end users have to clean new equipment and validate its cleanliness before use – and cleaning continues to be needed throughout the equipment's lifecycle. Cleaning is expensive in terms of utilities and labor costs, but perhaps more significant is the time lost. If you are running 40 campaigns a year using stainless steel, I'd wager you could increase this to perhaps 50 campaigns or more using single-use systems and components.

Single-use systems certainly have many benefits, but there are still industry concerns regarding their use. First of all, there is the hot topic of extractables and leachables that may affect the drug product. The BioPhorum Operations Group has been instrumental in considering these challenges, and stresses the importance of understanding the extractables profile. As a supplier, we are obligated to provide information about extractables and leachables upfront, and to demonstrate that there are very low levels of extractables (if any) leaving the plastics that we select and use in our processing. A second concern is breakage. Vendors must work with end users to help minimize breakage risks. We do a lot of user handling training, for example, and we are always looking for more robust materials to use for our products. Single-use assemblies are complex and can be fragile – they need to be handled carefully.

Pick and mix

There are also industry concerns around supply. Rather than the biopharma manufacturer controlling the inventory of their fluid management systems, this role passes to the vendor – and the end user is dependent on the vendor for ongoing supply. Some companies fear this loss of control and it certainly places a tremendous responsibility on the vendor. With demand for single-use systems increasing, vendors have to carefully consider their capabilities and their capacity to service customers in a reasonable amount of time. In some cases, lead times can be a real problem for biopharma manufacturers.

With this in mind, we launched the Mobius MyWay portfolio in March 2017. The concept is based on partnering with our end users to offer better supply predictability and to ensure that assemblies are ready when needed. The portfolio is divided into three categories:

- Mobius Stock. Some customers need single-use assemblies immediately and want to order them off the shelf as a standard part. Mobius Stock offers on-demand solutions for certain popular components – and these are ready to ship in 24 hours. We also offer stocking agreements if a company buys enough assemblies annually, where we prebuild and stock items that the customer can order at will.
- Mobius Select. This is a balance of speed and configurability of custom assemblies. Customers can pick and choose the components they need for a custom assembly (even complex assemblies) from an optimized pool of parts (around 300 components) – and this is delivered with a six-week lead time. Traditionally, lead times for custom assemblies in the industry are around 13 weeks. Most companies will find what they need in this category – around 90 percent of the assemblies we supply are made with Select components.
- Mobius Choice. Here, we design exactly what the user wants, including made-to-order parts, but orders are shipped in standard lead times.

With the MyWay program, many users mix and match between Stock and Select, which encompass the most in-demand parts – and we hope this will provide clarity around lead times, while getting components and assemblies to users as fast as we can. We aren't the first company to try a new approach to stock and delivery, but vendors tend to target standard assemblies with standard configurations. However, there is still a lot of specialized processing and customization in the industry too, so some customization, whether in tubing size or materials, is usually required. We believe it is important to supply exactly what customers want, and to offer them the ability to pick and choose – and the Choice category is crucial for those manufacturers that need very specific parts – but obviously extensive customization comes with different lead times to Stock and Select. The whole program is about being able to deliver parts accurately so that users can plan better. For us as a company, it's also about preparing for the future growth of single use too – 10 years from now, we want to be able to supply to the customer on an as-needed basis.

Supply and Support

As uptake of single use in the industry continues to grow, more industry discussions are taking place about standardization. I expect to see greater standardization in the future, but it will perhaps be the 80-20 rule – with 80 percent being standardized and 20 percent being custom. Bags sizes, for example, are a logical choice for standardization, but at the end of the day there will always be a need for custom solutions in the pharma industry.

I feel very strongly that single use will continue to grow. Today, single use is predominantly used in clinical manufacturing – around 30-40 percent of clinical drugs are processed with single use. For commercial manufacturing, it's around 20 percent, but this number will increase. In 10 years, it could be well over 50 percent for clinical drugs and 40 percent for a commercial drug – and Mobius MyWay will enable us a supplier to better respond to this increased demand. When a new drug is about to launch, manufacturers are increasingly looking at single use because of ease of use, flexibility – and because it avoids the need to invest in stainless steel infrastructure. Documentation also comes with our systems so users have everything they need to start getting approval in major markets.

Our role as a supplier has expanded away from simply supplying systems to also providing extensive support around single use to help customers get started. Our Mobius MyWay portfolio makes the supplier-customer relationship even more intimate – we discuss the customer's assembly needs, and whether certain parts can be tweaked to offer a six-week lead time rather than a 13-week lead time. It's all about collaborating to make sure our customers are able to begin processing faster.

Karen Green is Senior Product Manager at Merck KGaA.

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

Spray for Success

Vaccines are essential for public health and yet challenging to develop. We need more manufacturing techniques at our disposal.

By Devon DuBose, Head of Inhalation Product Development at Capsugel's Bend Facility in Bend, Oregon, USA.

Vaccines have a huge impact on global health. According to the World Health Organization, measles vaccinations alone have saved over 17 million lives since 2000 (1), and some diseases, such as polio and small pox, have almost been eradicated from many countries because of vaccination. Today, companies are developing vaccines for emerging healthcare threats, including Zika and Ebola, as well as bioterrorism threats, such as anthrax.

Vaccine development, however, is a time- and cost-intensive process. Determining new, viable viral targets involves consideration of a range of factors, including the frequency of disease, virulence, mortality, access to healthcare administrators, location, and socioeconomic impacts. And many vaccines have to be stockpiled (particularly with bioterrorism), which creates additional challenges.

Most vaccines are delivered by the parenteral route, using a needle and syringe. Such vaccines are often delivered in liquid form, which typically requires cold chain storage, or are lyophilized into a powder that is reconstituted upon delivery. Injections are a well-established form of drug delivery (although not always well-accepted by patients) and are easy to administer for specialized healthcare professionals. But is this the best delivery method for a vaccine? In developing countries, for example, where vaccines have the potential to save millions of lives, there aren't always enough professionals to administer the vaccine – and training in remote locations can also be difficult. Additionally, delivery to Zone 4 locations may require temperature excursions or long term storage at 35 ^{0}C or beyond for effective delivery to impacted populations.

In terms of manufacturing, the current processes for liquid and lyophilized formulations are still very much based on batch production – not the most flexible processing technology in an epidemic. And the range of excipients and adjuvants suitable for lyophilization can be limited when it comes to high glass transition polymers or aluminum adjuvants, which can be enabling for high-temperature stabilization or efficacy. Furthermore, certain antigens can be damaged during the ice nucleation and drying step despite the low temperature of lyophilization processing.

There is a growing opportunity in vaccine development to explore the potential of intranasal or inhalation vaccines, particularly as these vaccines can take advantage of the manufacturing benefits offered by spray drying. For parenteral vaccines, spray drying is limited because of a lack of aseptic spray drying infrastructure globally, but dry powders for intranasal/ inhalation delivery do not require aseptic

processing. Spray drying consists of a liquid feedstock being prepared and fed continuously to an atomizer inside a spray dry chamber. The spray plume is contacted by drying gas, converted to a dry powder and continuously collected. Powder aliquots are also removed during the process. Cycle times are short, and if more material is needed, the process is simply run longer. The continuous nature allows manufacturing volumes to be adjusted rapidly, which is useful given the uncertainties associated with supply chain predictions. The ability to ramp up production quickly in case of an epidemic is also a key advantage.

Spray drying can be used for a variety of purposes in the pharma industry. But the key point for vaccine developers is its ability to produce free-flowing particles in a range of particle sizes, particularly those suitable for inhalation (2-5µm) or intranasal (>30µm) delivery. In targeted vaccine delivery to the nose or lung – the point of entry for many viruses – there are notable opinions that the method may produce an enhanced antigen response (2). Moreover, such vaccine administration can be handled through passive devices that are controlled by inspiration, which requires less healthcare professional training and observation than needle injections.

Another benefit of spray drying is that it can process a broad range of excipients with a range of physical-chemical properties, including high molecular weight and high glass transition temperature excipients for improved shelf-life. In collaboration with vaccine development companies, my colleagues have demonstrated stability of a vaccine for up to six months at 50°C (3). Spray drying also allows for the incorporation of adjuvants, which may have compatibility challenges with lyophilization.

Spray drying isn't suitable for all vaccines, but it's a good technique for the toolbox – especially when traditional vaccine delivery routes aren't working out. The development and commercialization of a vaccine can require years – or even decades – but some epidemics take shape in only a few months. Vaccine development will continue to be a unique challenge, so the more tools we have at our disposal the better.

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Targeting Tuberculosis

Existing drugs can – and should – be repurposed to fight neglected diseases.

By Santiago Ramón-García, Principal Investigator at the Research Agency of Aragon (ARAID), Zaragoza, Spain, and Charles Thompson, Principal Investigator at the Thompson Lab, the University of British Columbia, Canada.

Although entering a new era of innovative and personalized medicine in industrialized countries, we still rely on drugs developed more than 50 years ago to treat neglected diseases, such as tuberculosis (TB). Since then, only two new drugs, Sirturo (bedaquiline) and Deltyba (delamanid), have been approved for treating TB. Because they are not known to be more effective than traditional frontline TB antibiotics, they are only used to treat multidrug or extensively drug-resistant cases, which sometimes are incurable. In recent years, governments and pharmaceutical companies are recognizing an urgent need to improve current TB treatments.

In addition to the well-recognized challenges of drug development, TB antibiotic development is particularly limited for a number of reasons, including:

- The causative agent of TB, Mycobacterium tuberculosis, is intrinsically resistant to most available antibiotics.
- TB is an airborne infectious disease that requires research facilities equipped with expensive, biosafety level 3 infrastructure, as well as dedicated, trained personnel.
- TB mainly affects developing countries lacking resources and infrastructure. It was not until recently that major US-based organizations invested in basic and applied TB research. Unfortunately, the European Union neglected TB funding in its Horizon 2020 program.
- The current reward system for drug development is based on company

profits from blockbuster drugs that are developed to treat chronic diseases in the industrialized world. Antimicrobials, in general, are not a good business investment under this model because treatment typically involves inexpensive drugs for just a few days or weeks – and in the case of TB and other neglected diseases, the cost of treatment must be minimal.
- There are only a handful of pharmaceutical companies with TB research in their current portfolio – many others have discontinued TB projects over the past decade.

In view of these challenges, new innovative approaches need to be introduced to quickly deliver new effective therapeutics to patients in need. To minimize the cost of developing new treatments for TB, we combined two innovative concepts: drug repurposing and synergy. These concepts for treating TB originated more than ten years ago in the laboratory of one of the authors – Charles Thompson, at the University of British Columbia, Canada. Santiago Ramón-García joined him there in 2007 as a postdoctoral fellow to start the drug discovery program, searching for inhibitors of mycobacterial proteins that confer intrinsic antibiotic resistance. In 2011, we demonstrated that antibiotics with no significant activity against M. tuberculosis could be repurposed for TB therapy if administered in synergistic combinations (1). A screen of a library of FDA-approved drugs, including around 150 antibiotics, identified lead compounds that increased the activity of an antibiotic (spectinomycin) that M. tuberculosis was able to resist. This led to the realization that available drugs, especially antibiotics, commonly act in synergy with one another against M. tuberculosis. In some cases, compounds used for other therapies also had their own inhibitory activities against M. tuberculosis. Recently, we also reported in vitro activity of cephalosporins alone and in combination with other antibiotics (2).

"To minimize the cost of developing new treatments for TB, we combined two innovative concepts: drug repurposing and synergy."

After a long period of screening, discovery, characterization, and development, we received funding from the Tres Cantos Open Lab Foundation to further develop this program. Santiago worked for two years in Spain at the GlaxoSmithKline (GSK) screening facilities with a focus on repurposing beta-lactams (and in particular cephalosporins) for TB therapy. Our observation showing that first-generation cephalosporins were active against M. tuberculosis was remarkable because they have been available for over 50 years – but no one previously noted their potential against TB. There is now a vast space to explore, including investigations of other beta-lactam families (a recent clinical trial led by GSK validated the potential of beta-lactams for clinical use [3]) and a vision: to translate in vitro activities of cephalosporins into clinical efficacy.

Cephalosporins could be effective antibiotics; however a single drug will be insufficient to control TB, especially in the long term, and we need to continue to fill the development pipeline. Clearly, more funding and commitment from all stakeholders (including funding agencies, governments, academics and the industrial sectors) are needed if we are to reach the WHO's goal of TB elimination. To this end, it is imperative to foster public-private partnerships such as the TB Drug Accelerator (TBDA) initiative, a groundbreaking partnership between pharmaceutical companies, research institutions, and the TB Alliance.

Given that drug development is a long and expensive process, repurposing old drugs for neglected diseases is a promising avenue. However, this area is neither sufficiently profitable to attract companies nor appealing to academic scientists supported by research grants that rely on publication and short term public disclosure. We believe more efforts and funding should be dedicated to this largely ignored and unexplored avenue, not only for TB, but also for other neglected diseases.

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DELIVERING ON A PROMISE

Developing a drug that hits a given target is one thing. Making sure it gets to that target is quite another. Fortunately, drug delivery approaches are becoming increasingly sophisticated. Here, we ask those at the cutting-edge how they plan to deliver a better outlook.

By Nick Miller, Stephanie Sutton and William Aryitey

Innovation in drug delivery is all around us – and almost every day brings the publication of new academic research, a new company announcement, or the formation of a new collaboration aimed at advancing the field. Some progression in drug delivery is conceptually simple, such as tweaking a formulation to reduce the number of doses, or developing a new version of a currently approved drug in a more patient-centric format. Other research focuses on complex and clever targeting methods that get a drug to precisely the right point in the body, or tackle difficult-to-treat diseases. Increasingly, a number of researchers are widening their innovation net to look beyond biological science and formulation, and to investigate the potential offered by electronics – miniature and ingestible – that can be incorporated into pills and capsules to help with targeting.

In the following pages, we explore a handful of fascinating drug delivery research projects that aim to go beyond incremental improvements in the field to offer brand new approaches.

HOLD IN YOUR STOMACH

How controlled release can lead to better compliance

Giovanni Traverso is a practicing gastroenterologist and biomedical engineer at Brigham and Women's Hospital and Harvard Medical School in the US. His research focuses on the development of novel technologies for drug delivery and sensing via the gastrointestinal (GI) tract. In particular, Traverso has an interest in developing extended release technologies, which could allow gastric residence times in the order of months. We speak with Traverso to find out more.

How did you get into gastroenterology?

While I was at medical school in Cambridge (UK), I did a summer research rotation at Johns Hopkins with the cancer biologist Bert Vogelstein. A PhD followed, during which we developed tests for colon cancer (incidentally, these were recently approved by the FDA). My thesis was very successful; I was awarded the grand prize in the Collegiate Inventors Competition, recognized by the MIT Tech Review as one of the top innovators under the age of 35, and published my work in the Lancet, New England Journal of Medicine, and Nature Biotechnology.

After my PhD, I completed my medical training back in Cambridge (I was a Fellow at Trinity College, Cambridge and a student at the same time, which was wonderful!), before moving back to the US for my internal medicine residency at Brigham and Women's Hospital and specialization in gastroenterology at Massachusetts General Hospital, both affiliated with Harvard Medical School. GI disorders include immune diseases, infectious diseases, cancer, and more, which makes the area very satisfying from both a clinical and an intellectual perspective. I've never regretted specializing in this field.

And what made you focus on drug delivery?

After my PhD, I wanted to explore something new, and the postdoctoral research component of my specialty medical training seemed like my last opportunity to dive into a completely different field. I was intrigued by the prospect of new technologies for GI drug delivery, so I joined Bob Langer's lab as a post-doc, working on systems for drug delivery and sensing in the GI tract. That relationship has grown into a long-standing collaboration, and although I'm now a Harvard faculty member, I still work closely with Bob. We jointly run a group of about 40 people, funded by parties including the Gates Foundation, Novo Nordisk, and the NIH. Our aim is to exploit the GI system's incredible capacity to accept materials and objects across a broad range of compositions and shapes, enabling extended release dosage formats which can be accommodated for over weeks or months. We're also developing GI-located sensors that can detect a range of analytes from vital signs to toxins.

Why is extended-release drug delivery technology so important?

In early 2012, representatives of the Gates Foundation – including Bill Gates – visited the lab, and subsequently we discussed the challenge of developing a system that could provide a full course of treatment with a single administration. This kind of development could not only minimize emergence of resistance, but also potentially minimize non-compliance with medication regimens. Only about 50 percent of patients in the developed world, and maybe 30 percent in the developing world, actually take medication as prescribed, so non-compliance is a big problem. Administration frequency has a significant effect – compliance rises as the interval between each dose increases – for example, once weekly dosing regimens are associated with higher compliance than once daily.

We decided to develop an orally delivered system that resides in the stomach and releases drug over many days. Our recent paper is one of a series of planned publications on this topic (1). Basically, we have developed a novel gastric resident dosage form that can easily be compressed into a capsule for swallowing. Once in the stomach, it changes shape, and it is this shape and its mechanical properties that ensure it remains in the gastric cavity, releasing drug for several days or weeks. Key to this was the development of a safe material for the dosage form; we wanted to avoid risks, such as the dosage form exiting the stomach and entering the small intestine, where it might cause a blockage.

Therefore, we devised linkers that are stable in the gastric cavity, but that selectively dissolve in the small intestine environment. We are also working on systems to aid medication adherence in the pediatric population – although this is at a much earlier stage of development.

These new dosage forms have tremendous potential to combat non-compliance. Our start-up, Lyndra (see page 23), intends to get this technology to humans as safely and as quickly as possible – human trials are approximately 6-12 months away.

What are the obstacles facing extended release dosage forms?

The primary obstacle was evolution! Human GI tracts have evolved into very effective transit systems – if you eat something, it will be out of you in about a day. One way the body does this is through muscular compression waves that expel material from the stomach into the small intestine. Overcoming transit physiology requires dosage forms to be larger than the pylorus (the exit from the stomach) and have physical properties sufficient to withstand the compressive forces of the stomach. This is difficult to achieve, but essential if we are to develop a system that remains in the GI tract for long periods. Another challenge was to enable the dosage form to differentiate between stomach and small intestine; for example, by responding to alterations in pH, enzymatic profiles, or compressive forces. Exploiting these differences enables development of dosage forms that remain intact in one environment, but dissolve in another. Also, the GI environment itself raises challenges for extended release. It is difficult for drugs to remain stable for days or weeks at 37 degrees centigrade in very low pH and 100 percent humidity. The situation is further complicated by dietary diversity. It took a lot of work, and a multi-disciplinary team, to develop a dosage form that kept the drug stable in all such environments and released it in a controlled way.

What else might the future of drug delivery hold?

Other big challenges we are addressing include oral delivery of macromolecules, such as proteins. Protein therapeutics are digested after oral delivery and so are usually delivered via injection. Parenteral delivery, however, is associated with a significant delay in commencing treatment; for insulin, the delay between ideal and actual treatment initiation is about eight years! Delivery systems that don't require conventional needles could change how patients engage and comply with medication regimens. Hence, we are developing systems to circumvent this problem, such as a microneedle injection inside the GI tract, as well as ultrasound-mediated drug delivery to the GI wall or into the bloodstream.

We are also working on ingestible electronics. A swallowable capsule that could measure vital signs in real time would be valuable for individuals such as burn victims, where applying sensors to the skin may not be feasible. Currently, we can detect signals sent from within the GI tract and treat accordingly. Next, we will progress to ingestible closed-loop systems that monitor relevant parameters and automatically release medication as required.

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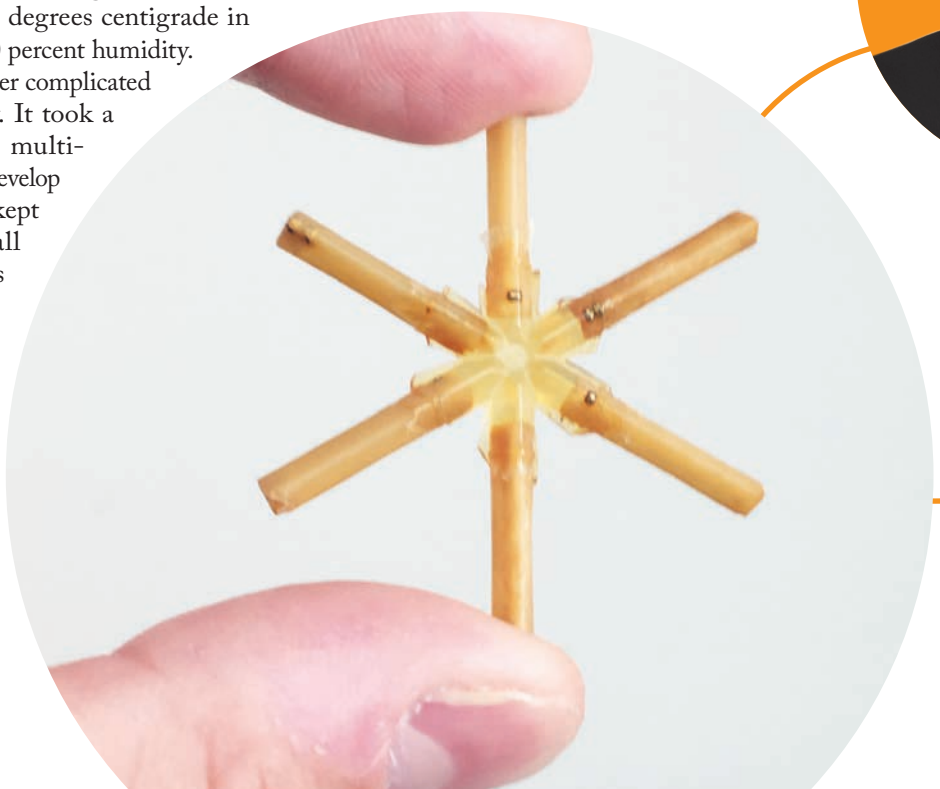


SEEING THE LIGHT

Optogenetics could lead to new ways of delivering drugs to the brain, central nervous system and spinal cord – and soluble circuits could have a role to play too

By John Rogers

For the last 15 years, my research group at Northwestern University has been applying materials science concepts to drug delivery applications. Our aim is to unlock the potential of functional electronic devices, such as sensors, by integrating them with the human body. This approach should enable functionality far beyond anything found in conventional electronic implants, such as cardiac pacemakers, but requires very sophisticated technology and manufacturing techniques.

In particular, my group has a strong focus on neuroscience. Since about 2010, we – along with colleagues at Washington University Medical School, St Louis – have been working on a device that uses light-emitting diodes (the size of individual neurons) that activate brain cells with light. Optogenetics – using light to stimulate targeted pathways in the brain – allows neuroscientists to identify and map brain circuits in behaviors from depression, to addiction, to anxiety and more, which could in turn lead to new treatments.

One of my group's focuses has been on improving the technology available for delivering light to the brain. When we started, the only option was a fiber optic telecommunication cable – a glass cylinder inserted into the brain so as to channel light to the neurons. This technique is invasive, damaging, and inconvenient as it physically tethers the subject to the light source. Our solution was to develop cellular-scale, battery-free, light-emitting diodes (LEDs) that can be embedded in the brain and wirelessly controlled. We mount the diodes on very thin, flexible plastic filaments that are much smaller and more biocompatible than fiber optic cables.

We are now extending our research to devices that can deliver drugs to targeted anatomical regions. Our recent paper demonstrates the advantages of combining our micro-scale LEDs with an ultra-miniaturized fluidics system fabricated from a flexible, biocompatible elastomer (1). This device allows us to deliver both drugs and light to optogenetically-controlled neurons, enabling

MAKE IT SO

How easy will it be to bring the new dosage form developed by Traverso and colleagues (page 21) to market? Lyndra, Inc. (Watertown, MA, USA) was formed to commercialize the gastro-resident system. Here, we catch up with Ray Knox (Senior Vice-President of Manufacturing) and Ellie McGuire (Head of Business Development) to hear about the company's recent progress.

What stage are you at with this innovation?

RK: We are starting human trials this fall. We've done extensive testing of our dosage form in both porcine and canine models – well over 300 animals in total. We can't release the animal data yet, but we anticipate using the information to support our first-in-human trial towards the end of this year. For our lead candidate, we will be pursuing a 505(B)(2) pathway.

What challenges has Lyndra faced?

EM: The main challenge faced by the inventors of this technology – Traverso, Langer, and Bellinger – was to achieve gastric residence and thereby permit ultra-sustained drug release. For a number of years, large companies have tried to solve the medication compliance issue by increased gastric residence. We've solved that problem in a new way, which was both our major challenge and our major achievement.

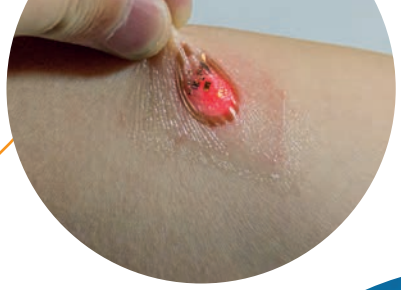
RK: That broad challenge was comprised of many smaller hurdles, like ensuring appropriate release kinetics over the duration of gastric residence. It required careful preformulation and formulation work to develop a blend of materials that will give us both the flexibility and tunability to achieve the desired target product profile for a range of compounds. It's always challenging to control sustained drug release in a variable environment like the stomach, but we are making progress. As this dosage form is novel, its manufacturing is a major area of focus for us; however, we do not anticipate any major manufacturing obstacles going forward.

Have you discussed your approach with regulators?

RK: Yes, the regulators love to get discussions going at an early stage! Certainly these conversations are ongoing, and they have been very positive, but we are still early in the process. Nevertheless, I can say that these preliminary discussions have not identified anything that would be a significant challenge from a clinical trial or drug approval perspective.

What commercialization strategy do you anticipate?

EM: We have a dual-track business model. We are developing internal product candidates, and at the same time we are working with strategic external partners. In addition, we are collaborating with several institutions, and we hope these efforts will lead to globally accessible products suitable for resource-poor countries.



simultaneous or sequential pharmacology and optogenetic control – in other words, we can study the neurological effects of new drugs at the point of delivery. This work was something of a technology milestone and is something the group is very proud of.

In the initial microfluidics embodiment, the drug reservoir is located in a helmet-like casing that fits on the head; from here, a thermal pump sends drug to the implanted microfluidic device. However, the thermal pumping mechanism is not ideal for temperature-sensitive APIs. We are now developing low temperature pumping mechanisms that are much more power-efficient and compact. This should allow integration of the pump and the drug reservoir in a single sub-dermal implant, enabling us to move away from the external helmet. We intend to deploy this triggered-release capability in the brain, spinal cord and peripheral nervous system.

Soluble circuits

A consequence of the size of our operation (my group includes 25-30 post-docs, 15 graduate students, 30-50 undergraduates, and maybe 12 visiting scientists), is that at any one time we're always pushing forward with multiple projects. Devices under development include skin-mounted appliances to continuously measure blood pressure, or to capture, transport, store and analyze sweat (to benefit exercise physiology). Another project involves a closed-loop feedback system such that a drug-containing device is autonomously triggered to release medication according to measurements it makes in the patient. The device sends data to a remote computer that carries out analytics and instructs the device to actuate the outlet and release the drug as appropriate. One near-term application for this device is bladder dysfunction.

One of our newest streams of research is "transient electronics" – biocompatible electronic systems that can dissolve in biofluids over a well-defined time period. It's the same concept as a bioresorbable suture, but applied to a fully integrated electronics system, comprising a power supply, radio transmission capabilities, an electrical stimulation capability, and sensors. One example is our intracranial pressure monitor for tracking the recovery of patients who have suffered traumatic brain injury (2). The device is implanted in the intracranial space. Normally, you would need secondary surgery to remove the device once the patient has recovered, but our device is simply resorbed over time. This notion of water-soluble electronics is very exciting; it could have applications not just in the biomedical field, but also in the environmental arena; for example, in helping to deal with the discarded electronics component of toxic waste streams. We are bringing this field forward very rapidly now.

Finally, in addition to needle-based fluidic systems, which deliver drugs by injection, we are developing devices with release valves that can be triggered to open as required – the drug is then released from a reservoir by diffusion. Again, these systems are wirelessly controlled, implantable and resorbable. Once the drug reservoir is empty, it is naturally eliminated.

In summary, the field has great potential and has picked up tremendous momentum. Many other groups are now getting involved, to the point where the concept of "bio-electronic medicines" is almost mainstream. Super-miniaturized, biocompatible devices allow you to treat disease in a way that is complementary to pharmacotherapy – think of devices that can interface with peripheral nerves to manage pain, or be applied to wounds to accelerate healing.

John Rogers is Louis Simpson and Kimberley Querry Professor of Materials Science and Engineering, Biomedical Engineering, Mechanical Engineering, Electrical Engineering and Computer Science, Chemistry and Neurological Surgery; and Director of Center of Bio-integrated Electronics Northwestern University, US.

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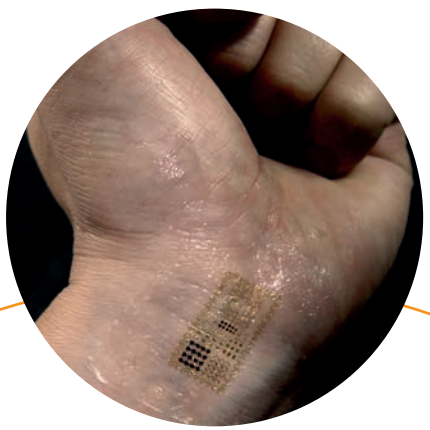

CAN A SPONGE COMBAT CANCER?

Mu Chiao, a professor in the Department of Mechanical Engineering at the University of British Columbia, Canada, has been leading an investigation to develop a powerless drug delivery device that can precisely control drug release on-demand. The result is Microspouter, which has shown promising results in the realm of controllable drug delivery for docetaxel (a drug in prostate, breast, and lung cancers) (1). "Although the pharma industry has done a fantastic job of developing new treatments and more efficient drug delivery methods, we can still do more, especially for cancer," says Ali Shademani, a PhD student working on the project with Chiao. "Current cancer treatments, such as chemotherapy, are expensive and involve frequent trips to the hospital. Patients would benefit from a smart, controllable drug delivery system that locally treats the cancer, while minimizing side effects."

Inspiration for the device came from a sponge. A sponge has the ability to store fluids and release them whenever squeezed. Microspouter is a magnetic sponge (comprising a reservoir, sponge, and membrane) that contains drug solutions within its porous structure. Applying an external magnetic field causes the sponge to shrink, deflecting the attached membrane inward and resulting in drug injection out of the reservoir, through the provided aperture on the membrane. The amount of shrinkage corresponds to the amount of release, which is adjustable by controlling the strength of the applied magnetic field. The aim would be to surgically implant the device in a patient and then pass a magnet (such as a commercially available strong magnet) over the skin to activate it.

According to Chiao and Shademani, other types of stimuli, such as electrical, laser or thermal, tend to have problems that restrict their usage inside body. For instance, electrical actuation demands power and a wired connection, and in thermal triggering body temperature could interfere with device performance. "A magnetic stimulus provides safe, remote, and powerless actuation – and we have also designed Microspouter to operate at a magnetic field strength range that is much greater than those generated by common electrical devices, such as smartphones and other everyday devices," says Shademani.

Magnets are also being investigated in a number of drug delivery projects. For example, some research teams are investigating the use of magnetic nano-particles (MNP) as drug carriers. The MNPs are coated with a drug, injected into the patient and subsequently guided by an external magnetic field towards the target (for example, a tumor) – but the challenge is generating a strong enough magnetic field gradient that enables the manipulation of MNPs inside the body.

As for Microspouter, many types of drugs should be compatible, although it will be preferable to use drugs with low solubility and lower effective dosages, such as docetaxel. "Furthermore, a nano-dosage of docetaxel is usually enough to sufficiently and dramatically impede cancer cell proliferation, which means the device is practically functional for a longer period and able to inject consistent drug dosages," adds Shademani.

Has the research team considered the potential cost of Microspouter in the real world? No, but they emphasize that it could help eliminate the costs associated with hospitalization and free up healthcare staff. "Patients can activate Microspouter at home with a magnet," says Shademani. "And the manufacturing process is relatively straightforward – large quantities may be achievable upon automation of the process."

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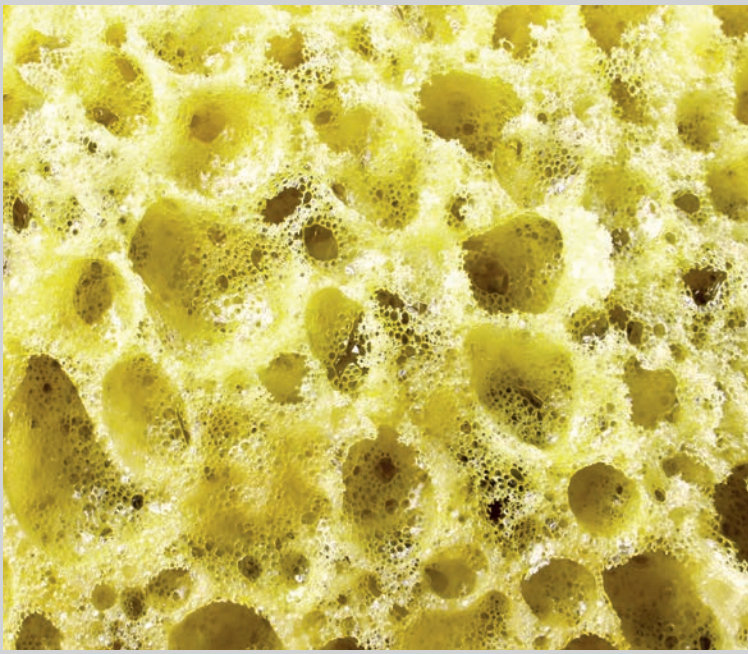

MICRO-SCALE MANUFACTURING

The big trend for small devices is carving inroads into drug delivery

One day in the late 1980s, Donna Bibber looked over the shoulder of a "mad scientist" colleague at Corning Life Sciences – he was working on lab-on-a-chip technology, and Bibber realized that it could be a game-changer. She is now Vice President of Isometric Micro Molding, which addresses the growing market need for expertise in device miniaturization. Isometric specializes in making and assembling tiny components, primarily for medical device companies. Some of the work is quite experimental – only around one approach in ten gets taken to the next level – and, as Bibber puts it, they have to "kiss a lot of frogs." Here, she divulges the current trends and challenges in the world of the production of micro-scale drug delivery devices.

What key changes and trends have you noted over your career?

Miniaturization is a very evident trend. During my 30 years in the industry, components have been getting progressively smaller and being made to ever tighter tolerances. At Isometric Micro Molding, a recent contract involved manufacture of plastic parts with a tolerance of single microns – which is crazy for injection-molded parts. We were able to execute the contract successfully because we had the necessary tooling – tooling is the true enabler for micro-device projects. You can't make highly miniaturized parts to 20 percent of permitted tolerance – regardless of absolute tolerance – without a robust injection mold.

As for application trends, I've observed growing interest in intraocular implants. One reason for this is an ageing population, but another is increasing recognition that the eye may be an avenue to treat the brain, as well as other parts of the body. Hence, many companies are examining the potential of ocular drug delivery for the treatment of neurological problems, such as Alzheimer's and Parkinson's, but drug delivery devices that are placed or implanted into the eye need to be as small as possible...

Is the miniaturization trend driven by cost or function?

It's a bit of both! For some materials, such as bioresorbable polymers, the driver is cost because those materials are very expensive – around $3,000 to $22,000 per pound. Similarly, polyether ether ketone (PEEK), which is broadly used in medical devices due to its strength, heat resistance and biocompatibility, is $400 to $600 per pound. These prices compare with dollars per pound for most plastics. In medical device manufacture, materials must be 100 percent virgin – you can't recycle the sprue, so it just gets thrown away.

Photo credit: Isometric Micro Molding, Inc.

For other devices, miniaturization is all about function. Drug delivery devices need to access tiny anatomical spaces in delicate tissues, often via a needle or a catheter. They must be flexible enough to travel through a narrow tube, but after implantation they must be strong enough to maintain function in a biological system. The polymer selection and physical properties are both critical in these cases.

How do you develop robust manufacturing processes for microscale devices?

Essentially, it's experimental design. You have a part with a particular specification, and you must identify the process variables that may affect how close you get to that specification. To find out which variable has the most impact, you vary each in turn during injection molding, and then compare the end-product with the specification. That enables you to tweak the process to ensure you consistently make parts within tolerance limits.

Key to this method is metrology – the measurement system. Comparing physical dimensions of dust-speck sized components is difficult. Most companies have metrology methods that compare a bunch of numbers on a page, which is non-intuitive and can require weeks of discussions between the manufacturer and the client. We do it differently; we use a CT scanner (which costs about three quarters of a million, so not a common asset) that generates 3D scans of each part, giving us an outline representation of the component, similar to a CAD model, called a point cloud. We overlay the point cloud on the original CAD model to compare the part we actually made to what we intended to make. It's very fast and very visual. The software gives us a color-coded deviation plot (purple for above tolerance and red for below tolerance) so we can see exactly where and how the part deviates from the intended dimensions. Then we simply adjust the process accordingly.

Thirty years ago, I would have been delighted if we achieved a tolerance of plus or minus 20 microns, but today we are making components with three-micron features. This is very important

because medical devices address critical applications, and the smallest part in an assembly is usually the bit that actually enables the device, so it's vital to get it right.

Another challenge to contend with during the manufacture of highly miniaturized parts is the effect of static. Once, when we were making some particularly small components – five hundred of them in a single pellet, each component being the size of a grain of salt – we had collected them in a plastic test tube. Inside this tube, the micro-components were dancing around, due to static. When the gentleman who was collecting them bent over the tube, the whole batch – hundreds of components – shot out of the tube and onto his head! Our entire day's production disappeared into his hair! We can laugh now, but at the time it wasn't funny at all. But it did help us to appreciate the importance of static electricity in micro-manufacturing. Our entire set-up is now a static free environment with deionized air, grounding straps and grounding rods. We even put in rubberized flooring with electrostatic properties, and the clean room walls are covered with electrostatic paint. We learnt our lesson well!

What are the challenges associated with manufacturing drug-device combinations?

The main challenge relates to tolerances. Imagine you are delivering drug through a tube; it is amazing how quickly the tolerances over the length of the tube stack up to cause significant dosing error, even if they are only plus or minus five microns. It's the same with valves. Valves the size of dust specks may have apertures of 20 microns, and you must meet the tolerance for these to enable accurate function. The tools can take up, say, 20 percent of the permitted tolerance, the press can use up another 20 percent, the measuring process can take up another percentage, and so on.

What exciting early stage technologies are you seeing?

There are so many, but if I had to pick, I'd say that the two fields of most interest are novel materials and 3D printing. Novel materials may permit all kinds of new functionality; however, if there is no predicate device for the new material then any device based on it may have to follow a more rigorous regulatory pathway (but that's another subject). 3D printing is also exciting, but isn't yet at the stage where it can make parts to micron-scale tolerances, and there still aren't many materials that are compatible with 3D printers. Nevertheless, I expect it to develop into a major enabling technology; it's already being used, albeit to make the molds rather than the parts themselves. If you combine new materials with 3D printing, it will also open up the field of biomimicry, such as the construction of artificial organs.

MAGNETIC ATTRACTION

What's the difference between a bacterium and a nanorobot? For solid tumor therapy, not that much, according to Sylvain Martel, Professor of Nanorobotics Laboratory in the Department of Computer Engineering, Polytechnique Montreal, Canada. Martel and his colleagues aim to take on solid tumors with magnetic fields and bacteria to deliver cancer drugs (1). Here, we present a summary of the work.

- Surgery may be impossible for some solid tumors; in these cases, treatment options may be limited to pharmacotherapy. But systemic administration is typically associated with side-effects. Worse, the drug may not reach the deep, hypoxic regions of tumors in quantities sufficient for a therapeutic effect.
- Autonomous drug-loaded vehicles that transport and release drug within the hypoxic region of the tumor could circumvent this problem. But tumor ingress is size-limited (2 microns or less), which makes nanorobots at this scale impractical, especially considering the functionality they would require for locating and penetrating tumors, and for transporting and releasing drugs.
- Bacteria could provide an answer: some species, such as Magnetococcus marinus, have evolved to seek low oxygen levels, and can be engineered to carry drug-loaded nanoliposomes on their surface. Furthermore, M. marinus strain MC-1 contains magnetic iron-oxide nanocrystals and consequently tends to swim along magnetic field lines. Drug-loaded MC-1 bacteria can be directed towards tumors by application of an external magnetic field, and once inside the tumor, autonomously seek hypoxic regions.
- The strategy can result in around 55 percent of injected drug reaching the tumor as compared with one to two percent with conventional systemic injection, and therefore would be expected to enhance the therapeutic effects and decrease side effects as compared with systemic pharmacotherapy (1).

Martel's approach to using bacteria as drug mules is expected to soon enter primate models, but initially it was seen as "science fiction". One of the most difficult challenges of the work has been changing people's mentality. Martel says, "Why does robotics have to be all about plastic and metal components? Why can't we use biological components in medical nanorobotics?"

Reference

1. *O Felfoul, et al., "Magneto-aerotactic bacteria deliver drug-containing nanoliposomes to tumour hypoxic regions", Nature Nanotechnology, 11, 941-947 (2016). PMID: 27525475*

Solving the Capacity Conundrum

Given pharma's new reality of niche products and diversified pipelines, flexibility is key – and modular technologies can go a long way to easing capacity dilemmas.

By Jan Makela

Over the past 20 years, the industry has moved away from traditional small molecules and embraced biopharmaceuticals. Today, large molecules make up around a quarter of the entire drug industry – more than $200 billion in global sales – with the sector growing at nearly 10 percent per year. In addition, seven of the top 10 best-selling drugs currently on the market are large molecules. Some companies, however, have struggled to keep up with the demand for these complex medicines, with growth often exceeding planned manufacturing capacity. Outsourcing the required surplus capacity is one obvious solution, but the price of working with contract manufacturing organizations continues to rise as demand increases.

Making capacity decisions is a tricky business. Stainless steel plants typically cost around $300-600 million, and take two or three years to build. Once you have reached the end of phase III and been awarded your marketing authorization, do you really want to waste the next few years building a plant? On the other hand, if you begin construction during a phase I trial you need to bear in mind that there's a 90 percent chance that the drug won't make it to market – leaving you stuck with a plant you can't use. Even assuming your drug does make it to market, you won't know what your sales volumes will be, when, years before approval, you decide on what sized plant to build. Underestimate demand and you'll have to use a contract manufacturer; overestimate and you'll be forced to saddle the cost of an underused plant.

Building for biopharma

One way to reduce the risk of making an incorrect capacity decision is to shorten the lead time. Being able to decide whether or not to build your plant later in the clinical trials process would clearly increase the chances of making the right investment decisions around demand. The primary problem with stainless steel plants, however, is that everything must be built sequentially: the engineering must be done on site, then the utilities have to go in, followed by the stainless steel tanks, which also need to be tested on site.

There is now growing recognition in the industry of the benefits of flexible and modular approaches to facility construction. With a modular approach, it's possible to carry out tasks in parallel. For example, with our KUBio factories (see sidebar: The Russian Doll Approach), we build and test the single-use plant in another location whilst the company prepares the site. Then, we ship the portable modules over once ready. The ability to make the separate elements at the same time significantly reduces construction time, allowing companies to decide later in the clinical trials process when to add capacity, and how much capacity to add.

The flexible approach lends itself particularly well to the types of drugs currently in pharma pipelines. Over the past two decades, medicines – particularly large molecules – have become increasingly targeted to smaller patient populations. In the past, pharma companies would produce tons of their blockbuster drug to meet global demand, but today, many new molecules in development only require 500 kilos per year.

On top of the growth in large molecule drugs, we're also seeing more cell and gene therapies edging closer to market, which have even smaller patient populations. Some companies are developing truly personalized approaches, where they take a patient's blood to a production facility, separate the cells from the blood, modify, grow and purify them, before finally injecting them back into the patient. These kinds of therapies require individual production lines for each individual patient; in other words, many tiny batches run in parallel.

As the industry moves towards targeted biopharmaceuticals – including personalized cell and gene therapies – companies may need to consider moving away from stainless steel plants. Let's say a company has 10 candidate large molecules in clinical trials, with expected demand of 500–1000 kg/year each. If the firm is set on stainless steel, they will have to consider whether to build four separate 20,000 liter plants, or one big plant. If three of the 10 drugs pass phase III, each at one ton/year, they'll have to contend with huge changeover times. If six of the

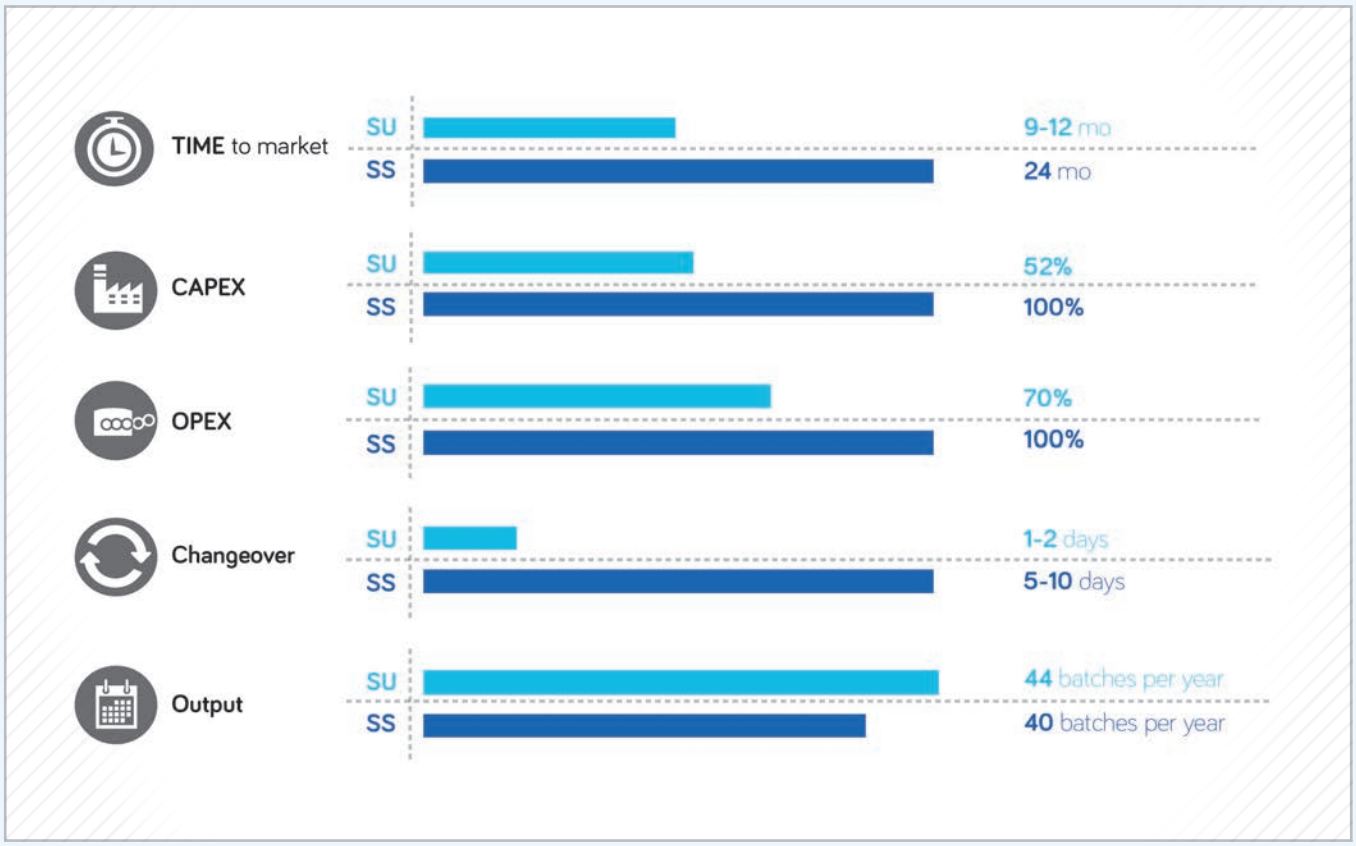

Figure 1. Single use versus stainless steel.

10 are approved, the company would not have the capacity to produce the drugs. In short, it's clear that stainless steel plants are geared towards making tons of drug substance per year rather than smaller volumes and target populations, which tend to require flexibility.

Another key challenge for biopharma companies is the management of Net Present Value (NPV). With the long timelines associated with stainless steel, companies need to be patient as they wait for sales to come in. But if sales aren't as good as hoped, or if drugs fail before approval, NPV can turn negative – a massive turnoff for investors. Modular, single use technology reduces the investment costs and decreases the time from investment to launch, thereby reducing the risk of a negative NPV. Investments can be repurposed depending on whether or not drugs pass or fail, and it's relatively easy to build another plant, in parallel, if a drug happens to take off.

Some companies have been quicker than others at "dipping their toes" into flexible manufacturing, but it is only during the past 10 years or so that the productivity of processes has sufficiently improved to make single use viable. In the past, titer would be around half a gram per liter, but today they are closer to 5 grams per liter – reducing the size of the bioreactors by a factor of 10. Smaller bioreactors have made single-use bags more viable, which in turn has sped up the cleaning process. Today, there are 100 stainless steel production facilities in the world and around 80 single use production facilities. Of course, the single use facilities tend to be smaller, but there is a clearly established footprint.

Moving to modular

For companies thinking of using flexible manufacturing technology, there are a number of factors to consider. Two key aspects are the range of drug substance volume and the complexity of the pipeline; if a company has multiple drugs at early stages, at uncertain volumes, then a more modular, single use approach is sensible. Again, if a company has a cell line expressing more than five grams per liter, they should consider single use. Single use systems can generate the same protein mass with a smaller production footprint, enhancing process economics. GE Healthcare

The Russian Doll Approach

FlexFactory

FlexFactory is a bioprocess platform using predominantly single-use technology – comprised of 100 to 200 individual pieces of hardware. FlexFactory is built into an existing process, with process control. The aim is to allow companies that want to add capacity to do so, provided they have cleanroom space available.

KUBio

KUBio is a cGMP-compliant facility that includes a FlexFactory bioprocess platform for the production of monoclonal antibodies. Whilst the company is adding the groundwork, foundations, pipes and so on for a new facility, we build the KUBio plant in parallel, in another location. We assemble and test the whole factory, with all the air handling, and then we disassemble and ship it in modular containers to the site. In a third location, we also build the FlexFactory, which arrives at the same time as the KUBio – when the site is ready.

BioPark

Although a KUBio is a production plant, it still requires some support services, such as a quality control lab, offices, a warehouse, a water supply and so on. Customers often have to build these things next to the KUBio. In 2016, we announced that we would be setting up a BioPark in Cork, Ireland. The aim is to allow different KUBio customers in nearby locations to share certain services. We are building a site in Cork on which four KUBios can be supported. The customer will buy their own KUBio, with their process, people, IT systems, security, and so on, but the support buildings are shared facilities run by GE – for which customers pay a fee. Working with the IDA and Cork County Council, we've announced 150 million euros of investment and are currently towards the end of the planning approval stages.

differentiates itself by being able to design the whole production process. Rather than buying different bits of hardware – the bioreactor, column, filtration unit, and so on – we take over the process and deliver a standard design. We manage the production line as well as the automation. Overall, it's a less engineering-resource heavy approach, and also faster because we have a standard configurable production line, which we call a FlexFactory (see sidebar: The Russian Doll Approach). If a company buys multiple FlexFactories, they can use the same production line in multiple locations. Firms also have the same IT control systems, the same physical process, and the same contact surfaces, making it easier to move drugs between sites or to add a second site to manufacture the same drug. And that introduces another advantage to single use technology – two drugs can be put down the same line because changeover between drugs can be done with a single use bag. If a company runs two drugs simultaneously, and if one takes off, then it's easy to dedicate a second line to that same drug because the line and control technology is identical.

A flexible future?

Although there's a vast number of large molecules in the pipeline with forecast demand at <500 kilos, blockbuster molecules in the pipeline, small molecules are not going away – there still remains an underlying base of blockbusters, and for these drugs, stainless steel will continue to be the way forward for the foreseeable future. For drugs with demand of one-plus tons of substance per year – even with new single-use processes and higher process yields – stainless steel is still the lower cost option.

"All of this suggests that the demand for capacity will continue to grow."

But as for the future of flexible manufacturing? The indications we see at GE Healthcare are very strong. Today, around 70 to 80 percent of large molecules are used by patients in the West, which translates to a huge unmet need in countries, such as India, China and other developing markets. Investment into local production in those markets is rapidly increasing, with biosimilars, as well as a strong pipeline of new molecules. All of this suggests that the demand for capacity will continue to grow. Flexible manufacturing can help companies build this capacity more quickly and with lower risk when compared with a stainless steel approach.

Jan Makela is General Manager, Bioprocess, at GE Healthcare Life Sciences.

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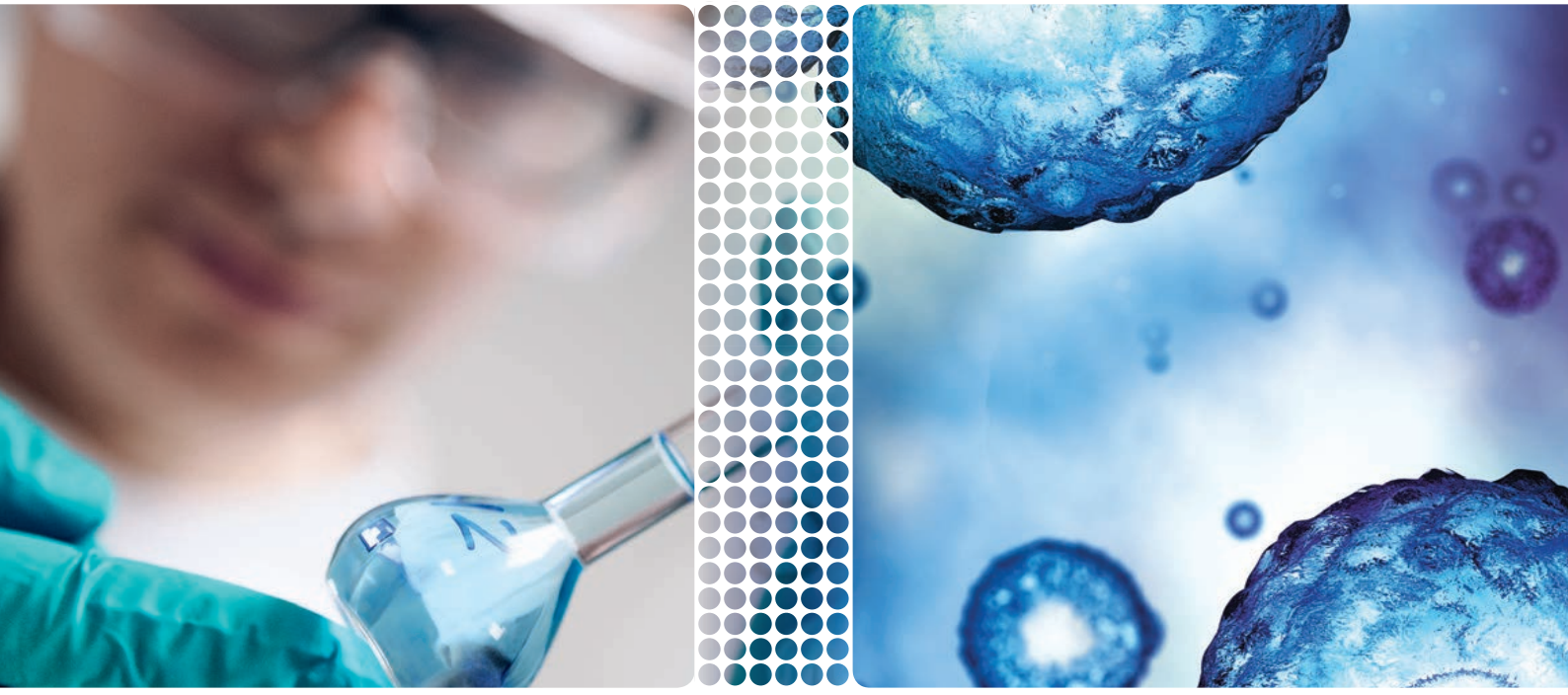

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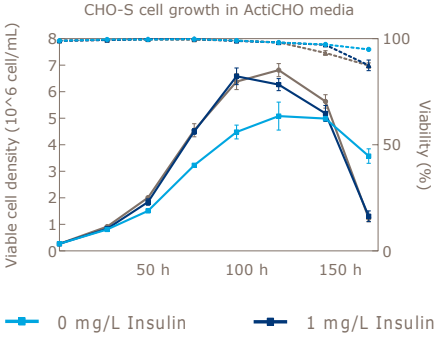

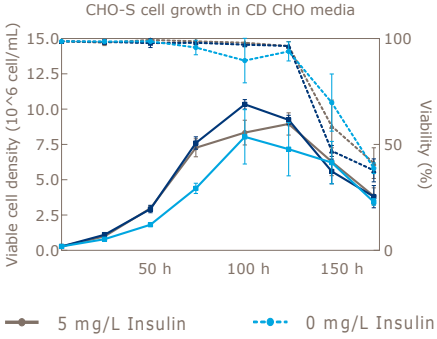

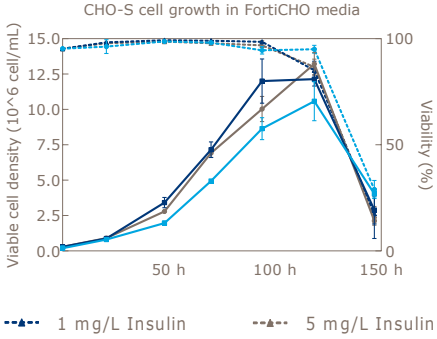

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Business

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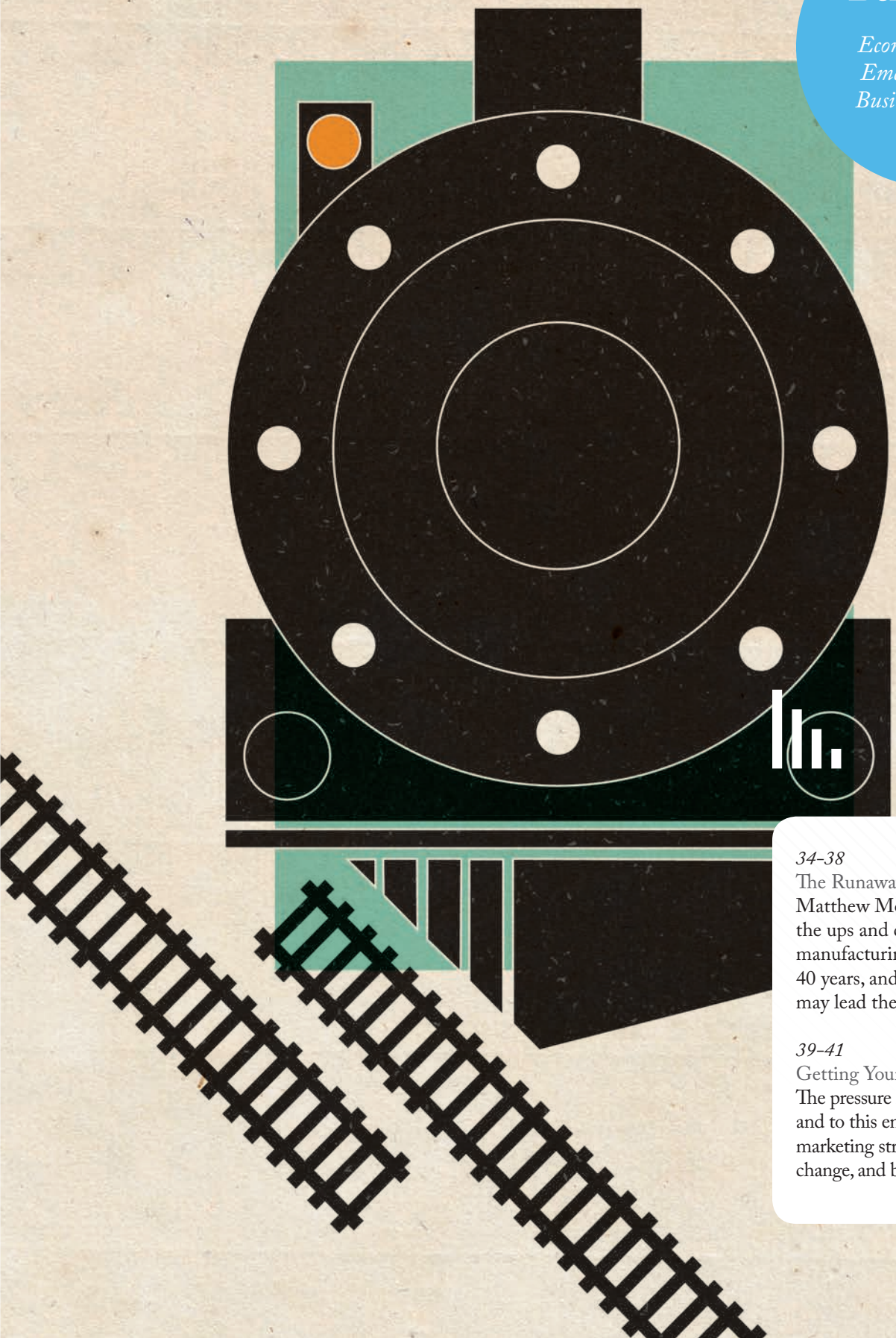
Business strategies



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The Runaway Outsourcing Train
Matthew Moorcroft covers the ups and downs of contract manufacturing trends over the last 40 years, and asks where the tracks may lead the industry next.

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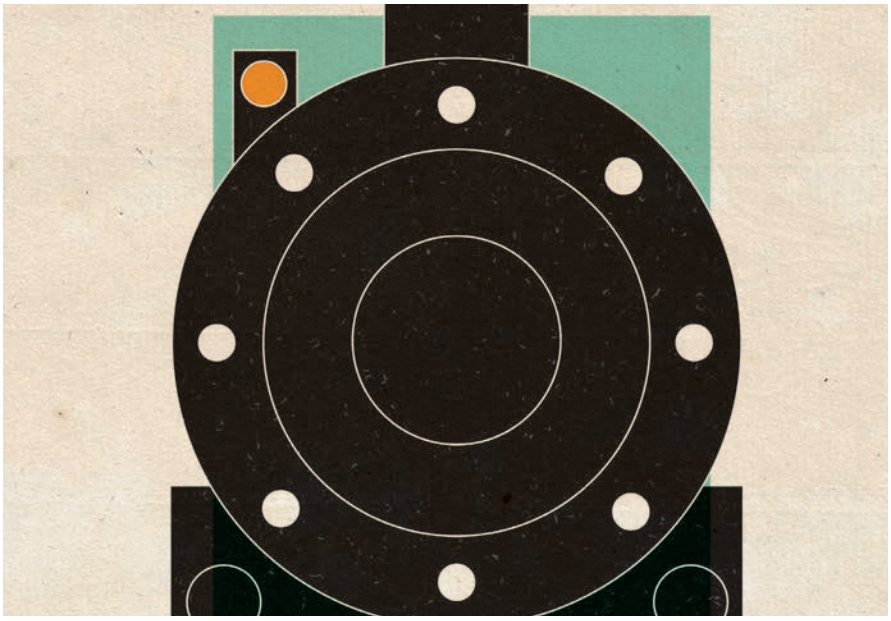
Getting Your Skates On
The pressure is on to reduce costs – and to this end the industry needs new marketing strategies, a willingness to change, and buy in from leadership.

The Runaway Outsourcing Train

What can we learn about outsourcing trends from contract manufacturers' bumpy ride over the last 40 years?

By Matthew Moorcroft



How many contract manufacturing organizations (CMOs) are operating in the pharma industry today? There are far too many to name – and outsourcing is now such an important part of pharma manufacturing that it's hard to imagine a time when there were just a few CMOs. Back in the early days of pharma outsourcing, the role of CMOs was to undertake specialized or hazardous chemistries that pharma companies were unable (or unwilling) to carry out themselves. Tracing the development of the outsourcing sector becomes more difficult the further back in time you go because of the lack of reliable data points, but learning about the history of the industry is always a fascinating exercise. Reflecting on the success stories – and mistakes – of the past can be very useful in guiding decisions about the future. To this end, my colleagues and I have been studying the changes in supply and demand in outsourcing of small-molecule drug manufacturing that have occurred since the 1970s (1).

Unraveling the winding track

After World War II, there was flurry of activity in drug discovery, including antibiotics, antihypertensives and oral contraceptives. As for contract manufacturing, this began to take off in the mid-1970s, with the emergence of blockbuster drugs and big profits. Some of the earliest blockbusters to involve outsourcing were Tagamet (cimetidine) and Zantac (ranidine), which both needed difficult sulfur chemistry. Ranidine was an unexpected success; initial forecasts of 10 metric tons quickly jumped to 900 metric tons. Demand also outstripped supply for a number of antibiotics.

It was a booming time for the industry and demand for extra capacity and services continued to grow until the mid-90s, boosted by the Hatch-Waxman Act and the consequent rise in consumption of generic products as prices eroded. Further expansion in outsourcing followed as the BRIC countries – Brazil, Russia, India and China – emerged as growing consumers for prescription drugs. In the last decade, demand for the manufacture of small-molecule drugs has continued to increase – the result of patent expiries and a surge in new drug launches. Figure 1 shows the rise in demand for small molecule manufacture from less than 25,000,000 kg in 1976 to well over 300,000,000 kg in 2015 – an increase of more than 1100 percent.

The number of approvals of new chemical entities (NCEs) in the US adds to the demand picture. In the 1970s and 1980s, the number of launches ran anywhere from 10 to 30 new drugs per year, speeding up towards the launch of blockbusters in 1990s. There was a peak in 1996/97, which was attributable to administration issues, followed by a notable decline in the early years of the new century, as a result of cost-cutting among big pharma and a switch to more complex modalities, such as recombinant proteins and monoclonal antibodies. Approvals picked up again in the mid-2000s because of greater demand for orphan therapies and the introduction of expedited approval processes in the US.

The first crop of truly pioneering CMOs – as opposed to extensions of big pharma manufacturing sites – appeared in the UK, Europe and the US in the 1960s and 70s, and then from the 1980s to 2000, there was an upsurge in CMO entrants in the US and Europe, largely made up of generic API manufacturers and those eager to join in what they perceived as a lucrative market. The upsurge was followed by the entry of large numbers of new CMOs from India and China from 2000 to 2010. Figure 2 shows just how the number of CMO entrants has changed since the 1930s.

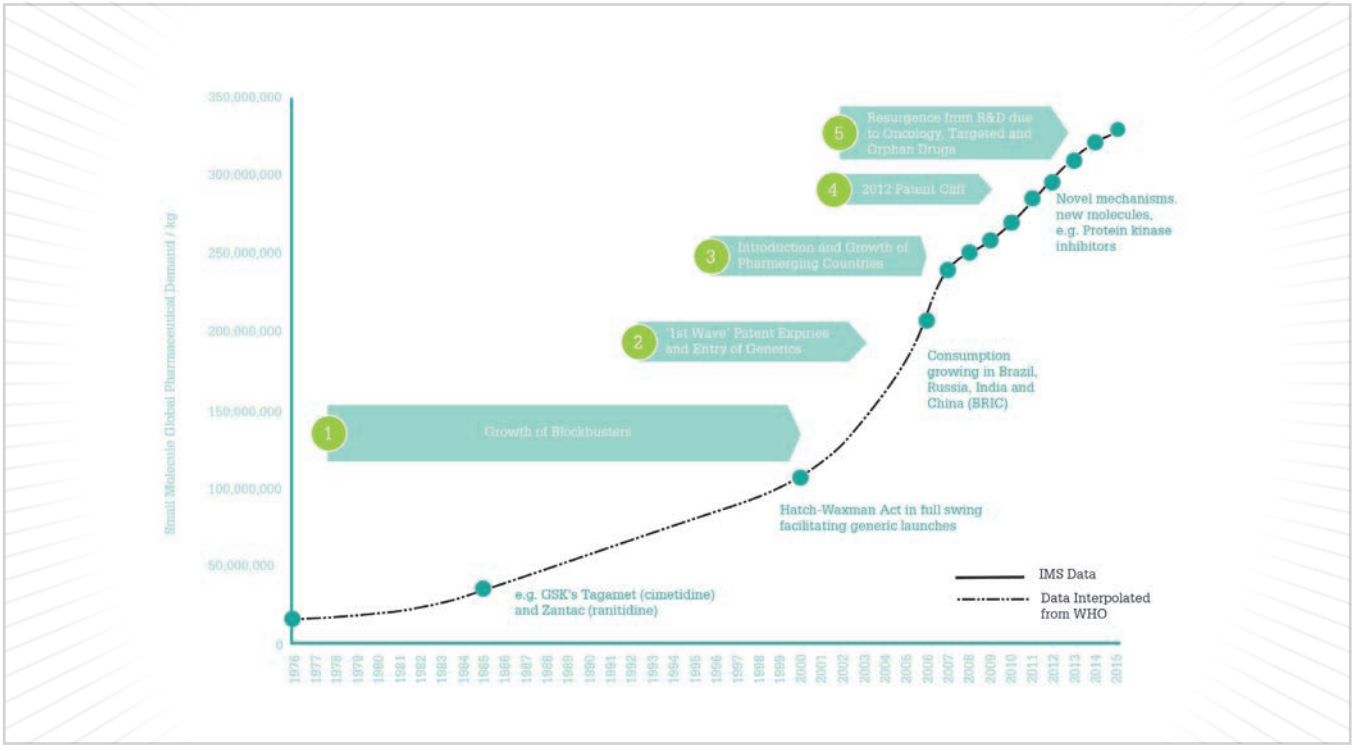


Figure 1. Volume demand for small-molecule prescription pharmaceuticals (API).

Early growth to gold rush

As part of our research, we spoke to a number of industry experts, together representing cumulative experience in the sector of more than 330 years (see page 36 for more study details). Essentially, there have been four distinct phases in the CMO industry.

In the early years (pre-1975 to 1980), CMOs were very much technical specialists, often manufacturing intermediates rather than APIs. One of the experts we spoke to explained, "Outsourcing to CMOs was often driven by the need to handle dangerous or difficult chemistries, such as sulfur chemistry, brominations or phosgenations. The early CMOs had often developed these specialties outside of the pharma industry. Large pharmaceutical companies did not want to handle the Safety, Health and Environment (SHE) risk of such chemistry at their large, expensive manufacturing plants, so it led to the use of off-site suppliers. Typically, this would be for a single chemical step, often for an intermediate in the process and often many steps away from the final API."

From 1980 until 1996, there was then something of a "gold rush" in the market – the growth years – fueled by a shortage of capacity in the booming pharma industry. Large R&D budgets and expectations of a rapid growth in NCE approvals led to the birth of strategic outsourcing, characterized by bidding wars, and a race to the top for NCE launches. Many CMOs became involved in multiple-step synthesis and some even started producing their own APIs. Meanwhile, quality audits were relatively lax compared to today's standards, which further boosted entries into the sector. Here are some interesting comments from the experts we spoke to about this era:

- "Despite the fact that CMOs were recognized as technology specialists, they previously only focused on a single chemical step before sending the molecule back to the pharmaceutical customer for additional chemistry to the API. This era was the start of multi-step synthesis in CMOs and, before long, a handful of companies were adopting the same business model."
- "The large barriers to entry – such as access to capital, know-how and engineers – meant that in the early days only a handful of CMOs could offer this. However, as the lucrativeness of the approach became obvious to all, the floodgates soon opened."
- "Pharmaceutical CEOs were embroiled in a heated battle and a race to out-bid each other, bidding up the number of NCEs they were

About the Study

Research phase
- 500-600 hours of research to decide which data to discount (e.g., due to poor value)
- Mining of data from 20 existing databases (commercial and in-house)
- Refine in focus to data that could help explain supply and demand elements of the industry, without excessive ambiguity

Data sources
- Cambrex
- QuintilesIMS
- Peter Pollak
- FDA
- Jan Ramakers Fine chemical consulting Group
- Newport (Thomson Reuters)
- World Health Organization
- Nice Insight

Experts spoken to
- Simon Edwards, VP, Global sales & Marketing, Cambrex
- Kent Kent, Senior Director, Chemical Manufacturing, Gilead
- Paolo Russolo, President, Cambrex Profarmaco Milano
- Peter Lyford, Commodity Director, GlaxoSmithKline
- Carl Johansson, Global Director, Proprietary Products, Cambrex
- Dix Weaver, Consultant, Weavchem LLC
- Jan Ramakers, Consultant, FCCG
- Rob Miotke, Consultant, Advantage Pharma Solutions LLC
- Jim Miller, president, PharmSource
- Steven Cray, Director, Supplier Relationship Management, Shire

Special mention

Dr Peter Pollak

Dr Pollak was recognized as one of the pioneers of the pharmaceutical fine chemistry industry. He was active in the industry from 1968 until 2016.

forecasting launches per year. This created a feeding frenzy for the industry. Analysts were giving super high valuations for pharmaceutical companies as well as predicting a boom period for CMOs. Some banks and analysts even authored reports claiming that the CMO market could expect 15 to 20 percent growth for the next decade based on the success of R&D in pharmaceutical companies."

1996 to 2010 saw a highly competitive period in the industry. Expiration of patents led to price erosion and growth in generics. Consolidation in the industry resulted in rationalization and cost-cutting as a result of loss of exclusivity. And some pharma companies took the calculated gamble of choosing price over quality, with many CMOs in the US and Europe losing business to India and China. There was a shift away from custom synthesis to toll manufacturing, and the ingenuity and expertise of the CMO was taken out of the equation, making price the only point of differentiation. It's fair to say that many western CMOs were not prepared for the rapid change in business and found it hard to compete. Experts told us:

- "The entrance of China and India into the CMO industry was largely facilitated by the need for these companies to supply domestic manufacturing for their own drug industries. The majority of them had drug products launched in their local markets and used their captive manufacturing assets to supply APIs into these generic brands. When they faced excess capacity due to peaks and troughs in drug product demand, they turned their captive manufacturing towards the open market and offered API manufacturing on a CMO basis."
- "The effect of this increase in competition from low-cost countries such as India and China led to differentiation based purely on price. And the Indian companies had the advantage that they were keeping their plants at a base load of capacity with generics when needed. Whether it was this, or the lower expectation on return on capital or lower labor costs, or a combination, it soon became difficult for western suppliers to compete when Big Pharma just went on the hunt for lower prices. As a result, pharmaceutical companies would often adopt a dual continent sourcing strategy between western and eastern CMOs, whilst being aggressive on low pricing."
- "A handful of big pharma companies led the way during the 2000s in the 'race to the bottom' where they were looking to make cost savings from their supply base (to help fund recent M&As). Whilst quality was not considered equal amongst CMOs, they were willing to take a risk on the API quality if it led to a 20 to 30 percent reduction in price. From a political standpoint, it was easier to focus on the short-term corporate

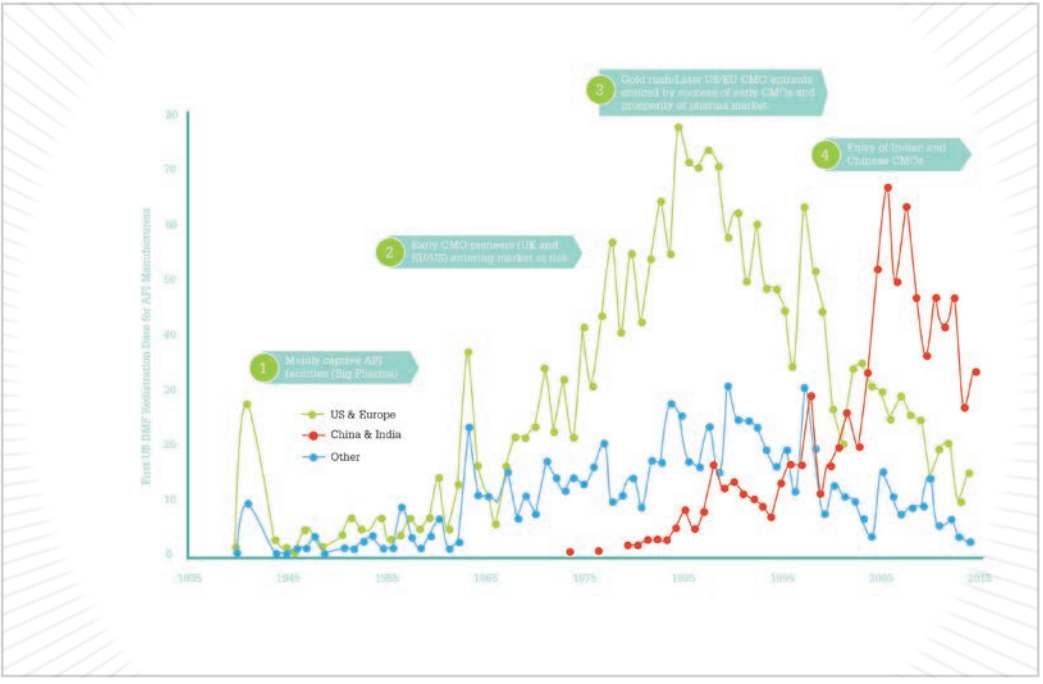


Figure 2. Entrance of API manufacturers by region.

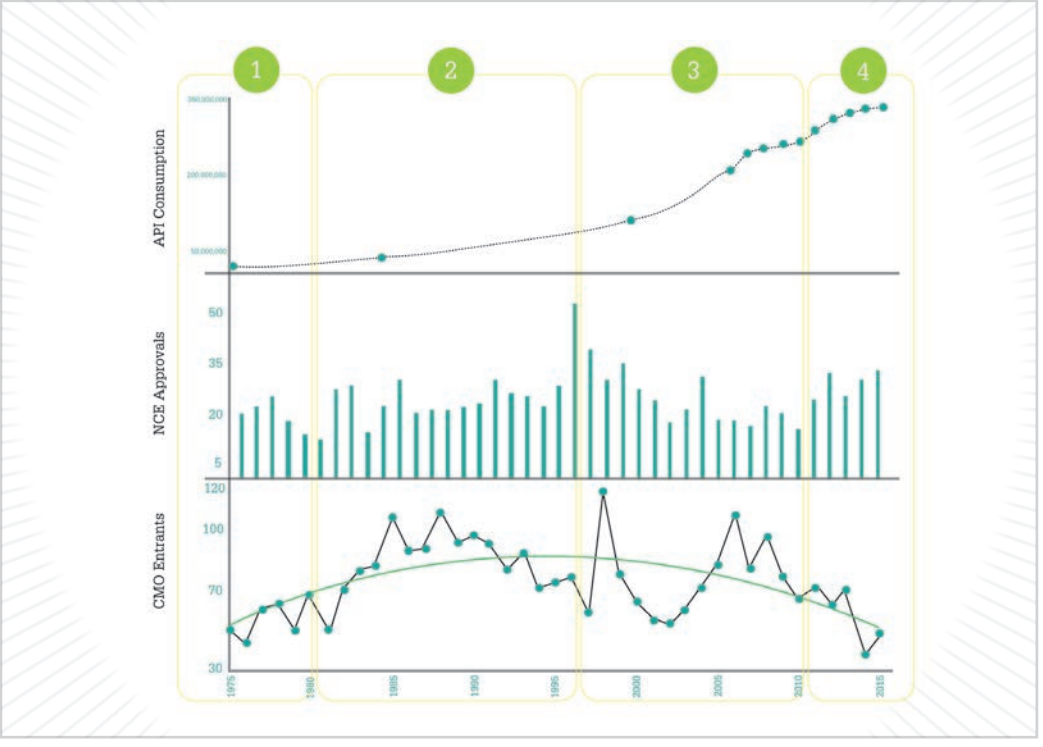


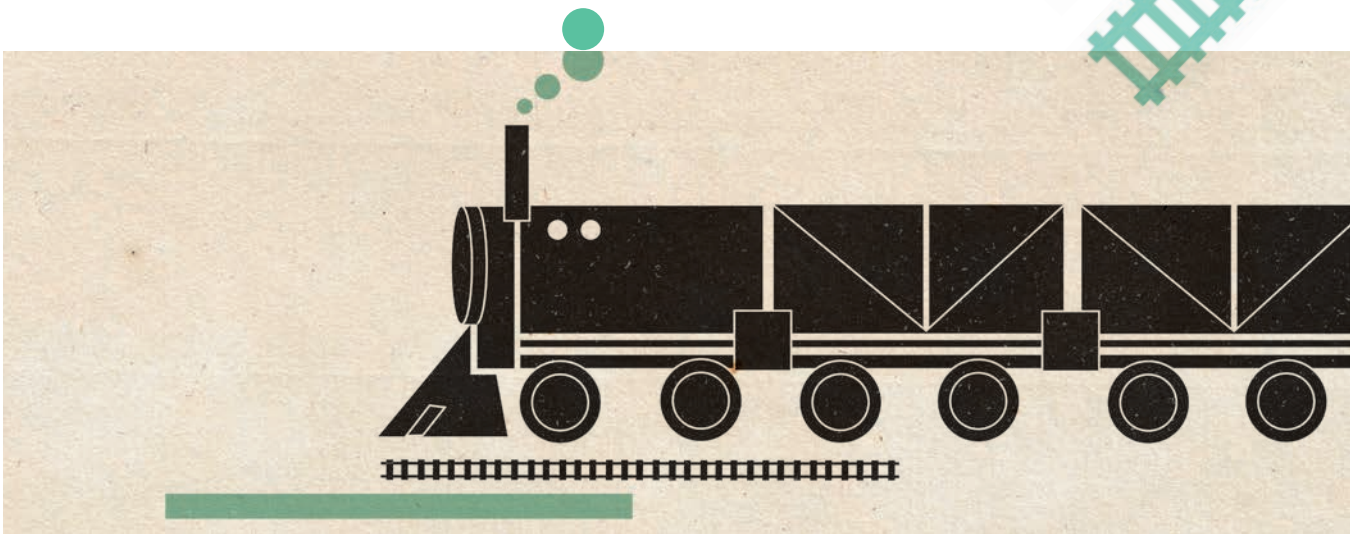
Figure 3. A supply and demand model highlighting four distinct stages of activity. The numbers of CMO entrants (supply side) is shown in comparison to the NCE approvals and pharmaceutical drug consumption data (demand side).

cost-saving targets then to worry about the longer-term issues of quality (and the ultimate problems in the supply chain it would and did create)."

- "Given that the API makes up a small fraction of the total product cost – did it really make a difference? No, not really! It only affected certain mature products where the API and the tablet costs were a bigger fraction of the price, such as large volume CV products. However, on NCEs and respiratory products, achieving a lower API cost did not make a big difference at all. We knew this and the company knew this, but everyone was geared up to a 'sheep dip' approach where everyone had to be seen to be achieving cost savings whether it made a difference or not."

Today's outlook

Some western CMOs went out of business in this time. Others battened down the hatches or adopted new business strategies. Fortunately, since 2010, things have started to look up for western CMOs, with the sector enjoying what I like to call the "resurgent years". The increasing availability and access of medicines to patients, as well as large numbers of patent expirations, have ensured a steady increase in drug consumption, accompanied by rising NCE approvals. At the same time, rising labor costs in China and India have made outsourcing to these countries less attractive, and some sourcing decisions are now being unpicked and work repatriated to the US and Europe. Pharmaceutical companies are now divesting and closing some mature API plants, and with the number of new entrants to the CMO market falling, there is high demand in the US and Europe for outsourcing partners with the right capacity. Because the market



is still heavily fragmented, many of the high quality CMOs have filled their capacity and there are substantial lead times for new projects. Experts said:

- "Some smart thinking Western-based CMOs have kept pace with changing customer demands and requirements, whether this is based on changing product forecasts or a required flexibility from manufacturing scale and assets. Having a finger on the pulse from a market intelligence – 'what's next' – perspective allows them to be ahead of the curve."
- "Whilst from a technology and capability perspective, there is not much differentiation between Western and Indian/Chinese CMOs – they all have a similar expertize in chemistry, such as high potency, similar plants, similar assets, etc. – there is a big difference in management and leadership style. Western CMOs typically have stronger management teams and people who can adapt to customer requirements and be less rigid to work with."
- "During the previous decade, many procurement teams had made poor sourcing decisions in the use of Indian and Chinese CMOs. They had outsourced the wrong molecules to the wrong CMOs and created problems in the supply chain. Presumably this was during the 'race to the bottom' period."
- "A lot more of the US and EU-based CMOs are now full when compared to the period pre-2010. The market is a lot tighter for high-quality CMOs. For these CMOs, there is no capacity available before 6 months. Even after 6 months, only 10 percent have available capacity. That said, despite the resurgence, some have accumulated a high debt-to-EBITDA ratio, which they need to service/pay off. This is a worry to any customer using them given the possibility of cash-flow issues or even insolvency."

"Many of the high-quality CMOs have filled their capacity and there are substantial lead times for new projects."

We can learn a lot from history; reflecting on the successes and mistakes of the past can help guide us in the future. So what comes next for the CMO sector? In the June issue of The Medicine Maker, I'll be looking at how the trends of the past 40 years are influencing current developments in the industry and what trends we can expect in the lead up to 2020. As a preview, here are some of the trends we expect:

- Increasing consumption – the trend towards smaller volumes of API manufacture will by offset by the trend for more people to continue to take more medicine.
- Steady innovation – chemistry and small molecules will continue to be the backbone of the pharma industry.
- Dynamic CMO space – CMOs will continue to evolve. We will also continue to see shake-out of under-performing CMOs, as well as sustained merger and acquisition activity.

Matthew Moorcroft is Vice President at Cambrex, New Jersey, US.

Reference

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Getting Your Skates On

In a price-challenged environment, the successful companies are the ones that embrace change and new marketing strategies. But without leadership on board, efforts will be in vain.

By Phil Matton

I've spent most of my career in marketing and commercial strategy – most recently at AstraZeneca (AZ) where, as Vice President of International Projects, I was involved in helping the company divest older brands to focus on more specialty care brands in three core therapy areas. Before that, I spent time in China as the VP of Commercial Strategy & Excellence, where I developed a real passion for new business models and finding ways to make pharma move more quickly. China is a very competitive market – if you stand still someone else will quickly knock you aside, so you need to "scale fast and partner to win".

I'd been thinking about starting my own strategic consultancy for a number of years. And recently I did just that, with SPiCE Healthcare. I'm passionate about helping companies transition to new business models that create more value for our customers and the company; in particular, relying less on the traditional sales rep model by introducing new ways of working with online telecommunications, new service channels and the integration of digital technologies to create a better customer and patient experience. This is something I discussed recently in Barcelona at eyeforpharma 2017. New digital channel approaches are already being used extensively in other industries, but there is a long way to go in pharma.

Specialties, skills and strategies

Introducing new, innovative thinking in the traditionally conservative and slow-moving pharma industry can be difficult – especially given issues around pricing. As the industry comes under increasing pressure to reduce drug prices, resource allocation problems are bound to grow, which will encourage (or force) the adoption and integration of new technologies – or new ways of selling and marketing. I often see companies that want to maintain all their old brands, while also needing significant budget to launch new ones. There's a clear challenge here, and it's one that is compounded by the fact that the industry is undergoing a significant shift; more and more new drug releases are niche, specialty pharmaceuticals that cater to a small subset of the population. The launch of such drugs requires a different set of capabilities, including new medical and marketing skills.

Year-on-year, the FDA approves a higher proportion of specialty drugs, with a large amount of sales coming from the US. However, it's well accepted that the healthcare population is shifting towards emerging markets – these nations have many more unmet needs and will not be able to afford to pay for specialty drugs (see sidebar, "The Challenge of Healing the World" on page 40). Brian Smith, a professor and expert on the evolution of the life sciences industry, has just launched a new book about how the industry is going to diversify over the next ten years. He expects to see many niche biotechs, as well as mass-market players, seeking a broader market, such as big generic houses. It's actually already happening – some companies, such as AZ, are trying to become more specialty driven and are divesting older drugs, whereas others are still investing to reach mass market as well

as specialty populations – Pfizer springs to mind here.

Overall, it's about adapting to change. The large companies still create value by reaching a broad set of patients around the world, which is really important for these populations, but we will also see more and more niche companies focusing on rarer diseases. It's amazing to see how Gilead has grown into a large company so quickly – with their amazing drugs coming through. The company is doing well with approximately 8000 employees. Smaller companies can be nimble – and many have not started to move into the emerging markets yet but, when they do, the results will be interesting to see, as their small set-up may allow them to move and partner more quickly than larger players.

Embracing change

Going forward, I believe that pharma companies should seek to embrace an omni-channel approach, which involves identifying the different motivations, goals and pain points of the customer/patient at different stages of the customer journey – and then applying appropriate channel and content strategies to improve engagement. In particular, it's time for companies to look at the potential of new channel approaches that can enable a digital experience. One excellent example of an omni-channel digital approach is the online GP service, founded by Ali Parsa, called Babylon. You can book a face-to-face virtual consultation with a GP via the smartphone app, and the consultation is recorded to watch later. They can also refer you onto a specialist or a nearby pharmacy. It's a fantastic example of how you can make use of mobile technology to make it easier for the patient and improve their experience. In healthcare, there are many ways in which pharma can better engage with its customers.

However, when introducing a new channel, it's important to think about the whys and hows – why are you introducing the new channel? And will you integrate it with your current field force channels, as well as the customer journey? People often say, "It's all about digital today," but you have to integrate digital with your other channels, such as sales representatives, key account managers and medical science liaisons. If you can make it work, you'll be moving in the direction of focusing on true customer engagement, both in terms of patients and healthcare professionals, which in time will come with other rewards.

"More and more new drug releases are niche, specialty pharmaceuticals that cater to a small subset of the population."

For big pharma companies, it can be beneficial to partner with a service company who is a specialist in a new channel. Sometimes, building a new capability in-house isn't the right approach, or takes too long – especially if you don't have the right expertise to begin with. A recent example was a client who was trying to coach internal sales representatives to sell over the phone – the problem being that the client didn't have anyone in-house who actually had experience to make this channel work successfully. But companies – specifically senior leaders and management – need to really understand these new approaches to support their teams through the change process to be successful – otherwise you can end up with internal challenges, whilst also confusing customers rather than improving customer engagement!

Leading the way

I've seen firsthand how a company can be ahead of the curve when it comes to focusing on new channel capabilities that are required to engage customers in new ways and create value for the company. I've also seen a company move backwards after a shift in a senior leadership team – changing leadership is a constant with implementing new initiatives to drive sustainable impact with appropriate resources and time. If the leadership team withdraws visible support, then the new channel approach will make way for the old, traditional habits.

"There is a great deal that Western pharma companies could learn from emerging markets – particularly China."

I would say that there is a great deal that Western pharma companies could learn from emerging markets – particularly China – with regards to moving quickly and embracing change. In the digital arena, China has gone from a standing start – and being 5–10 years behind the US and Europe – to the point where they are probably going into a leading position.

Phil Matton is the Managing Director of SPiCE Healthcare.

The Challenge of Healing the World

Gilead is an interesting example of a relatively small, nimble company. When mentioning Gilead, however, it is difficult to overlook the price of some of their medicines. In particular, many people were unhappy with the price of Solvadi, which was priced at around $84,000 for a three-week course (though it should also be said that the drug did demonstrate remarkable efficacy). Gilead is not the only company to put a high price on medicines – and the increasingly high costs of many new drugs is feeding the industry's growing image problem. I have friends who work in the tobacco industry – and I sometimes think that tobacco does a better job of managing public perception than pharma. Why? At times, it feels as if the pharma industry is just looking after a very narrow group of patients with very expensive drugs.

I have spent a lot of time in Africa and there are millions of people who just need drugs of slightly better quality than those of 20 or 30 years ago. Those patients are being forgotten. China has a slightly different problem; patients used to go to Hong Kong to buy drugs (for example, lung cancer treatments) because they were cheaper and more widely available. Today? Generics from India and Bangladesh are flowing in and being sold on the black market (which brings with it additional problems in terms of quality and counterfeiting). The government makes no effort to try and stop the drugs leaking in because they can't afford the manpower – and the consequences could be a huge spike in patient deaths. Unless patient access programs are put in place, such problems will continue. And issues around patient access aren't limited to the developing nations. AZ recently launched a lung cancer specialty drug in the UK, but the UK's National Health Service limited the drug to only a handful of patients.

Striking the balance between getting a return on investment and reaching enough patients is a huge challenge for the industry.

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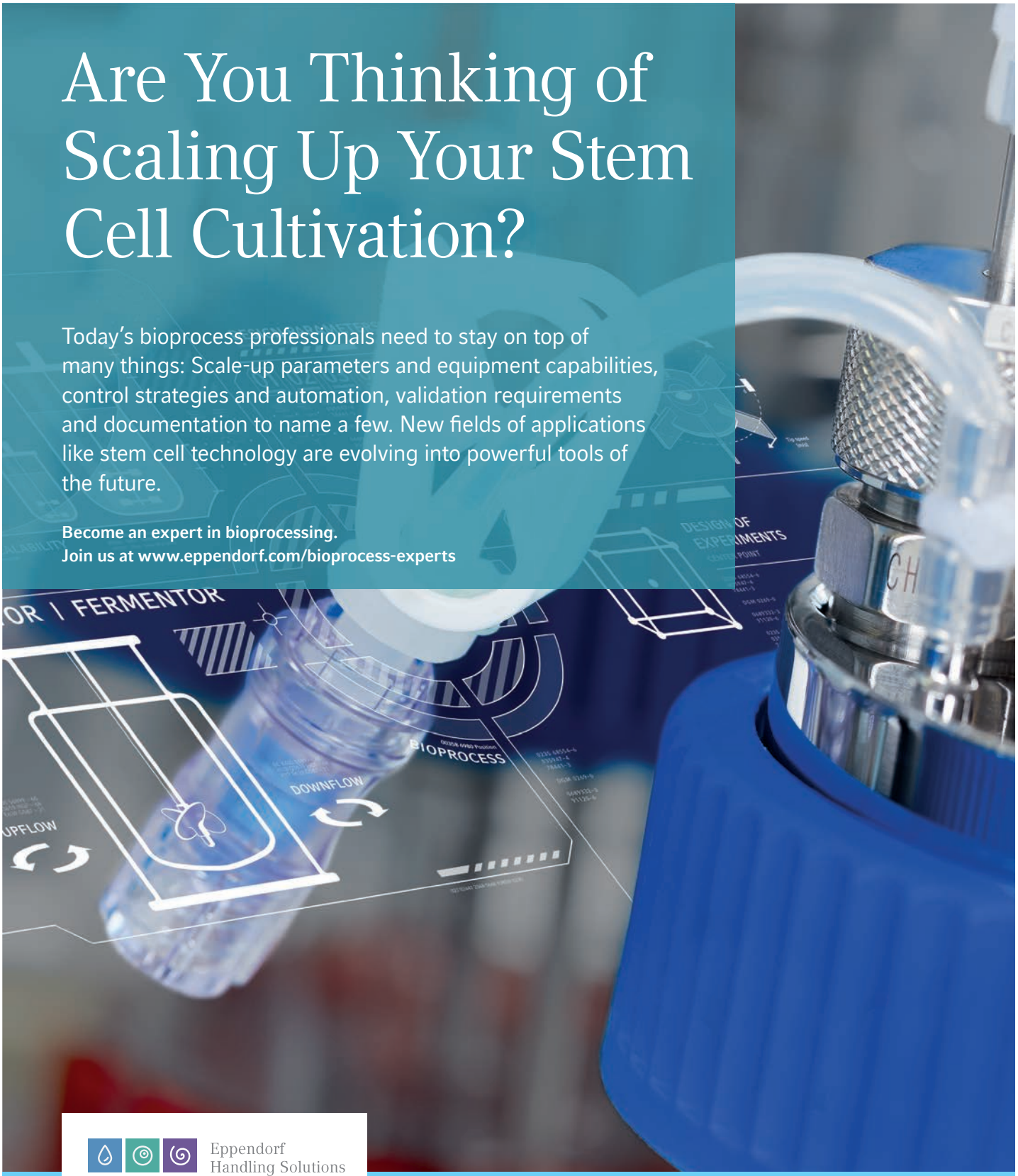

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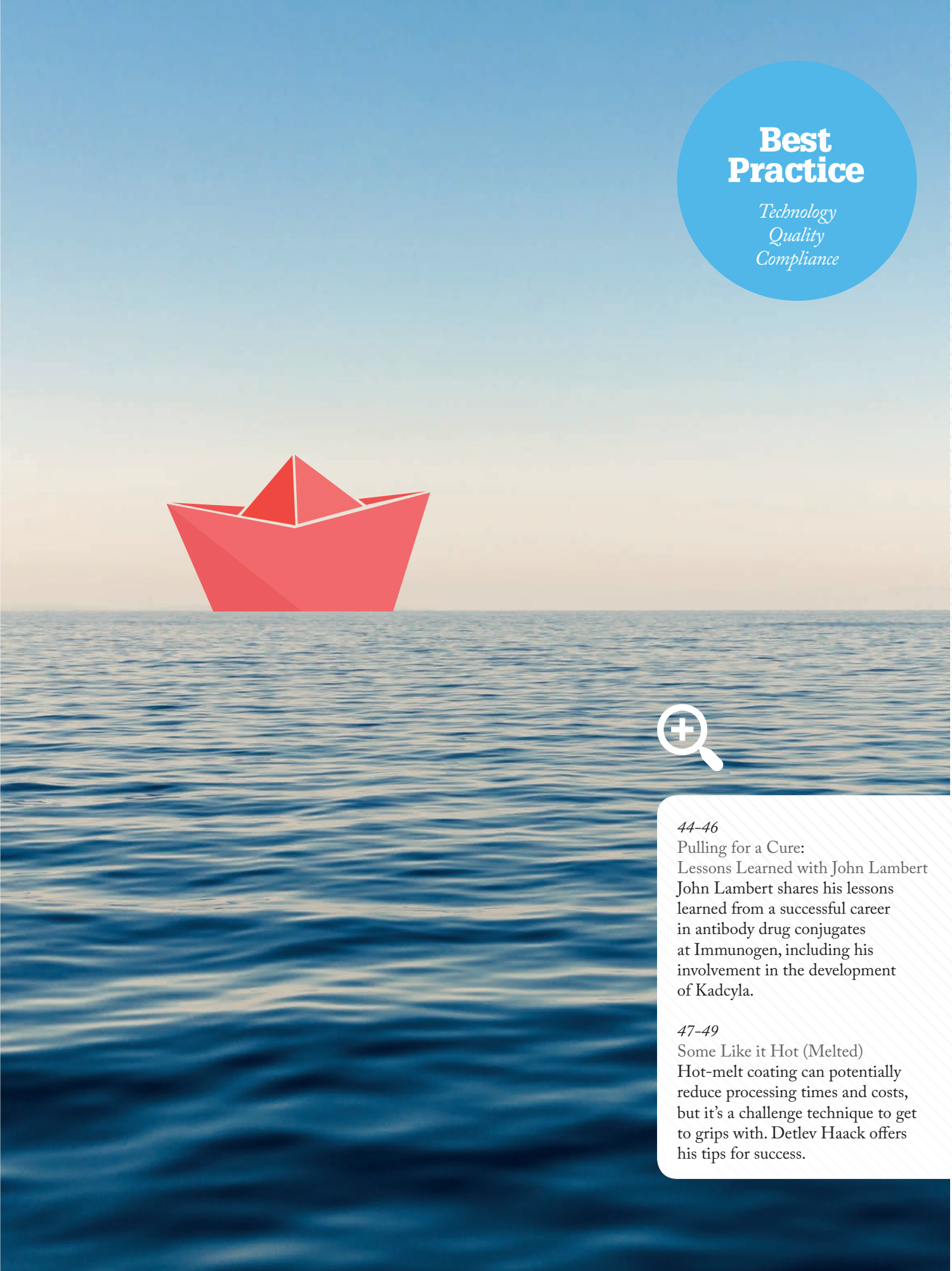

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Pulling for a Cure:
Lessons Learned with John Lambert
John Lambert shares his lessons learned from a successful career in antibody drug conjugates at Immunogen, including his involvement in the development of Kadcyla.

47-49
Some Like it Hot (Melted)
Hot-melt coating can potentially reduce processing times and costs, but it's a challenge technique to get to grips with. Detlev Haack offers his tips for success.

Pulling for a Cure: Lessons Learned with John Lambert

Over the past four decades, John Lambert has spent most of his time either on the water or in the lab. Today, Lambert is Executive VP Emeritus & Distinguished Research Fellow at ImmunoGen, and a Director of the Head Of The Charles Regatta. Here, he talks antibody-drug conjugates and his involvement with Kadcyla.

By James Strachan

In 1632, some 700 Puritan colonists made the long journey from England to Massachusetts. Their leaders were University of Cambridge alumni looking for opportunities in a far-away land – and they called their new settlement "Cambridge" after the ancient University. John Lambert's career has taken a similar (though less perilous) path – beginning at Christ's College Cambridge in the UK in 1969 and still going strong in Cambridge, Massachusetts, on the banks of the Charles River.

And though Lambert says he can't claim a history quite as exciting as those original colonists who sailed out for the New World (but he's probably spent more time on the water given his love of rowing!), he has been able to watch – and help – the antibody-drug conjugate (ADC) field develop from a concept into real therapies. Here, Lambert shares his lessons learned.

It's good to expand your horizons

My studies at Cambridge consolidated my love for biochemistry and also kindled my second passion – rowing (see sidebar: A second love). After completing my PhD in 1976, I made my first voyage to the States to work as a post-doc at the University of California, Davis, where I worked on ribosome structure – specifically the use of cross-linking agents to map ribosomal proteins. After that, I returned to the UK to do a second post-doc at the University of Glasgow, from 1980 to 1982, working on a multi-enzyme complex. Although I wasn't aware at the time, I was laying the foundations for a career in ADC development.

I actually wanted to stay in the UK as a lecturer in biochemistry, but university grants were being cut at that time, forcing me to consider alternatives. The US biotech industry was booming in the early 80s and seemed like a good opportunity. I ended up responding to an advertisement in the journal Science in 1981 for a position at the Sidney Farber Cancer Institute (now Dana Farber Cancer Institute) for a project that aimed to exploit the specificity of monoclonal antibodies – which had only just been invented – to deliver toxic agents to cancer cells. As a protein chemist, I was familiar with conjugation and I had modified proteins and antibodies to analyze their structure, function and activity. So my experience fit the idea of applying the concept of antibody-drug conjugates to the goal of making medicines. I got the job and have stayed in the US – and the field – ever since!

Persevere!

Although I was technically an employee of the Sidney Farber Cancer Institute (SFCI) when I arrived to begin my job in March 1982, I had, for all intents and purposes, joined ImmunoGen, a company specializing in ADCs, as its second scientist, joining Swiss chemist Dr Walter Blattler to build up the research team. At the SFCI, we were answerable to ImmunoGen's scientific advisory board and the company's investors paid a grant to SFCI that covered our costs – including wages, materials and equipment. This is essentially how the company started. Then in 1987, a second round of financing came in and we moved into ImmunoGen's own labs in Cambridge, Massachusetts, and became employees of ImmunoGen directly.

We were early movers in the ADC

field. The 1980s was the era of mouse monoclonal antibodies and humanization hadn't yet been invented. Our initial idea was to use mouse antibodies conjugated to derivatives of potent protein toxins – ricin in particular. Unfortunately, we found those to be highly immunogenic in the clinic and realized that we needed to invent a method for humanization. In collaboration with Professor Anthony Rees, who was at the time head of the department of biochemistry at the University of Bath, UK, we developed a humanization method called "resurfacing." It essentially allowed us to make antibodies non-immunogenic in humans – the first of two major hurdles in developing an effective ADC.

The second hurdle was choosing the right agent to link to the antibody. The chemotherapeutic agents at that time were not potent enough to kill cancer cells when attached to antibodies, when one calculates the number of antibody molecules that can be bound by tumor cells following biodistribution of the antibodies in the body. Thinking back to our original plan of using potent toxins like ricin – where attaching one molecule of ricin per antibody certainly made a potent antibody-payload conjugate – we explored whether we could identify small molecular weight compounds that were as potent as ricin, and adapt them for conjugation to our humanized antibodies. The combination would allow us to target cancer cells with a potent toxin without eliciting a host immune response, while minimizing exposure of other tissues to potent cytotoxic agents. We eventually landed on maytansine – a potent tubulin-binding compound that disrupts microtubule/tubulin dynamics – as a parent drug. The challenge for our chemistry group was to create a maytansine derivative that was linkable to antibodies without destroying the activity of the toxin.

Once we developed our maytansinoid technology for ADCs by the mid-1990s, we knew that if antibody-drug conjugate technologies were going to be successful, HER2 would be a good target. It was already established that HER2 was highly overexpressed on a subset of breast cancers (~20 percent) that were particularly aggressive cancers, and it was under active investigation as a tumor-selective target for antibody-based therapies. Genentech were already in clinical trials at that time with the anti-HER2 antibody trastuzumab, so in the late 1990s we approached them to suggest a collaboration – our maytansinoid payload combined with their HER2-targeting antibody. Ultimately, a deal was struck in 2000. ImmunoGen made several maytansinoid/trastuzumab constructs with a variety of different linker-maytansinoid chemistries, and Genentech evaluated all of them in a variety of preclinical studies in order to select the development candidate, which went into phase I clinical trials in 2006. Ultimately, the pivotal phase III trial data were presented at the American Society of Clinical Oncology (ASCO) in 2012, and the FDA granted a product license to Genentech in February, 2013. It was an exciting moment for ImmunoGen! The product, whose generic name is trastuzumab emtansine, is marketed as Kadcyla for treating HER2-positive breast cancer. To date, Kadcyla is the first and only ADC to receive full approval based on a randomized phase III study.

Always focus on your target

Having worked in ADC development for 35 years, my most important piece of advice is to focus on the target – and Kadcyla illustrates this point well. Because we used an already approved antibody –

A Second Love

Some careers take twists and turns as people's interests shift over the years, leading them into different roles and industries. I was lucky to fall in love with a field fairly early on, and I've spent the majority of my career working in ADC development. It's been fascinating to watch as we overcame the technical hurdles – learning how to humanize antibodies and select the right therapeutic agents – culminating in the approval of Kadcyla. Few other things in my life have managed to keep my interest for so many years – except rowing.

I took up rowing at the University of Cambridge when I was 18, and aside from a brief hiatus during my post-doc at UC Davis, rowing has been a part of my life for the subsequent 47 years. I'm currently a member of the Board of Directors for the "Head Of The Charles Regatta" – a two-day event in Cambridge, US, which involves over 12,000 rowers and more than 2000 boats. It takes place on the third or fourth weekend in October (always a pretty time of year with New England fall foliage) on the Charles River and attracts around a 250,000 spectators. I've raced in 31 consecutive Head Of The Charles Regattas since 1986! I compete in other races throughout the year, and recently have had success with my doubles partner in lightweight sculling events. At the annual US Masters Championship regatta, we've won the lightweight "F" (average age 60 – 64) event for double sculls in both 2012 and 2016.

Did I go to Boston for the rowing or the science? Honesty, I went for the science, but I couldn't believe my luck once I had arrived – there isn't anywhere better for a rower-slash-scientist in the biotech world!

The Pull for a Cure Challenge at the Head Of The Charles regatta aims to raise money for the breast cancer research efforts of the American Cancer Society. You can find out more and even donate at http://bit.ly/2qsWOPM.

trastuzumab, marketed as Herceptin – the development was relatively rapid. Commercial manufacturing of the antibody was already in place. And with a ready-made test to select patients overexpressing the HER2 target protein, patient selection wasn't something Genentech really had to think about in early clinical development. Selecting the right patients who could potentially benefit from treatment was important for its rapid clinical development.

A couple of ADCs have received accelerated approval after phase II studies for treating hematologic malignancies. Pfizer's gemtuzumab ozogamicin (Mylotarg) is one, but its approval for treating acute myeloid leukemia in 2000 was withdrawn in 2010 after an unsuccessful confirmatory phase III study (although recently, Pfizer has re-submitted a marketing application to FDA on the basis of subsequent phase III studies that have shown clinical benefit). The second ADC to be approved was brentuximab vedotin (Adcetris) marketed by Seattle Genetics and Takeda for treating Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Hematologic malignancies generally have well-defined lineage-specific targets. The emerging data for solid tumors seem to support the hypothesis that greater antigen density increases the effectiveness of the ADC. Higher target expression leads to more ADC accumulation at the tumor, and more uptake of ADC into cells on a per cell basis. So one of the key lessons we've learned was that target expression is very important when thinking about the application of ADC technology to cancer patients. In retrospect, if some of those early, discontinued, ADCs had applied better patient selection in early clinical trials, they may have been viable agents.

Think like a biologist and medicinal chemist

The second most important thing to remember, when working with ADCs, is that that when one evaluates them pre-clinically, one has to take into consideration that they have characteristics of both biologics and cytotoxic agents. And that means one has to think like a biologist and a medicinal chemist. One has to take into consideration that most antibody is metabolized somewhere other than the cancer, and medicinal chemists tend to pay attention to the overall catabolism of a compound, as well as to its therapeutic effect.

The idea behind ADCs was to increase the activity at killing cancer cells whilst decreasing the side effects from the uptake and metabolism of a toxic compound by every other cell in the body. In other words, the goal was to widen the therapeutic index. However, it's important to remember that only around 0.1 percent of the injected dose of antibody per gram of tumor ends up in the tumor. This means that even for a tumor as large as 1 kg, 90 percent of what you inject doesn't end up in the tumor, but it's still got a cytotoxin on it which will eventually be metabolized elsewhere in the body. This highlights the challenge in designing an efficacious ADC that is active at tolerated doses.

ADCs are an exciting field to watch for the future

Over the next 12 to 24 months, there are going to be several compounds moving forward in pivotal clinical studies. ImmunoGen's folate-targeting ADC called mirvetuximab soravtansine for treating ovarian cancer is one example, and Bayer's mesothelin-targeting ADC developed in partnership with us for the treatment of mesothelioma is another. Both these ADCs require an assay to select patients expressing the tumor-target above a certain threshold level for inclusion into the trials. There are five or six more ADCs currently in pivotal clinical trials for treating a variety of different cancers, both solid tumors and hematologic cancers, and we can be optimistic that several more ADCs will gain marketing approval over the next few years.

I also think we're seeing an explosion of innovation in the ADC space with new payloads, particularly ones that alkylate or cross-link DNA. There are several currently in the clinic, including an ADC with our indolinobenzodiazapine compound. Besides the development of several new payload classes beyond the potent tubulin binding agents, I see that the field is moving towards new and creative chemistries for linking the various payloads, and engineering the antibody component in various ways; for example for bispecific binding, with the goal of increased potency and decreased toxicity of the ADC. The next few years will see emerging clinical data from the new payload classes and new antibody and linker technologies which will be very exciting – and hopefully highly informative.

James Strachan is Associate Editor of The Medicine Maker.

Some Like it Hot (Melted)

Hot-melt coating may require vast process knowledge and formulation expertise, but when the outcome is reduced processing times and costs, who cares?

By Detlev Haack

Coating has been used in the pharmaceutical industry for decades – initially beginning with sugar coatings. Today, film coating is the most common, with continuous advances being made towards improved environmental protection, aesthetic qualities and more complex drug release profiles. Films coatings generally rely heavily on solvents to dissolve the coating material – and those solvents have a number of drawbacks, including cost and environmental issues. Aqueous coatings are now very popular in the industry but, although they overcome some of the downsides of solvents, they can cause drug stability issues.

An increasing number of companies are turning to novel coating technologies, with one of the most interesting examples being hot-melt coating (HMC). It's a very clever technology with a simple premise. The API particles are wetted with a molten excipient mix (often including lipids), which is then cooled to form a homogenous coating. The coated API can then easily be combined with excipients like flavors depending on the needs of the patient. Broadly speaking, HMC offers a number of advantages to manufacturers – importantly, no solvent is required and process times are usually short. This results in low energy consumption during production, making HMC a sustainable and ecofriendly technology. It also tends to be very cost effective. All these benefits have been well discussed in literature (1,2).

The technique has been used outside of the pharma industry for many years, including in the food industry. HMC has a variety of purposes in food, but one interesting use is in coating seasoning mixes used in ready meals. HMC helps minimize hygroscopicity of the seasoning throughout the logistics chain and improve the food's taste and smell throughout its shelf-life.

The coating challenge

Although the HMC process is fairly straightforward, there are many process input parameters that can lead to unexpected product outputs – and when I first became involved with HMC I discovered there was a lot to learn. The coating process must be performed at a closely controlled temperature, so you need to thoroughly investigate the thermal behavior of your API, excipients, and their interactions. The main drawback of HMC is the amount of formulation and process knowhow required, which is why many companies turn to outsourcing or academic partnerships. For HMC, both the formulation and processing parameters need to be individually optimized depending on the API, which takes time (although such a high level of optimization does bring benefits in terms of intellectual property).

From a chemical point of view, there are almost no limits to the APIs that can be hot-melt coated – it's even possible to coat thermosensitive APIs – but some physical attributes can cause problems. APIs that are only available as needle-shaped crystals, for example, are almost impossible to coat. At the moment, HMC is very popular for

over-the-counter medicines – where usability and sensory aspects, such as taste and odor, can be key market differentiators. Nutraceuticals are also common candidates for HMC, since many vitamins have an unpleasant taste. Increasingly, HMC is being used for oral prescription drugs, including extended, as well as immediate release tablets, and other more complex oral forms, such as orally disintegrating granules (ODGs) – but it's still early days (and pharma can be slow to embrace change).

Close control

Improved analytical technology has enabled one of the biggest advances in HMC in recent years. For a long time, lipid characterization – essential in the optimization of HMC processes – was expensive and time-consuming, but newer technologies allow us to characterize all polymorphic behaviors of lipids. Process analytical technology (PAT) has also advanced significantly since the US FDA first issued its PAT Guidance for Industry in 2003. Today, state-of-the-art PAT can control manufacturing processes in line, in real time – and be applied to HMC processes. For example, by directly controlling the fluid bed granulator process, inhomogeneities can be identified as they occur. It is also possible to estimate particle size distribution, which helps ensure the quality of the final product. With this type of advanced monitoring technology, you no longer need to perform quality control afterwards.

I believe any development process should be kept as simple as possible. Therefore, it makes sense that companies using HMC technology should ideally opt for granulated or round particles as starting materials. As API particles are often provided in different size distributions, different amounts of lipids are necessary during the coating process; you can measure the thickness of the coating layer during the process using PAT (we use near infrared spectroscopy), modifying the amount of lipids accordingly. The process is easier with a narrow API particle size (optimally 200 to 500 microns) and a lipid with a defined melting point, but other scenarios can work too, with optimization.

It is typically desirable to have almost no crystallographic changes of the lipids during the shelf life of the final product, which can be achieved by using lipids with a specific melting point (rather than a melting range). Though such lipids appear poor from a chemical point of view, they result in stable polymorphs at the end of the process – and that means fewer changes during shelf life. Gaining a solid understanding of the lipid, therefore, is important.

"Importantly, HMC can help deliver better medicines to patients."

When it comes to equipment, we use a fluid bed granulator specially designed for HMC. And when choosing a coater, it is important to pay close attention to the air system, which helps improve the reproducibility of the layers on the

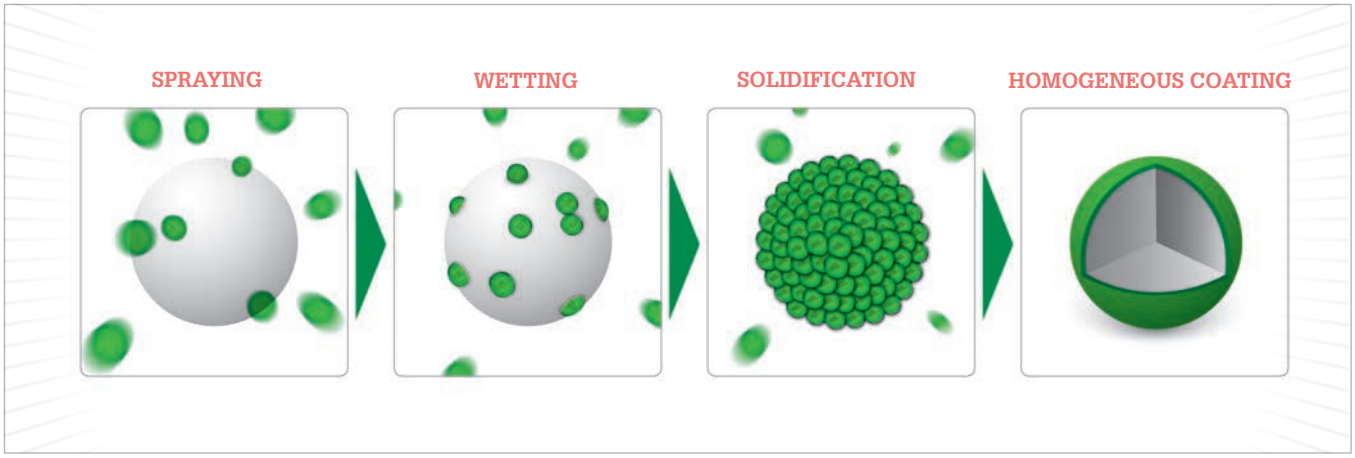
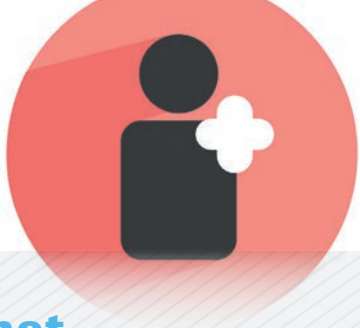


Figure 1. The hot-melt coating process: Molten coating excipients are sprayed onto a seed particle maintained at a lower temperature than the excipient mix. Due to the temperature difference, the droplets attach to the seed particle and solidify upon contact, forming a homogeneous coating.



What Patients Want

Healthcare companies must pay more attention to the usability and sensory aspects of their products. Patients are increasingly demanding products that are easy to swallow and that taste pleasant. They also want more choice over how they take their medicines – and our research has shown that 50 percent of people in the US have difficulties swallowing tablets or capsules (1).

More complex oral dosage forms, such as orally disintegrating tablets (ODTs) and orally disintegrating granules (ODGs), are starting to emerge – and since they reside in the mouth for much longer than a tablet, a bad-tasting API can be a huge problem, potentially impacting patient compliance. Last year, we used HMC to mask the sour and sulfuric taste and smell of acetylcysteine (NAC). NAC is also a thermosensitive compound – and yet we were able to optimize the HMC process to develop an ODG that had a stable, immediate release profile and unaltered polymorphic form of the coating during storage.

Historically, it has been easier to formulate and produce tablets because the manufacturing processes are well established – and there are certainly many advantages to the humble tablet. Many of these advantages, however, are from a technical rather than a patient point of view. With modern technical capabilities, medicines can – and should – be made more patient friendly. It is now possible to produce almost anything conceivable – and everything is automated. For example, you could make a granule formulation of aspirin taste like cola, if you so desired. If a drug needs to be dosed at a high amount (resulting in a very large tablet), then it makes sense to consider an alternative dosage form. Instant drinks are an effective way of incorporating up to 15 grams of API, and they are becoming increasingly popular. It would be interesting to see more alternative dosage forms, such as instant drinks, ODTs, ODGs and chewable tablets make in-roads into prescription drugs.

Tablets will never be replaced, but patient demands will inevitably lead to an increasing proportion of alternatives.

Reference

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particles. Once the parameters for the HMC and the excipients mix have been optimized, there are no curing or sintering effects, and very little risk of forming unwanted agglomerates. In addition, the lipid coat can increase the overall hydrophobicity of the final product.

Better medicines

Perhaps most importantly, HMC can help deliver better medicines to patients. Many APIs and pharmaceutical products could benefit from improved taste – and HMC is very effective at taste masking, while also retaining control over the API release profile. Note that the FDA is encouraging developers to pay more attention to what patients want, as it could ultimately improve patient compliance (see sidebar, "What Patients Want").

"I believe any development process should be kept as simple as possible."

I've been working with HMC for years and I'll admit that the learning curve is steep. It is a specialized technology that is challenging to get up and running, so it's worth seeking expert advice in the early days. Nevertheless, I expect to see more and more companies adopting HMC for their products – particularly new releases. Who would turn down faster processing (less than two hours to coat a 600 kg batch) and lower costs? So, when making your coating decisions, first consider the advantages – cheaper, quicker and more eco-friendly – for these are particularly compelling in modern manufacturing.

Detlev Haack is Head of Research and Development at Hermes Pharma, Germany.

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The Contract Career Path

Sitting Down With... Ian Muir,
Managing Director, Aesica, UK.

Why the pharma industry?

My father was a retail pharmacist for 35 years. And though we all like to think we make our own choices in life, our parents often have an influence on us! I'd always been interested in science and how things work. I started out in GlaxoSmithKline's graduate training program, where I worked in operations with Ventolin and Becotide inhalers. My time was actually split between industry and the Royal Liverpool Teaching Hospital, where I was able to experience a hospital pharmacy. I loved the industry side – the variety and scale of industry operations was fascinating. And the 1980s was a great time to enter the industry. Arguably, pharma was at its peak in terms of new launches – blockbusters seemed to launch every year and the industry was building factories as fast as it could. It was a period of tremendous growth and also, I might add, a time when the pharma industry was seen as a shining light… A stark contrast to today when the industry does not have such a good reputation and when consumers seem more willing to spend money on electronics than a tablet to cure disease.

How did you get into management?

My career path was pretty conventional. I worked my way through product development and technical operations – and the experience with big pharma was really useful. I also had the great opportunity to travel and move around (I've lived in both Australia and the US). But the key change in my career was around 2000 when I jumped from big pharma to the contract development and manufacturing (CDMO) space, which was just starting to gather pace. The great thing about working for a CDMO is that you are able to learn a lot about the commercial side of the pharma industry. The commercial aspects of business and technical development are very closely linked as you are working on client projects. Ultimately, I moved from technical operations, into project management, and then into a commercial role.

How did you find the leap?

There were two big differences. In a CDMO, there is a complete focus on customer service in a way that isn't as direct as a traditional pharma environment. There is also the burden of regulatory audits in a CDMO. Working with different customers in different markets means that we are exposed to customer or regulator audits every week. I think more needs to be done to ease this. Over the years, there has been a move to greater regulatory harmonization but it hasn't gained much momentum. The EMA and FDA recently announced they were aligning more, but we've yet to see much of a change.

Despite this, I love working for a CDMO. You get to deal with many different customers and products. The CDMO sector is a service industry and has a lot in common with accounting firms, law firms and even hospitality – your focus is on delivering for the customer and this is a good skillset to have in addition to technical skills. A big issue with the industry today is that it is very siloed – people need to focus on breaking these silos down for their career development. Many people in industry move from job to job, but only focus on advancing their development in a specific discipline. Taking the risk of stepping outside your area of expertise exposes you to other aspects of the industry and provides a wider perspective, necessary for reaching full career development potential.

What are the big trends facing the outsourcing sector?

There are always phases where companies prefer to outsource or prefer to manufacture in house. I think we are moving into a time where there will be greater demand for contract services. In general, mid- and large-size pharma companies are not investing in new plants and equipment in the way they have done historically, and there seems to be a trend to move out of manufacturing as a core skill. The big questions for those of us in the CDMO sector are: what are people looking for in a supplier? What is the critical size of a CDMO and what capabilities should be prioritized? And, most importantly, how do you differentiate yourself from a service point of view in an industry where many people have very similar capabilities?

How else is the industry changing?

Some of the themes from the past year will continue, including price pressure on products and healthcare costs. We also don't know how the US administration and Brexit will affect the industry. Innovation is continuing, however. There was a period where the investment market wasn't very good, but this is starting to pick up again and more start-ups are appearing as a result. We have a foot in the device side of the pharma industry and one interesting trend is that there is a lot of innovation being seen in devices, as well as increasing interest in end-to-end health from diagnosis, through treatment and the drug delivery device (the interface with the patient), and the whole ehealth dynamic. With the advent of smartphones and other devices, the integration of health, monitoring and devices will continue to increase. Also, different companies are getting involved in the pharma industry – such as data providers and electronics companies. It will be interesting to see how this all plays out. There will be people who make devices, people who work on the interface of the device, and people who own the data. Who will make the money and who will control information? We will find the answers in time.

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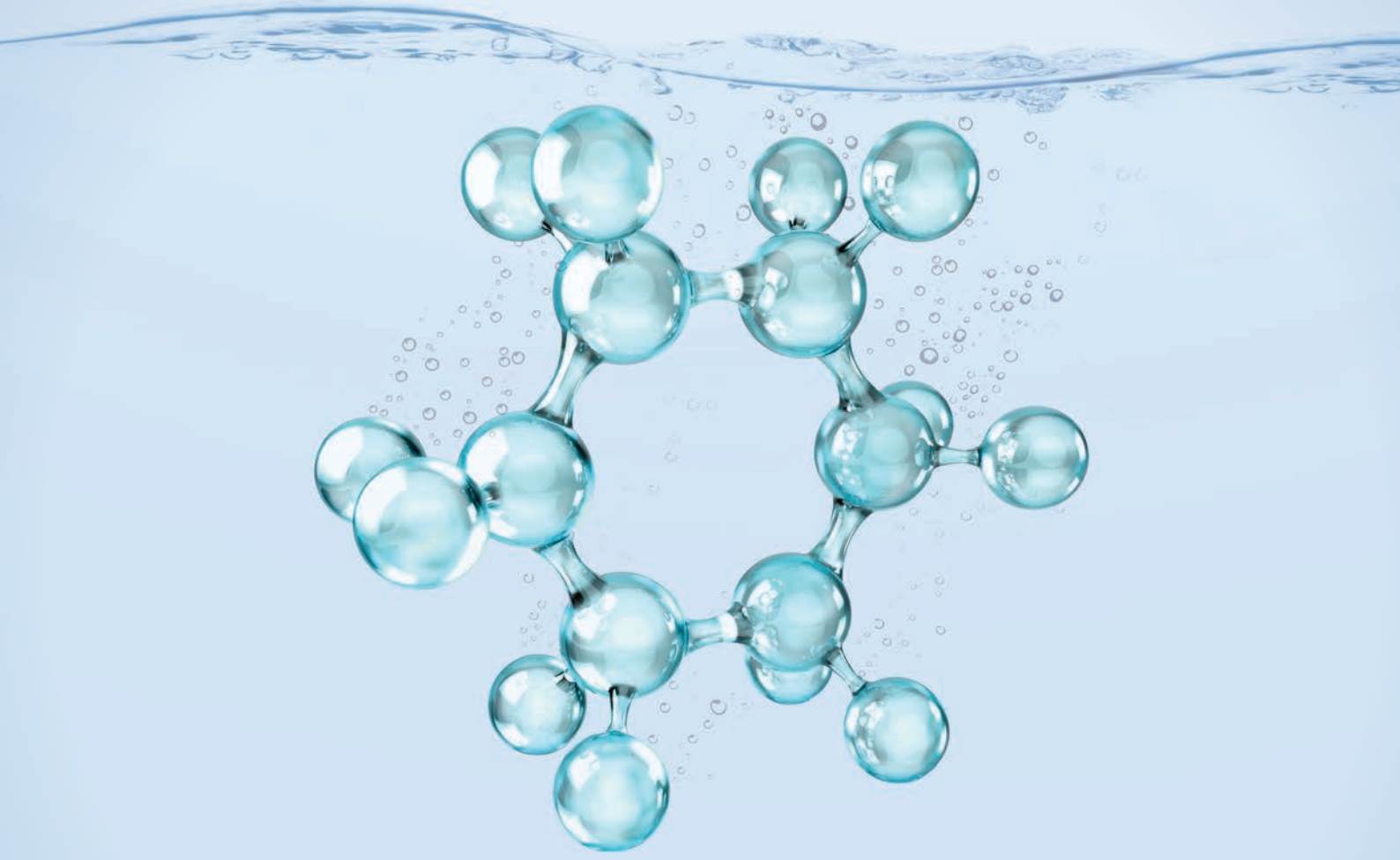

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