MARCH 2017 # 28

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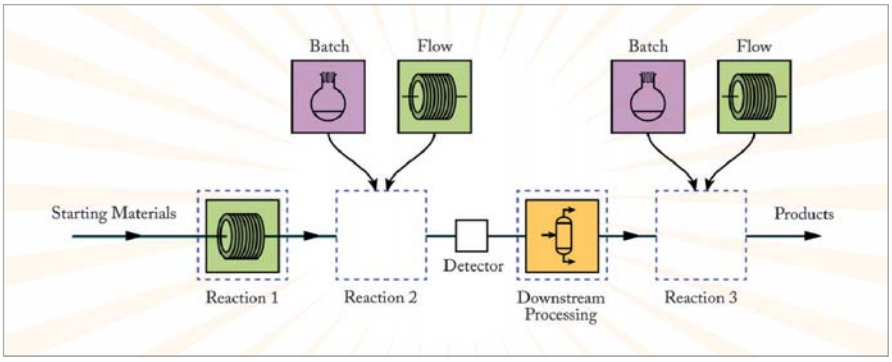
Online this Month

Fighting Generic Drug Price Gouging

In a recent letter to the BMJ, Karim Meeran, Sirazum M Choudhury and John Wass discuss the problems of generic drug price gouging and suggest a solution for the UK: developing a new part of the National Health Service to manufacture essential, generic drugs. Meeran discusses this plan on page 38, but you can read more on our website.

http://tmm.txp.to/0317/meeran



On-Demand Medicine Making

In this month's cover feature on page 20, Tyler McQuade from the US Defense Advanced Research Projects Agency (DARPA), as well as a variety of researchers, explain how it's possible to synthesize both small- and large-molecule drugs on demand, in remote locations. Another research group working with DARPA is the Ley Group, run by Professor Steven V. Ley at the University of Cambridge, UK. The Ley Group is working to synthesize a range of APIs on a single reactor platform that uses flow chemistry (see diagram). Learn more online.

http://tmm.txp.to/0317/ley

Marathon Sells Emflaza

Last month online, we reported on the pricing storm around Marathon Pharmaceuticals and Emflaza (deflazacort) – Marathon had wanted to charge $89,000 per patient per year for the drug, which was recently approved in the US for treating Duchenne muscular dystrophy. Following the public backlash, the company has now decided to sell the drug to PTC Therapeutics for $140 million in upfront cash and stock.

But what happens to the price tag? PTC have said they will re-evaluate this.

http://tmm.txp.to/0317/marathon

Coming Up Next Month

Look forward to the print and online publication of the much anticipated 2017 Power List!

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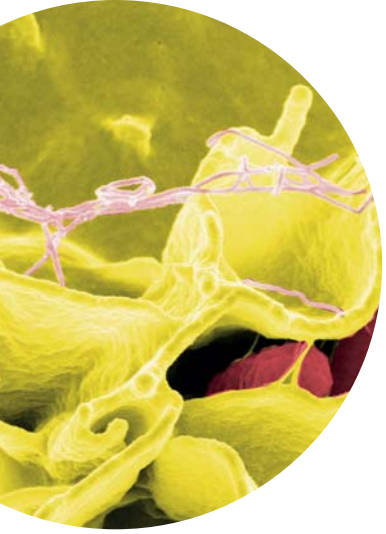
How can access to medicines be improved on battlefields or in other remote locations that lack infrastructure?



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Weeding Out Pain

What does patient preference for pot over prescriptions mean for the pharma industry?

A recent study showed that patients being treated for chronic pain, mental health and gastrointestinal issues would rather use cannabis than prescribed medicines. The study was performed in Canada, and the researchers say it is one of the first studies to track medical cannabis use under Canada's new system of licensed products – and that means all participants had the OK from their doctor to access cannabis in addition to their prescribed medicine (1). Overall, 63 per cent of respondents reported using cannabis instead of their prescription drugs, which included opioids, benzodiazepines and anti-depressants. The lead researcher involved in the project, Philippe Lucas, suggested that the preference for cannabis stemmed from reduced side effects, better symptom management, as well as a feeling that cannabis is safer than prescription drugs.

Only a handful of countries have legalized cannabis for medical purposes, but the number is growing. In the US, cannabis for medical purposes is legal in certain states, but the US Federal government does not recognize any medical qualities in cannabis. But given that a number of pharma companies are pursuing the development of cannabis-based drugs, we could be set for a shake up. GW Pharmaceuticals is hoping to nab the first FDA approval for a cannabidiol-based drug with Epidiolex – a treatment for children with Lennox-Gastaur syndrome (a rare form of epilepsy). The company already has a cannabis-based drug, Sativex, approved in a number of countries for treating MS pain, although the drug failed cancer pain clinical trials in 2015.

Research has shown that cannabis legalized for medical use can reduce opioid overdosing (2), but, for the most part, large pharma companies have opposed its use. In the US, PhRMA is considered a serious opponent – and skeptics believe that the resistance stems from concerns that pot may eat into profits. A recent report from the National Academies of Science, Engineering, claims that cannabis is effective for treating chronic pain, especially for patients with multiple-sclerosis (3). And given that MS drugs were recently declared the most over-priced in the world (4), it's little wonder that patients are looking for alternatives.

Stephanie Sutton
Editor

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2. *The Washington Post, "One striking chart shows why pharma companies are fighting legal marijuana" (2017). Available at http://wapo.st/2ndoVRz. Last accessed March 10, 2017.*
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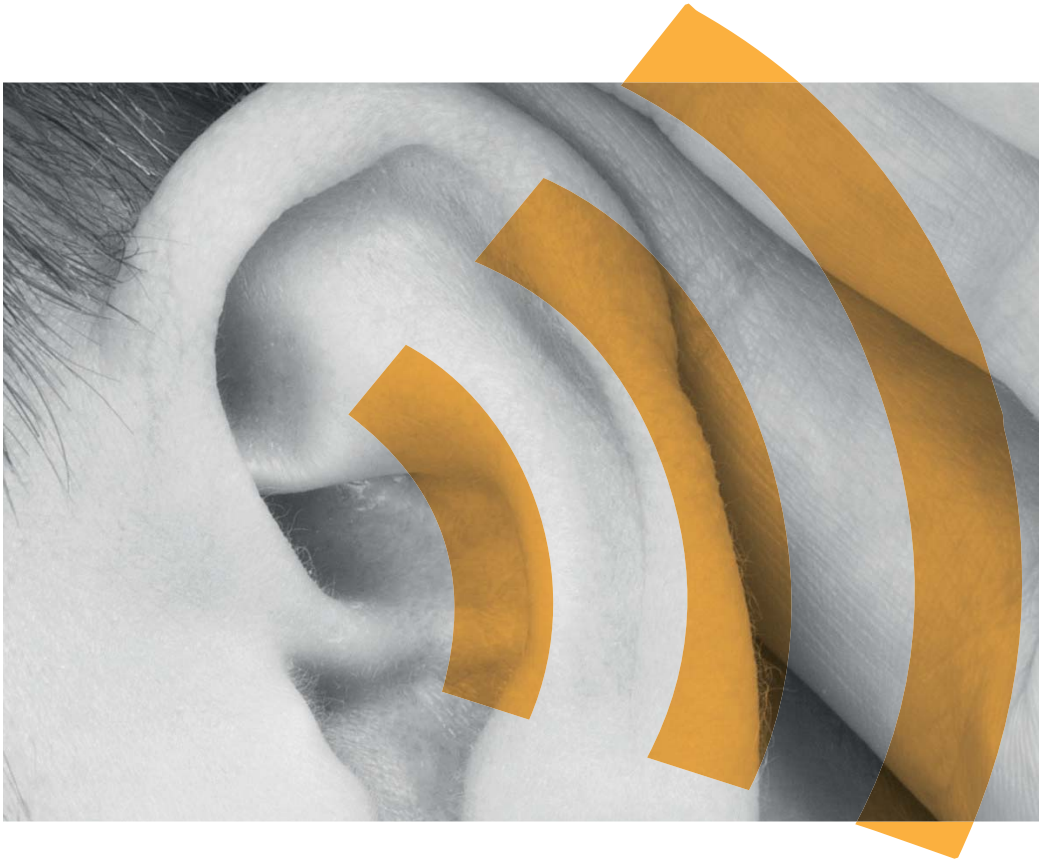
Upfront

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

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



Return of the Cells

Drug injection could treat noise-induced hearing loss by unlocking the ability to regenerate inner ear hair cells

According to the World Health Organization, approximately 360 million people suffer from hearing impairment. Noise-induced cell death is the primary cause, and once hair cells are gone, they don't come back – at least in humans anyway. Birds and amphibians are able to regenerate their sensory hair cells, and the human intestinal lining regenerates every 4 to 5 days. These facts prompted Jeff Karp, Associate Professor of Medicine at Brigham and Women's Hospital, and his team to ask a question: what is the biological mechanism that prevents mammalian inner ear progenitor cells from dividing and forming new hair cells?

"In regenerative tissues, a progenitor cell will divide before becoming a differentiated cell type," says Karp. "Mammalian inner ear cochlear progenitor cells lose this ability after fetal development has completed."

This means that drug discovery for the inner ear is limited by the inability to acquire enough primary cells to explore drug targets. But Karp and his colleagues have developed a way to create large populations of progenitor cells and hair cells, via a method they call "Progenitor Cell Activation."

In a recent study (1), the team identified a combination of small molecules that enable inner ear progenitor cells to form large pure colonies, which can be subsequently converted into fully developed hair cells in high yield. These molecules were effective for inner ear progenitor cells isolated from young mice, old mice, monkeys, and humans.

"With the same molecules, we were able to regenerate lost hair cells when applied to isolated cochleae that had their hair cells destroyed," says Will McLean, one of the co-lead authors of the paper, and Vice President of Biology and Regenerative Medicine at Frequency Therapeutics – a company set up in 2015 by Karp and Robert Langer, David H. Koch Institute Professor at Massachusetts Institute of Technology, to develop disease modifying therapeutics using Progenitor Cell Activation.

"Our next step is to bring this proprietary platform approach into clinical testing, which we plan to do within the next 18 months after the required toxicology and safety studies," says Karp. *JS*

Reference

1. *W J McLean et al., "Clonal expansion of Lgr5-positive cells from mammalian cochlea and high-purity generation of sensory hair cells", Cell Reports, 18, 8, 1917-1929 (2017). PMID: 28228258.*

Mutual Respect

FDA and EMA forge an agreement to mutually recognize drug manufacturing inspections

The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have agreed to mutually recognize inspections of drug manufacturing sites for human medicines. Under the landmark agreement, which is set to begin on November 1, 2017, the need for an FDA authority to inspect a site located in the EU, or vice versa, will be limited to exceptional circumstances.

In a press release (1), the FDA said, "Ultimately, this will enable the FDA and EU to avoid the duplication of drug inspections, lower inspection costs and enable regulators to devote more resources to other parts of the world where there may be greater risk."

Both agencies have been edging closer to mutual recognition for a number of years. In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act, which gave the FDA authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities, as long as the FDA determined those authorities were capable of conducting inspections that met US requirements. And since May 2014, the FDA and the EMA have been working closely to evaluate the risk and benefits of mutual recognition of drug inspections.

"The agreement is underpinned by robust evidence on both sides of the Atlantic that the EU and the US have comparable regulatory and procedural frameworks for inspections of manufacturers of human medicines," said the EMA in a press release (2).

According to an FDA document (3), the agreement is between the US and the EU (not with individual national regulatory agencies), but the FDA has set out to conduct an assessment of each country's regulatory authority individually by July 15, 2019. The agreement will cover "a broad range of human drugs and biologics and veterinary drugs with specific exclusions." The document also states that inspections of "facilities manufacturing vaccines and plasma derived products are not immediately included within the scope of the agreement," but that this will be re-evaluated no later than July 15, 2022. *JS*

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2. *EMA, "European and US regulators agree on mutual recognition of inspections of medicines manufacturers", (2017) Available at: http://bit.ly/2lBCcRL. Accessed March 8, 2017.*
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Outsourcing Boasts Growth

Outsourced manufacturing set to grow by 6.6 percent over the next four years, according to Results Healthcare

Results Healthcare have published a review of outsourced manufacturing in pharma and biotech – and the news is good for the sector (1). The headline figure is an expected growth figure of 6.6 percent – well above the expected global GDP growth. This, the authors claim, is driven by the strong growth of the overall pharmaceutical sector, as well as an increase in the amount of outsourced manufacturing work. Over the next four years, growth is expected to be dedicated to small molecules and commercial manufacturing supply. Here are some of the key findings.

Top five major investments in recent years:

- New HPAPI facility in Shanghai by WuXi in 2014.
- Expansion of existing capacity at UK HPAPI facility by DPx/

CMOs	*EV/EBITDA multiples*
Patheon	17.1x
Recipharm	13.0x
Lonza	12.7x
Catalent	12.6x
AMRI	12.4x

CROs	*EV/EBITDA multiples*
Quintiles	17.9x
PRA Health	15.8x
INC Research	13.7x
Charles River Labs	12.6x
ICON	12.5x

Top five CMOs and CROs by EV/EBITDA multiples – EV/EBITDA ratio is a comparison of enterprise value and earnings before interest, taxes, depreciation and amortization.

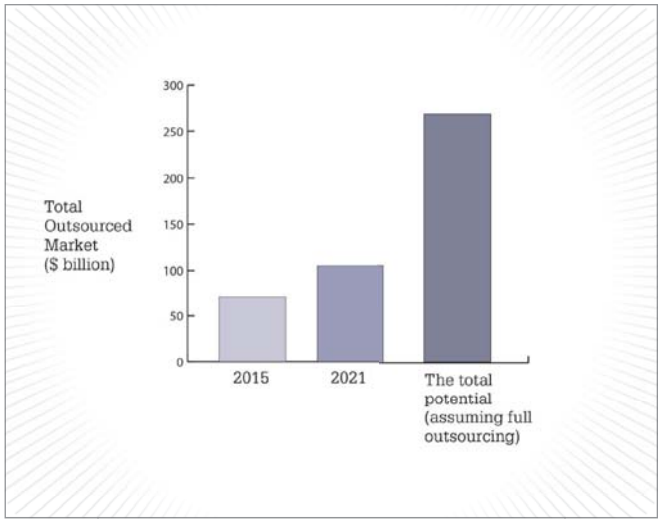
Patheon in 2014.
- Fareva announcement of a €25-million investment in a recently acquired asset in La Vallé, France, to add HPAPI capable facilities in 2015.
- Fermion announcement in 2016 of a €30-million investment in its Hanko, Finland, facility which will add additional HPAPI capacity.
- Alcami due to open a new 500 m2 kilolab-scale facility during Q1 2017.

Company strategy findings:

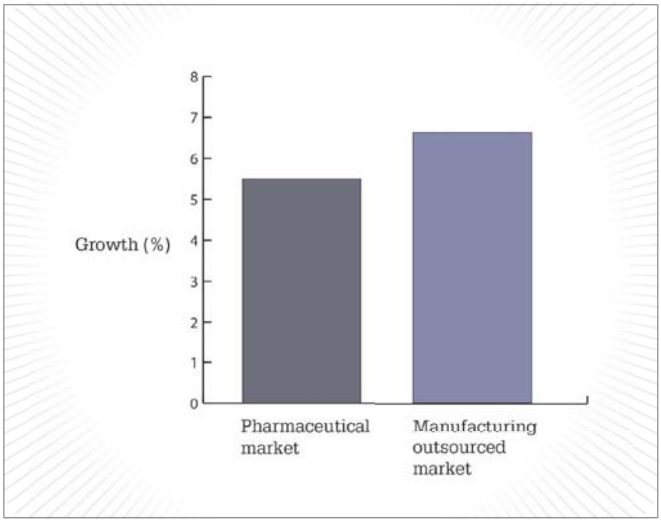
- Most western companies see themselves as differentiated players.
- One-stop-shop is a popular strategy pursued by the large players.
- In the atmosphere of consolidation, size has been a goal for acquisitions.
- M&A is not a strategy followed by all, linked to the peculiarities of private and family ownership.

Reference

1. *Results Healthcare, "Pharma & biotech 2017 Review of outsourced manufacturing", (2016). Available at: http://bit.ly/2k3gppE. Last accessed February 28, 2017.*



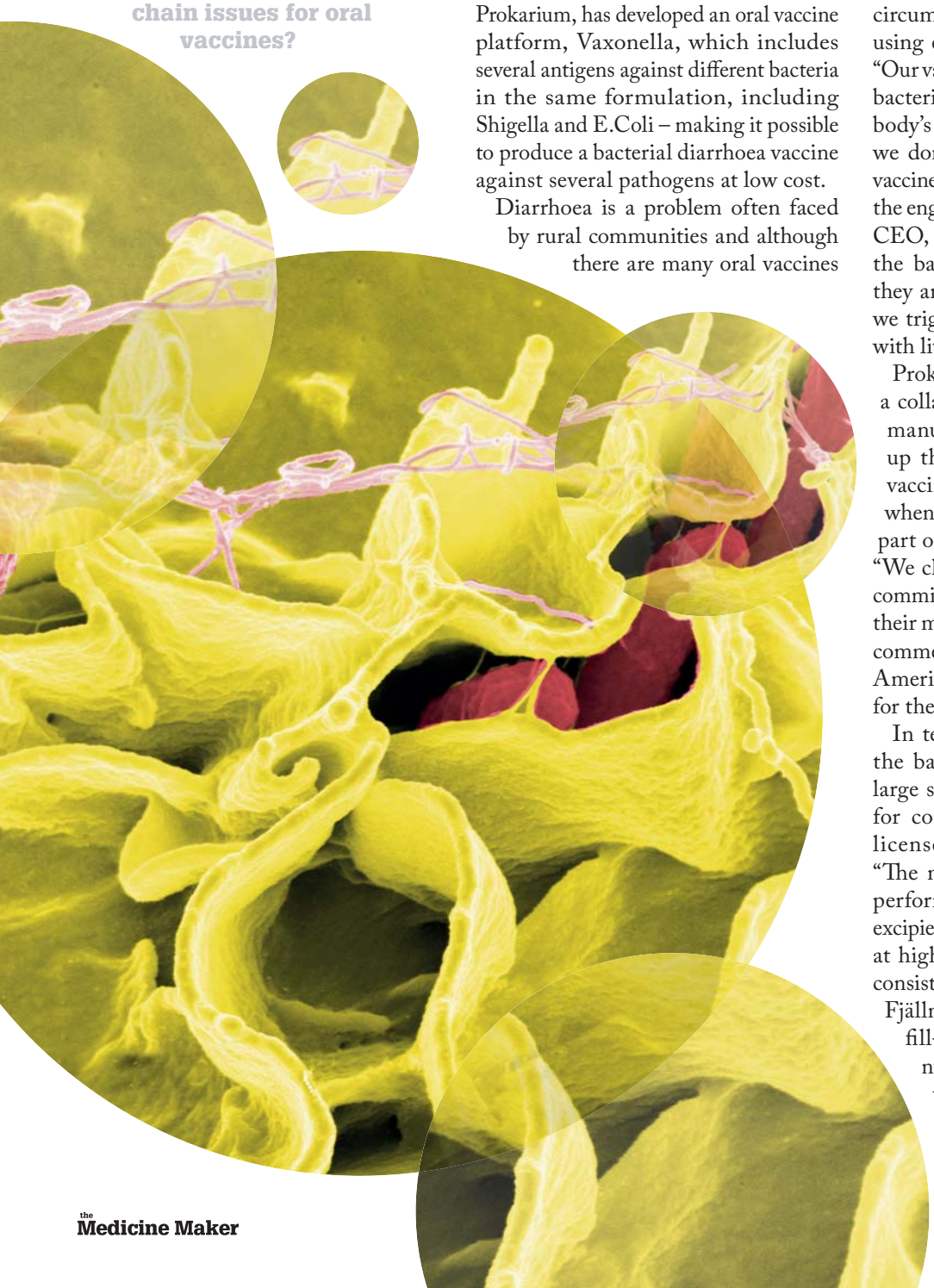
The total outsourced market has above GDP growth expectations at 6.6%, driven by the outsourcing trend and strong growth of the underlying pharma sector.



The outsourced manufacturing market grows ahead of pharmaceuticals, helped by increased outsourcing and outperforming sub-sectors (e.g., biologics).

Oral Vaccine Innovator

Can genetically engineered bacteria help alleviate cold chain issues for oral vaccines?



Shigella and E.Coli are the two main causes of bacterial diarrhoea – accounting for one billion cases and 600,000 deaths per year. So far, a broad-based vaccine that protects against the various bacterial species that cause diarrhoea has eluded scientists. However, UK-based company, Prokarium, has developed an oral vaccine platform, Vaxonella, which includes several antigens against different bacteria in the same formulation, including Shigella and E.Coli – making it possible to produce a bacterial diarrhoea vaccine against several pathogens at low cost.

Diarrhoea is a problem often faced by rural communities and although there are many oral vaccines based on live attenuated organisms on the market, modern subunit vaccines are not amenable to oral delivery, and must be refrigerated and injected. This results in significant logistical and cost concerns – especially for warm or remote locations.

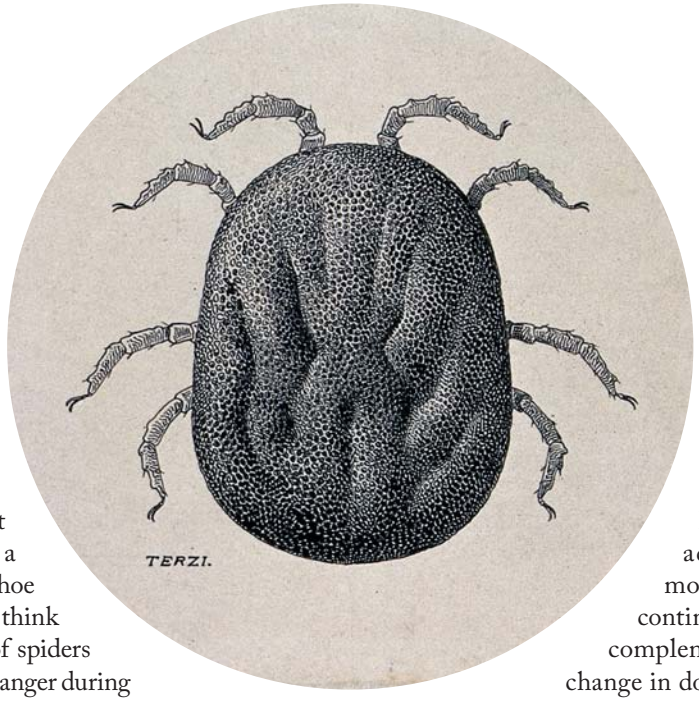
Prokarium have managed to circumvent the cold chain problem by using engineered Salmonella bacteria. "Our vaccines are produced by engineered bacteria only once they are inside the body's own immune cells. This means we don't have to stabilize the protein vaccines, but rather 'only' have to stabilize the engineered bacteria," says Prokarium CEO, Ted Fjällman. "By programming the bacteria to produce vaccine once they are engulfed by the immune cells, we trigger strong and broad immunity, with little or no side effects."

Prokarium have recently announced a collaboration with Mexican vaccine manufacturer, Probiomed, to scale up the production of the diarrhoea vaccine. The collaboration came about when Fjällman was visiting Mexico as part of a UK trade delegation in 2015. "We chose Probiomed because of their commitment to biopharma development, their manufacturing expertise, and their commercial reach in Mexico and Latin America, which could be key markets for the vaccine," he says.

In terms of scale up, Fjällman says the bacterial vector can be grown at large scale and packaged into capsules for consumption (as is done with a licensed typhoid vaccine, Vivotif). "The main challenge is to be able to perform the process with all the new excipients needed to stabilize the vaccine at high temperatures – and to do this consistently from batch to batch," says Fjällman. "We also need to perfect the fill-finish process to minimize the number of capsules that a person would have to swallow in order to get the appropriate dose." *JS*

What's Your Poison?

Could compounds derived from tick saliva make effective pharmaceuticals?



For many people, the mere sight of a creepy-crawly can evoke a fight-or-flight – or perhaps a shoe or scream – response. Scientists think we've evolved an innate fear of spiders because they presented a great danger during the evolution of our species. And the same goes for scorpions, snakes, ants and other potentially venomous creatures. Ironically, however, a number of dangerous biological poisons make excellent medicines. We spoke with Gur Roshwalb, CEO of Akari Therapeutics, who told us how therapeutics are being developed from venomous tick saliva.

Why are venoms good candidates for treatments?

One of the most fruitful places to look for human medicines is the vast array of poisons and venoms that organisms have evolved over the course of millions of years to ward off predators or to attack prey. The bodily mechanisms that venoms derail often turn out to be the same ones doctors need to manipulate in order to treat disease. These naturally occurring substances already do what human-made drugs do: target and modulate key molecules in cells. By controlling the dosage or slightly altering the chemical composition, scientists can turn toxins into treatments.

Why tick saliva?

A tick takes a blood meal from its host for anywhere from 12 hours to two weeks, depending on the tick. To stay on the host for that long, we believed the tick had to be suppressing the local immune system of the host. Our CSO, Miles Nunn, was tasked with discovering the presumed complement inhibitor – which he did in the saliva of the Ornithodoros moubata tick.

Mile's discovery was important because it is known that complement inhibition can also play a key role in addressing a range of immune disorders. We have derived a new inhibitor of the complement protein C5, called Coversin. This is our company's lead product. C5 modulates the host immune system to allow the parasite to feed without alerting the host to its presence or provoking an immune response. Coversin acts on complement component-C5, preventing release of C5a and formation of C5b – 9 (also known as the membrane attack complex or MAC).

How has the compound performed in the clinic?

We have demonstrated clinically meaningful symptomatic improvement in an eculizumab-resistant, paroxysmal nocturnal hemoglobinuria patient self-administering Coversin for more than a year. The patient continues to demonstrate complete complement inhibition without any change in dose, neutralizing antibodies or injection site reactions. Paroxysmal nocturnal hemoglobinuria is a rare, and often fatal, blood disorder with no current treatment.

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

Think Small, But Smart

Small molecules already represent the bulk of the contract manufacturing market and FDA approvals are on the up. For CMOs, this presents opportunities and challenges.

By Matt Moorcroft, Vice President at Cambrex, New Jersey, US.

Ten years ago, the pharma manufacturing industry looked very different; the age of the blockbuster drug had reached its zenith and sites across the US were being shut down, mothballed, or consolidated. Indeed, many believed the industry was heading to low-cost countries in Asia, lost forever from the West.

The times have changed and today's reality is a stark contrast. There is a critical lack of capacity within small molecule manufacturing in the US and other Western countries. Pharmaceutical companies are repatriating projects from Asia, and at the same time FDA approvals for small-molecule new chemical entities (NCEs) are increasing. Biologics and biosimilar drugs are also seeing high growth, but when it comes to outsourcing, the market is still dominated by small molecule APIs (both originator and generic products). Biopharma products represent only a fraction of the contract manufacturing market.

For contract manufacturing organizations (CMOs), the growing demand for small molecule manufacturing capacity presents new business opportunities, but also challenges. Given that many thought manufacturing would move to Asia, a number of companies have neglected investment in recent years and only taken on projects that fit with legacy capacity, which means they now face problems in terms of responding to newer market demands.

The key, of course, is to have the right capacity, but this is easier said than done. First of all, what exactly is the "right" capacity? Contract manufacturing is notoriously difficult to predict. Investment in the wrong capacity costs money – and finding projects to fill these assets can be a lengthy exercise. Finding the balance is crucial and to this end it's important to understand industry trends.

"It is wrong to assume that a small patient population means a small annual volume of API."

We've spent a great deal of time looking into historic market trends and analyzing the current pipeline of drugs to assess what the future market demands could be. One clear trend is a decline in the number of NCEs with a volume range above 10 metric tons (mt) a year. Of the 27 NCEs launched in 2014/2015,

12 are forecast to reach volumes of just 1mt at their peak. To frame this in the context of blockbuster drugs, however, there are small molecule drugs in the region of 1-10mt volumes that can create sales in excess of $500 million, especially in the area of oncology, where drug pricing per pill can be orders of magnitude higher than other drugs.

The number of drugs requiring very low manufacturing volumes – less than 10kg of API per year – has also dropped. With their significance to patient care, orphan drugs are very much promoted by the FDA, but it is wrong to assume that a small patient population means a small annual volume of API. Not all orphan drugs are low volumes – some are taken in high doses and consumed daily.

For any CMO, being able to offer a range of manufacturing services and options to customers – no matter what stage in the lifecycle or the volume of the drug – is a great advantage, as is offering key late-stage intermediates and starting materials for security of supply. But it's important to not just focus on capacity. The CMO market is highly competitive and new technologies can be a key point of differentiation – particularly technologies that meet the specific needs of drugs in the pipeline. At the moment, I see a trend towards contained facilities that can safely handle potent and highly potent molecules. While not all high potent drugs are exclusively oncology products, an increasing percentage of new oncology drugs coming on to market could be nominally classified as highly potent, although experts differ somewhat in their potency assessment. For a manufacturer, being in the position to meet this demand relies on having undertaken the investment and accruing the expertise in handling these projects to attract customers. Building new capacity from scratch can be difficult, which is why the market has seen so much consolidation and M&A activity – some think it's easier to buy than to build.

These are just a few of the key trends that I've noted, but overall the market is bright for CMOs. Far from the predictions that the rise of biologic drugs, as well as competition from low cost providers, would consign Western manufacturing of small molecules to history, the market is flourishing. Of course, nothing is constant and it would be foolish to think that CMOs should rest on their laurels, but through smart investment strategies, companies can aim to be flexible and responsive to the needs of the market.

"The number of drugs requiring very low manufacturing volumes – less than 10kg of API per year – has also dropped."

Time for Ethics and Honor

The pharma industry can't fix its reputation until it honestly faces up to its problems. Is it time for an industry ethical code?

By Mike Rea, CEO of IDEA Pharma.

In many ways, the pharma industry deserves its bad press. But treating the industry as a single, unified entity is unfair to the many ethical companies that wouldn't dream of price gouging. However, I think that lobby groups (for example, the Association of the British Pharmaceutical Industry, the European Federation of Pharmaceutical Industries and Associations, and the Pharmaceutical Research and Manufacturers of America) are doing the industry a disservice by defending unethical behavior. Of course, the industry does a lot of good, but we must

"In our industry, drawing the line between what is acceptable and what is unacceptable can be difficult – and is often blurred."

acknowledge and take action against the bad. It is for this reason that I have set out to develop an ethical code for the pharma industry.

In our industry, drawing the line between what is acceptable and what is unacceptable can be difficult – and is often blurred. My aim is to draw that line and ask companies to put themselves on one side or the other. We need to ask ourselves, what's the difference between 9 percent, 400 percent and 4000 percent? Who decided that Brent Saunders' 9 percent rise per year is okay and Martin Shkreli's 4000 percent isn't? Shkreli may be hard to like, but he's not all wrong: he makes the point that when a large pharma company realized what he was planning to do with the drug he wanted to buy, they stopped the sale. And then immediately increased the price themselves by 400 percent. If we are no more ethical than he is, we have a problem. We should be having these conversations transparently with payers, physicians and patients. We should be comfortable that we have an ethical core to what we do.

When I first started developing my code, I was curious to find out whether I would get a positive response. And the good news is that there are a number of major pharma companies who are happy to get on board.

Developing an ethical code won't be easy. Am I the right person for the job? I'm sure I'm not. I have no training in ethics. But someone has to be the instigator – and we're surrounded by medical ethicists, ethical review board members, and other experts. By announcing that we're developing an ethical code for the industry, we are calling out for other experts to get involved – and we've had a number of great people come out of the woodwork with ideas on how to do it.

What will it cover? To start with, there's pricing, trial inclusion/exclusion, trial designs, data transparency, promotion, developing world access, intellectual property and generic competition – and over a hundred other areas. The first step is to figure out what questions we're going to answer. I don't feel that lobby groups and industry organizations should be part of creating the code. They can – and I hope they will – endorse the code, but I do not want them to coopt it. By November 2017, we've committed to have a 1.0 version of the code.

We all want to feel proud to work for pharma. And I bet each and every one of you is sick of being concerned about mentioning that you work for pharma in polite dinner party conversation. We have no defence. Yet, I have never met anyone (on the R&D side, particularly) who didn't come to work to make great medicines and a reasonable profit. We need the world to know that we have debated and discussed what we do, and that we believe we have an ethical position.

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Blistering Headspace

Stability challenges are a constant issue for new formulations, which is why packaging solutions should target headspace.

By Craig Voellmicke, VP of Business Development for CSP Technologies, US.

Oral solid dose (OSD) – a category that comprises both capsules and tablets – remains the most popular delivery method in use today. And it's easy to see why. OSDs are well understood from a manufacturing point of view and well accepted by patients. They are also convenient, cost effective and easy to transport and store. The industry continues to investigate other delivery methods, but OSDs are likely to be the preferred choice for the foreseeable future, especially given the continuing advances in formulation technologies that are allowing increasingly challenging APIs to be delivered orally. Additional innovation continues in the area of modified release specifications, such as sustained and controlled release, which offer more convenient dosing, as well as orally disintegrating tablets that can target patients with swallowing issues.

"Developing advanced protection solutions for blisters is more challenging than it may at first seem."

Unfortunately, new formulation approaches can come with a downside: instability in the face of moisture, oxygen,

"Incorporating smarter packaging solutions can sometimes be perceived as a headache by pharma manufacturers."

hydrocarbons and other gases. Instability can also come from reactive impurities, such as formaldehyde and formic acid, which have been implicated in the degradation of drug products and cross-linking in gelatin capsules. As a result, packaging solutions must advance to face these significant challenges. Though many packaging solutions today can effectively protect products from unwanted moisture and oxygen ingress, I believe the industry can do better. We need to be developing state-of-the-art packaging solutions that can proactively remove moisture and gases within the package headspace, as well as reactive impurities and off-gassing from OSDs.

Bottles and blisters, the OSD package options of choice, each face headspace management challenges, which begin at the time of production, and continue with ingress over time and in various environmental conditions. Despite the larger amount of headspace, bottles have a simpler solution than blisters for headspace management – it's very easy to incorporate sachets and canisters to provide desiccant and/or scavenger capabilities, and there are many solutions to choose from. Adding barrier technology to the actual bottle material can also provide enhanced degradation protection.

But what about blisters? Developing advanced protection solutions for blisters is more challenging than it may at first seem. The headspace within individual blisters is very small, but it can significantly impact shelf life, depending on the sensitivity of the OSD. Aluminum foils and high barrier thermoforms are popular options for reducing ingress, but headspace moisture, gases and impurities can persist.

Solutions have now started to emerge that can help control the internal atmosphere of each blister cavity. Desiccant and scavenging agents can be adhered to the blister's lidding via heat-staking just prior to sealing, so that they sit beneath the capsule or tablet and completely within the sealed space of the individual blister. The process can be performed without using adhesives, which is important as adhesives can generate the very additives that the technology seeks to remove. Using silica gel or molecular sieve technology, outfitted blisters can be customized to absorb tailored amounts of water vapor.

Incorporating smarter packaging solutions can sometimes be perceived as a headache by pharma manufacturers and contract packagers, but it's now relatively straightforward to identify the best options by using simulated modeling, which examines the impact of blister solutions with various blister materials and designs. Attractive options can be examined through prototyping and shelf-life testing to determine the desiccant or scavenger performance best suited to protecting a particular OSD.

With recent improvements in process machinability and cost-effectiveness, there are now far fewer reasons to pass up smarter blister packaging innovations that can add true value to a critical stage in the lives of OSDs: the varying timeframe between final packaging and ultimate consumer use. Pharma manufacturers who dedicate research and resources to creating advanced formulations are well advised to consider the totality of their products' lifespans. The technology now exists to more exactingly protect blistered products from stability issues throughout their supply chain journey. Why risk not having it?

Freezing Down Time in Bioprocessing

Can high density cryopreservation allow biopharma manufacturers to buy back time? The answer is "yes" – and specialized media (both catalogue and customized) for perfusion processes are being designed for this purpose.

By Jochen B. Sieck

Biotechnology, the industrial application of biological organisms, has fascinated me since school, so after obtaining my diploma, biopharma research and development was an obvious next step. For my PhD thesis, I focused on the response of mammalian cells to shear and other stresses. Subsequently, I worked as an industry post-doc on perfusion processes, including process development, medium development and high-density cryopreservation technology (HD Cryo).

Today at Merck KGaA, I am the head of the Cell Culture Media R&D Laboratory – my team works to improve HD Cryo in order to make bioprocessing more efficient and flexible.

At present, conventional upstream processes begin with 1 ml of banked (frozen) cells, which are then expanded to 15,000 liters for a classical fed-batch process. This takes weeks, during which time a part of the manufacturing site is blocked and unproductive. After thawing, cells typically go through a "crisis" with viability temporarily decreasing – sensitivity to this is very cell line dependent. Also, like many biological processes, cell growth after thaw isn't exactly predictable and there is some uncertainty as to when the final culture will be ready. So if you need to run different processes in a given plant, the facility will never be optimally used, due to bottleneck effects.

From my point of view, it seems odd to start with 1 ml in order to make several thousand liters. Compressing this phase would dramatically increase the flexibility and capacity of a manufacturing plant. Being highly conservative, however, the pharma industry has invested few resources in investigating methods for improving the efficiency of the expansion phase. That is why Merck has turned its attention to this field. In particular, we believe that HD Cryo has the potential to significantly enhance bioprocessing capacity.

Bioprocessing in HD

Briefly, HD cryo involves expanding cells of interest and preparing frozen seed train intermediates of them, not in 1 ml vials, but in larger vials, or in bags of up to 100 ml volume. Freezing culture aliquots in high volume and high density, dramatically shortens subsequent expansion processes because when you thaw one of the bags, you can start the expansion process at a later time point. In effect, you are freezing down time!

At present, there is no industry standard for HD Cryo technology. We have undertaken several internal case studies, focusing on different aspects, but pulling all the data together in a comparable way remains difficult. We are working to change this, and our overall aim is to look at the bigger picture and make HD Cryo simple, reproducible and effective.

Currently, we are investigating the criticality of the different components of HD Cryo processing – namely the freezing media, the bag assembly, and the filling and freezing process, all of which need to be performed without stressing the cells. We are examining different families of CHO cells and ensuring that we understand which aspects of the process they are sensitive to and why – and we are confident that our systematic approach will result in process technology suitable for all customer needs.

HD Cryo media have to protect the cells from stress during the freezing process, which is a significant factor in the viability drop-off after freeze-thaw. The idea is that the post-thaw cell population will be of very high viability and will start growing immediately, without any crisis/recovery lag phase. Development of the medium has required us to work backwards (upstream) from the medium we recently developed for intensified processing in production stage bioreactors (1), as it is critical that both media are compatible with each other. If they are too different then cells might go into a lag phase when the medium is changed, and the time advantage of HD Cryo would partially erode.

Our vision is of a seamless suite of mutually compatible bioprocessing products. Thus, having developed an intensified perfusion medium to boost productivity at the main stage bioreactor, we are now advancing HD Cryo to intensify processes upstream, while remaining cognizant of the need for both sets of products to work together effectively. Essentially, we are giving our

customers the tools to intensify all steps up to the main stage reactor. HD Cryo is a key component of the toolkit, making expansion processes, including N-1 bioreactor perfusion processes, faster, more reproducible and more flexible.

Reaping the rewards

I truly believe that the benefits of HD Cryo technology are very significant; for example, it can cut three weeks from the upstream process, enabling manufacturers to start the process two weeks prior to the main stage bioreactor, instead of five weeks prior. In fact, we've seen customers presenting at conferences who have increased the capacity of stainless steel manufacturing plants by two or three-fold through de-bottlenecking using HD Cryo. The technology is also advantageous in the context of disposable bioreactors in smaller plants, where it increases flexibility by enabling intensification of the seed train expansion process. It also enhances the capacity of processes run in small-scale bioreactors, which is very important for disposable systems with a maximum volume of only 2,000 litres. If you're replacing stainless steel plants with single use systems, you must be creative and intensify your process as much as possible, and HD Cryo can play an important role in this regard.

HD Cryo can play a role in R&D too. Freezing down 20 HD Cryo bags gives you 20 identical starting points (i.e., cell populations with exactly the same expansion history) for the process under development. The technology allows users to remove much of the variability associated with the manual steps currently used in expanding cultures from the first 1 ml vial through to shake flasks, and makes bioprocess R&D becomes much more reproducible.

Looking ahead, I foresee a continued trend for smaller and more flexible manufacturing plants based on single-use systems. This is partly a consequence of market fragmentation – blockbuster drugs are being replaced by drugs for smaller populations, and this implies smaller manufacturing volumes. Similarly, the advent of biosimilars puts downward pressure on manufacturing volumes because the innovator has to share the market with biosimilar competitors. Personalized medicine and the pursuit of niche indications also suggest relatively small product volumes. All this, together with a surge in innovative biopharmaceutical drug formats, indicates that manufacturers need to be ready to supply a greater number of products at lower volumes. This will require more flexibility – and that is one of the key advantages of HD Cryo. HD Cryo provides increased speed, flexibility and capacity, and for a given process these benefits are achieved without any detrimental effects on cost of goods, quality or yield. The pre-culture expansion can be done at any point and in any place; frozen HD bags can be shipped worldwide to carry out main stage production wherever and whenever it is appropriate. In effect, HD Cryo uncouples expansion from production in both time and space.

Jochen B. Sieck is Head of Cell Culture, Darmstadt, Merck KGaA, Darmstadt, Germany. Email jochen.sieck@merckgroup.com for more information about high-density cryopreservation.

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BATTLEFIELD PHARMA

Tens of thousands of soldiers are stationed on battlefields in remote locations where even the most common drugs can be hard to come by. Portable units that can synthesize both small- and large-molecule drugs on demand may sound like the work of science fiction, but efforts in this field are progressing at a surprising pace.

By Nick Miller

Patients expect that the medicines they need will be available when they need them. In the industrialized world, with robust supply chains and advanced infrastructure, this expectation is usually met. In remote areas, however, it's a different story – mainly due to the difficulties of transporting and appropriately storing medical supplies in the context of poor infrastructure. These issues are typically associated with extreme circumstances, such as natural disasters and epidemics, but they also apply to battlefields.

Accordingly, the Defense Advanced Research Projects Agency (DARPA) – the blue-sky research arm of the US military – has been investigating methods of overcoming the logistics barrier so that medicines can be reliably accessed by soldiers stationed in remote areas. DARPA's vision is of portable devices that can rapidly synthesize FDA-approved drugs, as required, in any location. In pursuit of this goal, the agency is funding a number of researchers under its Pharmacy on Demand (PoD) and Biologically-derived Medicines on Demand (Bio-MOD) initiatives. PoD, which has already passed beyond the proof of principle stage, relies on miniaturization of known reactions in order to quickly and cost-effectively generate batches of small-molecule drugs from shelf-stable precursors. The focus of Bio-MOD, an equivalent system intended for the production of biologicals, is on the development of systems that can produce several therapeutic proteins from a single cell line, or cell-free system, in a device the size of a laptop.

Portable, on-demand capabilities would transform drug logistics in extreme environments, but the implications may also extend to the whole pharmaceutical manufacturing industry, enabling distributed manufacturing and making it economically feasible to manufacture a specific drug and dose according to the specific needs of each individual patient. Some even speculate that each pharmacy or doctor's office may one day have its own API manufacturing capability.

How close are we to the real-world implementation of drugs-on-demand technology? To find out, we spoke to DARPA, as well as some of the researchers involved in this exciting field.

DRUGS ON DEMAND

Tyler McQuade has gone from chemistry professor to Deputy Director of DARPA's Defence Sciences Office. Flow chemistry processes have been a continuous theme in his research. Here, he explains how clever chemistry can help make drugs on demand.

How did you become interested in the idea of making medicines on demand?

Before joining DARPA in 2013, I spent many years in academia where I focused on synthetic organic chemistry, particularly catalysis technologies to enable new chemistries. As a result, I became very familiar with continuous processes in the context of flow chemistry. Like most academics, I expended a lot of time and effort to achieve tenure, but after reaching that point I decided that I was ready for something new, and I was delighted to have the opportunity to join DARPA. It's a unique organization where they are happy for us to push the limits of creativity, providing that the work is groundbreaking with the potential to improve national security. DARPA reaches for transformational change instead of incremental advances. I started out as a program manager, before becoming Deputy Director of DARPA's Defense Sciences Office in January 2017.

Before joining DARPA, I'd felt for some time that pharma manufacturers were ready for new manufacturing technologies, but that they needed somebody else to remove the major regulatory risks. DARPA's interests in battlefield medicine seemed to go right to the heart of the problem – the need for more flexible manufacturing technologies. And DARPA is not the only organization working in this area – there are many other excellent research groups working in this field too – in particular, Steven Ley and Lee Cronin are outstanding participants; so I think our programs are part of a broader revolution in medicine making. Perhaps that is partly due to the similarities between the logistical challenges faced by both battlefield medicine and personalized medicine. Personalized drugs specific to a given patient may be theoretically feasible, but unavailable in practice because of logistical or cost constraints – it's little different from a battlefield scenario.

What are the challenges of delivering drugs to the battlefield?

On the battlefield, doctors do not have access to all the resources and medicines they would in a normal hospital – and if you run out of a medicine you can't just request more stock and expect it to arrive quickly. It's very frustrating for physicians, but it's simply not possible to get everything they might require to the frontlines. Even with drop-shipping and helicopters, it can't be done; cargo space is limited.

Also, battlefield logistics is associated with a lot of wasted medicines. For example, chemical warfare antidotes must be carried at all times because if troops are exposed they must be treated immediately. But once the medicines are out of date, they are discarded. Ultimately, this means that a large quantity of military-specific drugs are being bought, transported and stored in case of a very low-probability event, and then thrown away. It would be better to have just a small amount of drugs on standby to kick-start the response to an emergency, and to have an on-demand machine to manufacture sufficient drug to cover any shortfall. This means that troops would be mainly stocking stable raw materials with an unlimited shelf-life, rather than an expensive drug with a relatively short shelf-life. It would eliminate a huge yearly cost.

What are DARPA's main medicine-on-demand programs?

DARPA's goal is to develop an on-demand API manufacturing platform that can produce up to 20,000 doses per day. We have two major programs in this area: PoD and Bio-MOD. PoD is the most advanced project and has been running since 2010; Bio-MOD was created in 2012. It would be better to have a single box that could manufacture both biologics and small molecules, but the techniques are too dissimilar to make that work. Even for small molecules alone, compressing all the different fundamental unit operations into a single box has been challenging, but our collaborators have made significant progress in this field.

In 2015, we also introduced the "Make-It" initiative – the objective being to develop the ability to manufacture any compound from just a few precursors. Traditional small-molecule API manufacturing begins with raw materials that are then refined into intermediates, which, in turn, are subjected to transformations prior to being made into final products. For example, BP purifies raw materials and gives them to BASF, which refines them and gives them to Pfizer, which conducts transformations, and so on, until you reach the final product. Make-It asserts that this entire stream can fit into a box – an ambition which has been made possible by advances in synthetic organic chemistry and artificial intelligence (AI). The AI's function is to apply organic chemistry knowledge and to design the optimum synthetic pathway from simple raw materials to any pharmaceutical product. Our partners have developed some amazing AI tools that are already equivalent to a well-trained post-doc in terms of the quality of the syntheses they design. We're also developing hardware to carry out those syntheses.

Ultimately, we hope to develop a stand-alone system from

which you can generate any molecule, whether new or known. The AI component will figure out how to make it, and the machine will produce it from a few simple raw materials.

Making drugs on demand sounds like science fiction. At the outset, did you believe it would work?

I was actually one of the few people who thought it would be possible! Before I joined DARPA, I was the first recipient of funding under the PoD program, resulting in a modestly complex continuous synthesis system, using solid-supported reagents, which allowed end-to-end PoD-type synthesis of ibuprofen with decent purity and yield. To give you the history, DARPA's medicines on demand effort was initiated by Geoff Ling (who served as served as the Director of DARPA's Biological Technologies Office from 2014 until 2016). In one conversation I had with Geoff, he suggested developing a flexible synthetic system that could make every possible medicine from basic materials – such as pencil lead, eggshells, fertilizer and a sprinkle of metal! While it is true that those materials are sources of the key elements – carbon, sulphur, nitrogen and metals – I wanted to back up a little, and suggested starting with themes, such as focusing on limited types of reaction that would give a broad range of output. We soon demonstrated that you could take essentially the same reactions that were used for making ibuprofen and synthesize atropine, although we never published this.

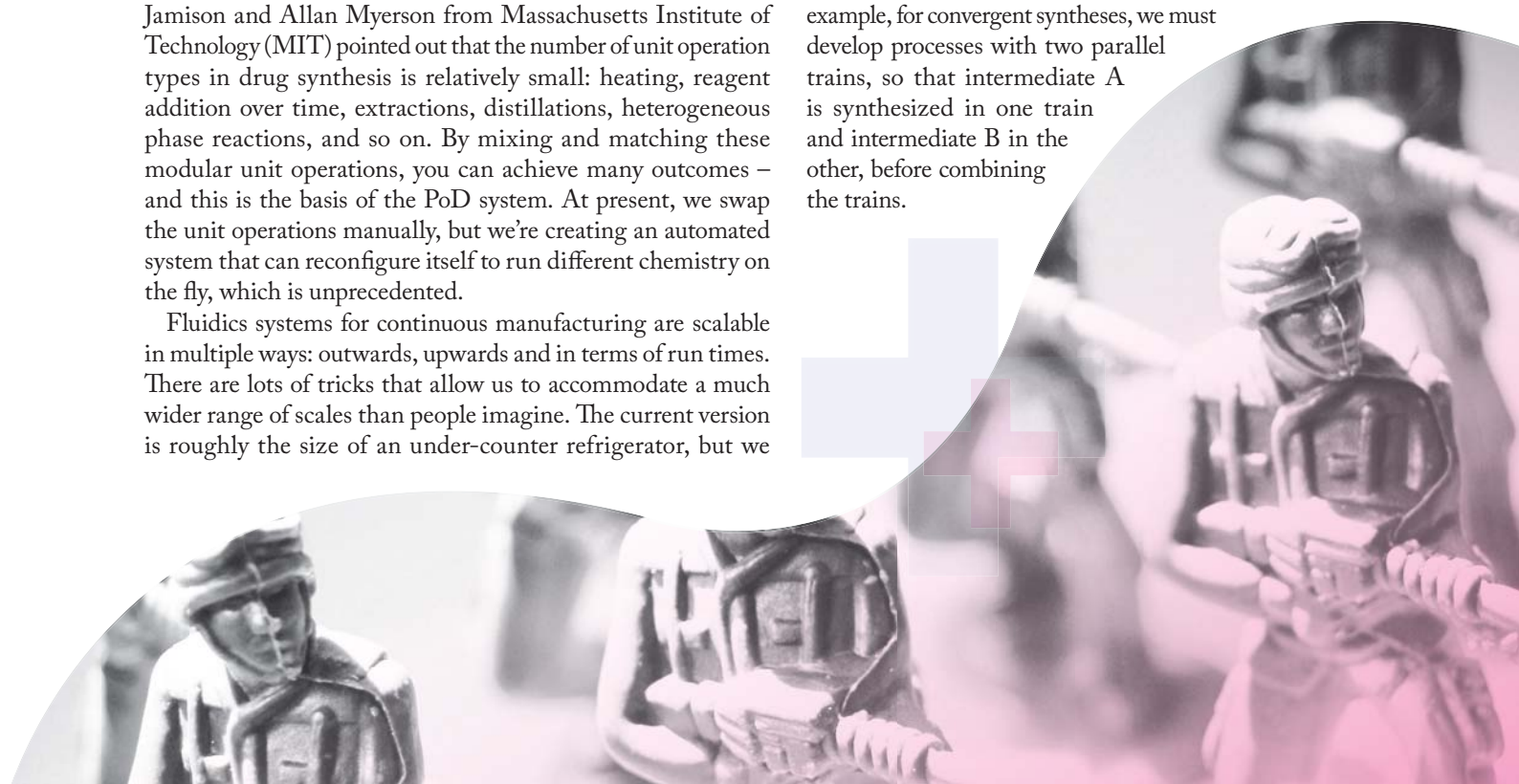
Since then, our collaborators have brought a chemical engineer perspective to the project. For example, Klavs Jensen, Tim Jamison and Allan Myerson from Massachusetts Institute of Technology (MIT) pointed out that the number of unit operation types in drug synthesis is relatively small: heating, reagent addition over time, extractions, distillations, heterogeneous phase reactions, and so on. By mixing and matching these modular unit operations, you can achieve many outcomes – and this is the basis of the PoD system. At present, we swap the unit operations manually, but we're creating an automated system that can reconfigure itself to run different chemistry on the fly, which is unprecedented.

Fluidics systems for continuous manufacturing are scalable in multiple ways: outwards, upwards and in terms of run times. There are lots of tricks that allow us to accommodate a much wider range of scales than people imagine. The current version is roughly the size of an under-counter refrigerator, but we can make the boxes smaller or larger. In Bio-MOD, we have made a handheld device that can produce a single dose, but we also have a bigger version that can make thousands of doses.

What is required to make these new technologies usable in the field?

The first hurdle is regulatory review. The FDA must be assured that drugs are produced in a verifiably safe way, and this could be challenging for distributed manufacturing systems. But I welcome that scrutiny – the agency's rigorous standards have helped us visualize the future as GMP in a box, and work out how to create and monitor GMP standards in that environment. Manufacturing in a box actually has many advantages; for example, it is easier to control particle count than in a big factory. Also, we are borrowing concepts from biomanufacturing, such as disposable linings for reaction vessels to prevent cross-contamination, and removable parts to reduce impurities. In theory, you could make a reactor that is hermetically sealed from site of production to product implementation. We are addressing all the regulatory concerns right now. In fact, we've built a box specifically designed to be part of an FDA regulatory filing, and we'll present data generated by this machine to the FDA in 2018.

Next, we must enhance the PoD system's capabilities so that it can make more complex molecules. At present, molecules with challenging chemistry, such as atropisomers, structures with 10 stereocenters, or really congested quaternary centres, are still beyond us. And some reactions that are trivial in batch processes remain problematic in our system. For example, for convergent syntheses, we must develop processes with two parallel trains, so that intermediate A is synthesized in one train and intermediate B in the other, before combining the trains.



How do you envisage the future of drug manufacture?

In an ideal world, when a patient visits the doctor, his genome would be quickly sequenced, and perhaps also screened at the epigenetic level. The information would be sent to the drug synthesizer in the doctor's office, which would immediately make the perfect drug for the patient. From my point of view, the exciting aspect of all the work in this area is that it could significantly improve the quality of medicine, while at the same time opening up new ways of interacting with patients and improving safety for the people who actually make medicines.

There may be bumps in the road, of course. But the people in the pharma industry are among the smartest I know, and I am certain that they will be able to adjust to this new reality and embrace it.

Another difficulty may be that the market is just not ready for these developments. In fact, I often liken these technologies to the first television. When the cathode ray tube was first assembled into a machine to disseminate pictures, it was in an uncomfortable marketing position: why would anybody want a television when there was no content for it, and why would you create television content if nobody had one? We are in a similar position now with medicine on demand. Of course, it's hard to envisage this kind of system because it's so new, and people are sceptical because they hear so much hype about the future (personally, I am still waiting for somebody to make a flying car). But our work is gaining traction and even the FDA believes it will be an important part of medicine manufacture.

GOING WITH THE FLOW

Three researchers at the Massachusetts Institute of Technology – chemical engineer Klavs Jensen, chemist Tim Jamison, and crystallization expert Allan Myerson – decided to collaborate and bid for a DARPA grant, resulting in a pharmacy on demand system based on continuous chemical flow processing.

Having previously collaborated in the MIT-Novartis Center for Continuous Manufacturing on the development of a scaled-down, end-to-end flow chemistry process to manufacture tablets from simple chemical inputs, Jensen, Jamison and Myerson were well-positioned to respond to DARPA's call for PoD proposals. However, the original system, although much more compact than a normal pharmaceutical process, was the size of a shipping container – hardly the portable device that DARPA was looking for.

"Since then, however, advances in flow chemistry have expanded the chemist's toolbox, allowing for faster reactions in smaller vessels," says Jensen. "We have now developed a fridge-sized, continuous flow system that can be reconfigured to produce a variety of different small-molecule drugs – with different chemical structures and synthesis routes – to US Pharmacopeia standards."

Considering that a normal pharmaceutical process operates in large batches requiring big vessels, squeezing it into something portable isn't straightforward. Part of the solution lies in the geometry of the upstream reaction tubes. According to Jensen, the right design means that the chemical synthesis reaction can be heated and cooled more quickly, achieving higher temperatures and completing the reaction in less time than a traditional batch process.

The downstream process required devices capable of crystallizing and purifying the API output from the upstream process. Initially, the team focused on liquid formulations. "The original project brief specified that the drugs would be used within 14 days, which means that solutions or suspensions are acceptable – these don't have a long shelf life, but if you're making medicines on demand and using them quickly then this isn't a problem," says Myerson. "Subsequently, DARPA has funded an additional project focusing on solid formulations. We've now built a device that blends the API with excipients, and forms the mixture into tablets. We're testing this now, but dealing with powders on such a small scale has been difficult."

"Building the whole system has been a significant challenge, especially in terms of making it relevant to the needs of DARPA. Counter-intuitively, it has resulted in fundamental research leading to new chemistry and other new technology," says Jamison. "For example, because we were unable to source commercial equipment suitable for the scale on which we needed it to operate, we had to develop many mechanical components ourselves. One challenge was designing a pump that worked reliably over extended periods with many different chemicals."

Initially, the team experimented with simple pharmaceuticals, such as diphenhydramine, lidocaine, fluoxetine and benzodiazepine, but they are now working to broaden the range of molecules that the system can manufacture. Recently they've been looking at drugs with more complicated structures: ciprofloxacin and doxycycline.

Jamison adds, "Keeping the device relevant to real-world needs has been a fundamental requirement of DARPA from the very beginning, and a longer-term goal is for the system to be useable

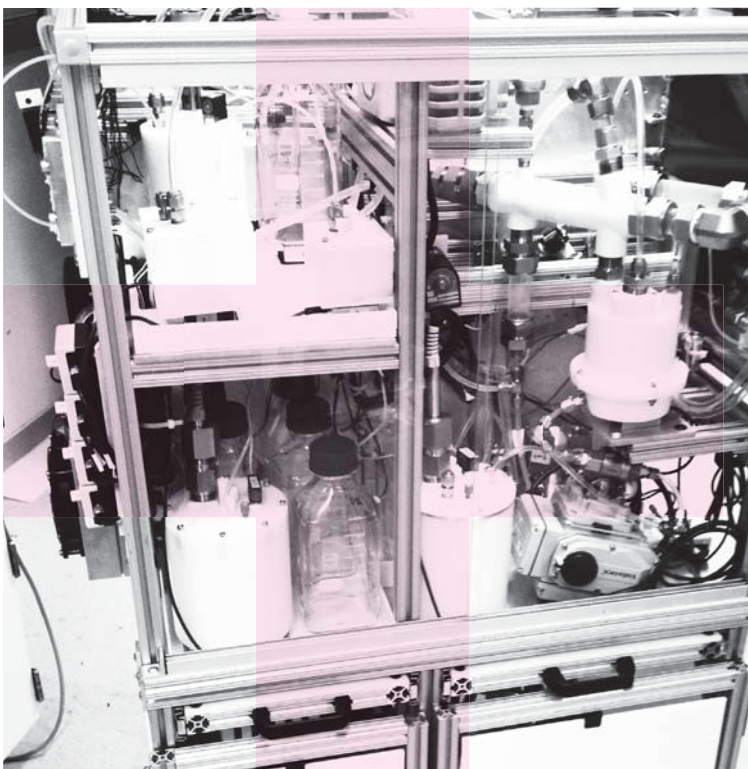
in the field by non-experts. DARPA also had very specific requirements regarding the number of doses that the equipment would be required to make. It wasn't enough to just run the process for 30 minutes and declare victory!" The system has been designed using a "plug and play" philosophy that allows components and units to be easily changed. For example, if it's not convenient to clean the system by flushing through a solvent then the contaminated tubing can be easily replaced and discarded after use.

"This type of device isn't just useful for the battlefield. For example, there's an industry trend towards drugs that target genetically defined populations – and manufacturers of personalized medicines would certainly benefit from flexible, fast production technologies," says Myerson. "Some companies are also interested in the potential of the technology for the cost-effective manufacture of clinical supplies in low volume."

"There are also benefits associated with the uniquely mobile nature of the system. It can be put in the back of a truck or on a plane, and it doesn't require much power, so it's ideal for remote locations," adds Jensen. "Others have raised the possibility of pharmacy-on-demand devices in drugstores and hospitals, so that organizations can make some drugs as required rather than keeping large, limited shelf-life stocks."

> "Others have raised the possibility of pharmacy-on-demand devices in drugstores and hospitals."

As Tyler McQuade mentioned on page 23, however, getting a distributed manufacturing system – particularly one that proposes to manufacture multiple drugs from a single device – to comply with regulatory requirements will be a challenge. "Essentially, our PoD system is no different from a pharmaceutical plant that makes several different drugs at one site," says Jensen. "In traditional manufacture, a site and process approval would be required for each product. In our case, as well as the device itself, each flow process would need approval."



Despite the challenges that lie ahead, the team are confident that portable systems will, in time, lead to important benefits. Jamison says, "Our post-docs and students put a huge amount of effort into this, and when it worked it was like a moon shot; we all felt that something new and important had been achieved."

Klavs Jensen is Warren K. Lewis Professor of Chemical Engineering, Timothy Jamison is Professor of Chemistry, and Allan Myerson is Professor of the Practice of Chemical Engineering, all at MIT.

CELL SCIENCE

The manufacture of cell therapies, antibodies, or other biologic drugs is a complex and time-consuming process that many would feel does not lend itself to "on-demand" systems. But synthetic biology could help to re-write the rules of biopharma production.

By Timothy Lu

I initially started out as a computer scientist, but I soon became intrigued by the emerging field of synthetic biology. People were talking about programming cells in a way analogous to programming computers. It sounded pretty exciting, so I switched fields and did a PhD in synthetic biology. I followed that with an MD, because I was interested in the clinical applications of the technology, and then, in 2010, I started my lab at MIT. We focus on the development of cell engineering tools for diagnostic and therapeutic applications, and we have been applying these technologies to enable on-demand biomanufacturing.

Moving from computer science to biology was a bit of a culture shock – after all, programming cells is much harder than programming computers! Synthetic biology is now in a stage that computing was in after transistors were invented – before we understood how to combine them in complex, scalable and robust systems. It took decades to develop design rules that enabled the development of modern computers, and learning how to program cells will require a similar effort. Just like computing power during the IT revolution, the core drivers of synthetic biology – the ability to synthesize or sequence DNA – are increasing at rates similar to, or greater than, Moore's Law (which noted that the number of transistors per square inch on integrated computer circuits would double approximately every year). We now have an opportunity to establish the design rules for creating complex, scalable, and robust biological systems.

> "We envisaged a laptop-sized system incorporating a cell line that could produce several different biologics."

Biomedicines on demand

DARPA sees synthetic biology as a potentially transformative technology. A few years ago, Geoffrey Ling launched Bio-MOD, but he knew that the relevance of such technology would extend beyond the military, into humanitarian applications, or even space exploration. I felt there was a good fit between our cell programming activities and other MIT expertise – for example, the micro-reactors for biologics manufacturing developed by Rajeev Ram in the Electrical Engineering and Computer Science department – so we jointly applied for DARPA funding, together with other colleagues at MIT and collaborating institutions with other relevant technologies.

We have focused on upstream processing, since this is where synthetic biology is most relevant. Currently, biologics are made in huge vats using cells that can only make single products. By contrast, we envisaged a laptop-sized system incorporating a cell line that could produce several different biologics. To achieve this, we had to develop two fundamental technologies.

First, we had to develop a micro-bioreactor that could accommodate a high density culture of our cells. Rajeev invented impressive little devices for culturing micro-organisms and even CHO cells at densities that matched or exceeded those achievable in a conventional bioreactor. Rajeev's system also allows us to dispense with batch manufacture – we rapidly flow

the media in, optimize the conditions and collect the output as a continuous process. Rajeev has been great to work; I think he's super-talented at making the portable devices necessary for medicine-on-demand applications.

Second, we had to develop cell lines that could produce any one of multiple drugs according to need. Currently, we are talking two or three products per cell line, but in the future it could be four or five. Basically, we program the cell with genetic circuits that allow us to modulate its gene expression – and therefore switch drug production on or off – according to components in the culture media (1). Applications include making small batches of combination therapies, such as anti-cancer immunotherapies, from a single cell line. It also raises the prospect of distributed biologics manufacturing. Highly centralized, capital-intensive manufacturing plants could be replaced by systems so small and flexible that anyone could have one. In fact, after we published the paper, we heard from people who were interested in making their own insulin! The system isn't ready for that yet though – there are many technical challenges, not to mention legal and regulatory hurdles. However, there are some potential near-term applications; for example, the ability to manufacture small batches of drugs for preclinical testing without having to invest in large-scale process optimization. Our system can help with that, so it could turn out to be a useful research and discovery tool. It could also help to reduce the price of R&D – and ultimately the price of biologics, which many people would welcome.

We are currently scaling up our system in terms of the number of drugs that we can express from one cell and the diversity of molecules that this approach can accommodate. Some of the key questions we'll be focusing on include how many therapeutic protein genes can you fit into a single cell? Does it make sense to make multiple different organisms for different sets of drugs? Is the upper limit 10 different drugs in a cell, or less? Also, are we working with the best organism? We chose yeast because it grows fast and gives high yields, but there are other possible hosts, and we are now testing alternatives. Hopefully it won't be long before we demonstrate production of FDA-quality drugs from our system.

Timothy Lu is Associate Professor of Biological Engineering and Electrical Engineering and Computer Science, MIT.

Reference

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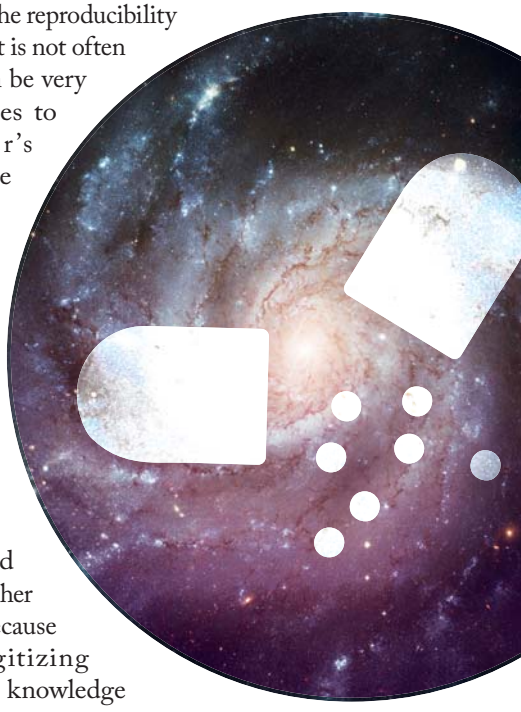
SPACE AGE DRUG DEVELOPMENT

Professor Lee Cronin, Regius Chair of Chemistry at Glasgow University, UK, has interests ranging from the origins of life to making drugs on Mars. Here, he shares his vision for the future of drug manufacturing.

The drug industry problem that DARPA wishes to address is very similar to the challenge I set for myself, and which I articulated in a 2011 TED talk on 3D printing for drugs (1). The problem is analogous to books going out of print in the publishing industry. Prior to the digitization of publishing, you would print a book by setting up a printing press and doing a printing run, but once the stock of printed copies sold out, the book would no longer be available. Similarly, drug manufacture requires constructing a complex and expensive production facility, but the know-how and infrastructure for making the drug is easily lost if, for example, the facility were to be adapted for a different product. This is because the facility is often bespoke. In the laboratory, the fact that some discoveries are done under bespoke conditions often means that it can be hard to understand how to reproduce them. This is part of the reproducibility crisis in chemistry – it is not often discussed , but it can be very hard for laboratories to reproduce each other's work. This issue of reproducibility, not just in chemistry but in all of science is now actively being discussed. It is a frustrating problem, but then I realized that "digitizing" chemistry could help not only solve the problem, but aid collaboration and further discoveries. This is because the process of digitizing chemistry combines knowledge



PROTEIN SYNTHESIS – BUT NOT AS WE KNOW IT

In a previous issue of The Medicine Maker, we reported on the work of James Collins, a faculty member at the Wyss Institute at Harvard University and the Henri Termeer professor of medical engineering and science at MIT (1). Collins and his colleagues are not working with DARPA or focusing on synthesizing drugs on demand, but they have developed a method for producing therapeutic molecules on-demand with freeze-dried synthetic gene networks (2). The technique could be used to produce complex biopharmaceuticals that do not require refrigeration – making them ideal for use in the developing world. "The lyophilized format negates the need for a cold chain, and is very simple to use – it requires only the addition of water to synthesize the protein of interest," explains Collins.

The work of the Collins Lab focuses on engineered gene networks using synthetic biology and systems. "Our work brings together engineers and molecular biologists to model, design and construct synthetic gene circuits, and to use these to reprogram living organisms for specific applications," he says. "The work stems from the Human Genome Project in the 1990s – the project produced large 'parts lists' for different organisms. We want to explore engineering these 'parts' into new and useful combinations."

To create the freeze-dried synthetic gene networks, a mixture of DNA, RNA, ribosomes and enzymes is removed from the cell and adsorbed to a solid support, such as paper. The preparation is freeze-dried and stored at room temperature – and protein synthesis takes place as normal once water is added.

"We have shown that these preparations can be the basis for rapid and inexpensive point-of-care diagnostics such as for Ebola and Zika (3). Now, we are investigating the use of similar cell-free extracts, but non-adsorbed, to make therapeutic proteins on demand (4)," says Collins. "These could be beneficial for providing biotherapeutics in remote locations, such as in emergency relief efforts, or in space."

Looking ahead, Collins and his colleagues are investigating the advantages of embedding the dried systems into clothing, for example, to serve as sensors to warn of exposure to an infectious agent, or as components of educational kits for students.

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of both the chemical instructions, the hardware for doing the reaction, and the precise way of executing the instructions complete with analytical data and observation, such that the entire process can be replicated without fail time and time again. I then realized that digitization meant that you wouldn't need to be a chemist to synthesize chemicals; and then I realized that you wouldn't even need a human present – the process could be fully automated as long as the system had the required software, hardware and wetware.

Coding chemistry

In my lab, we have developed an "app the industry" approach. Basically, we are pursuing the digitization of chemical space. The idea is to go from molecules to code, and code to molecules; once a manufacturing process is reduced to code, we can use the code to duplicate that process anywhere in the world. This will make drug manufacture very portable and easily distributable. In fact, it could disrupt the pharma industry in the same way that internet file sharing disrupted the music industry, but it's my job to disrupt. (I hope, however, that our chemical digitization will be enabling rather than destructive!)

In one approach, we have developed a device that can not only 3D-print reaction vessels, but also add chemicals to the vessels, run a reaction and purify the end-product. Essentially, this system can make a drug from nothing more than code and simple ingredients. What are the benefits of this? Remote chemical manufacturing is one key application. To demonstrate this, a few weeks ago we put our simplified version of the system on a nanosatellite, making drug manufacture possible (here we selected a reaction that makes a drug like molecule and the molecule is purified by crystallization) using a remotely operated device 500 km up, traveling at 8 km/s!

This has obvious applications in manned space exploration, where weight constraints limit the number of drugs we can transport. With our system, we can take a pallet of chemicals and a synthesizer, and make any drug, as required. So perhaps Elon Musk will take one of our drug synthesizers to Mars! At present, you'd need maybe fifty or a hundred different chemicals in order to synthesize any known small-molecule drug, but that is only because the technology is so new. Image recognition software needed thousands of lines of bespoke code at the beginning of its development, but now requires much less as the standard libraries are available to be applied to many different situations as a module. Similarly, as we get better at digitizing drug manufacture, we will learn how to perhaps reduce the number of chemicals needed. We may also be able to add in more steps, or develop new approaches to design chemicals that can be used to expand the number of accessible drugs. For example, the chemical outputs from one process could be used as inputs for another process, so you wouldn't need two sets of chemicals.

> "When Elon Musk gets a headache on Mars, he'll be able to synthesize his preferred analgesic!"

The internet of chemistry

The idea is to digitize the synthesis of every known molecule using a common chemistry set. Just as Google Maps records every street, so we will digitize molecules, such that every year the number of digitized, downloadable synthesis code for the molecules will increase, until the doubling time comes down to just years or months. And just as the increasing processing power described by Moore's Law revolutionized computing – think of the capabilities of your smartphone – so the digitization of chemistry will transform the speed and efficiency of drug discovery.

This chemical digitization – the internet of chemistry – will have huge implications. It will take the manual labour out of R&D, allowing chemists to focus on discovery. Maybe chemists will not need to be spending such long hours in the lab. Rather, they'll be able to design incredibly complex molecules, and validate the synthetic pathways using software alone before implementing the correct practical solution in the laboratory. Once this occurs, I can imagine that advances in automation will dramatically increase the productive throughput of interesting molecules, as a result of digitization. In this way perhaps drug discovery and manufacturing will be conducted from the computer interface. And for industry, chemical digitization will offer practical, low-cost ways to manufacture drugs. Centralized facilities may be replaced by massively distributed manufacturing, such that drug manufacture directly responds to individual prescriptions. This would reduce costs and eliminate logistical difficulties in drug manufacture; for example, these systems could be easily deployed in remote regions where drug access traditionally is inadequate. It also would enable cost-effective manufacture at low volume, thus supporting personalized medicine. Furthermore, it would reduce drug counterfeiting – if you can access the real drug at reasonable cost, why buy a potentially dangerous fake? Hopefully, big pharma will recognize the advantages, club together and use this digitization approach to streamline manufacturing, reduce costs, increase flexibility and simplify logistics. Distributed manufacturing sites, say a small unit in every city (not a massive refinery, just a small industrial unit), would make the industry more resilient and drug shortages should become a thing of the past. However, I don't see it ever getting to the point where every home has its own drug synthesizer; the health risks would be too great, and there would be no incentive to do-it-yourself because getting it made up at the pharmacy would be so cheap.

Nevertheless, developing the technology will require much investment and collaboration. In particular, it may be tricky to ensure that drugs produced from distributed facilities comply with regulatory and safety requirements. We'll have to address this issue at some point, but looking ahead, I am confident that the digitization of chemistry, and the development of new synthetic methods using networks and robots, will generate a vast number of new markets. We may end up doing chemistry in the Cloud; certainly, research will be transformed and many more molecules than are available now will be discovered. Low-cost drugs of improved efficacy will become available to everyone on the planet, just as low-cost mobile phones are now almost ubiquitous. And when Elon Musk gets a headache on Mars, he'll be able to synthesize his preferred analgesic!

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Make Global Pharma Great Again!?

President Trump's verbal assault on the industry is a manifestation of long-standing underlying structural issues that have been poorly addressed over time. It's time for a change of direction for the industry.

By George Chressanthis

Comments made by pharma CEOs at the recent 2017 World Economic Forum in Davos, Switzerland, about the effects of President Trump's potential policy actions (1, 2). Comments suggest a future of risk and uncertainty for the industry, at a time when executives are already facing a myriad of difficult challenges. The quotes focus on pricing, innovation and intellectual property (IP) issues – with the latter two in particular being the life-blood of any pharma company. At the same time, pharma executives are weighing tremendous opportunities as R&D pipelines generate new pathways to treat unmet medical needs.

The industry's failure

The industry used to focus on small-molecule drug formulations, catering mainly to primary care physicians, for large patient populations – where patient access and payer reimbursement were of lesser concern. Today, companies face stiff price competition from generic entry across many therapy classes, and increased payer influences on physician prescribing have further depressed business margins. In response, companies correctly leveraged new scientific developments to fill R&D pipelines and launched specialty medicines to address a plethora of previously unmet medical needs. The results are expensive, large-molecule medicines that cater to small or orphan-like patient populations, and that face far less competition from biosimilars.

It was assumed that these medicines would boost company margins and to an extent this is true. A 2016 study noted that biologics in the US comprised less than 1 percent of all prescriptions filled, but accounted for 28 percent of total drug spending (3). Growing company revenue mainly through price increases, however, is economically unsustainable in the long run – and this pricing approach has been met by growing patient access and affordability issues, as well as provider and payer cost-resistance. In short, the commercial model design of companies being used to develop and launch these new drugs has not adjusted to the current and future market dynamics.

The industry now finds itself facing President Trump and a form of populism driven by the socio-economic attributes of his supporters. Similar criticisms about the industry are coming from progressives in the Democratic Party. Both groups, despite their different political origins, are highly critical of

industry pricing, as well as other pharma business practices. In short, the pharma industry as a whole has done a poor job of demonstrating the value of its new medicines (4).

Aside from industry leveraging an antiquated commercial model design not geared to today's realities, there is also a more fundamental cause to the industry's problems. Pharma companies mostly operate within a framework that is more focused on the business of pharmaceuticals (drug utilization, market share, financial return on investment and shareholder return), than the service of pharmaceuticals (addressing patient-access, affordability and key healthcare system outcomes). Of course, this is not to say that for-profit companies should ignore establishing, tracking, and meeting key market and financial targets. But by focusing on the service of pharmaceuticals, I believe that the former objectives will also likely be met, alongside additional benefits that are unlikely to be attained by simply looking at things from a business point of view.

"It is insufficient for pharma companies to see themselves as business enterprises."

Time for change

What changes must occur within pharma companies in order to address President Trump's policy actions in the long term? My last article for The Medicine Maker discussed why a Trump presidency has targeted the biopharma industry and how the presidency could affect the industry through specific policy actions (http://bit.ly/2m5Mlar). Here, I focus on what role analytics can play in mitigating the increased risk and uncertainty caused by these policy actions. In order to take advantage of the benefits offered by analytics, however, there must first be an underlying environmental change within pharma companies. I believe there are four elements needed to bring about a more aligned organization that is better placed to demonstrate the value of its products (5).

Culture

It is insufficient for pharma companies to see themselves as business enterprises; they need to be healthcare enterprises that benefit patients and the healthcare system. This means focusing on the science of medicine and delivering drug value (e.g., improvements in health outcomes, drug costs and treatment costs). Demonstrating drug value is not just the responsibility of one department – it should be a goal for everyone in the organization. A well-defined, known, practiced, and incented company culture is the glue that keeps a great company together – and it starts with strong leadership. If companies truly took a comprehensive view toward adopting a patient/healthcare system-centric approach to their practice, many commercial activities currently done would likely stop or be dramatically reformed. As a result, the reputation of the industry would improve, and people would better understand the value of the drugs they take.

Organizational design

Pharma companies are highly specialized, siloed organizations that also promote siloed thinking, inhibiting the interdisciplinary solutions needed to demonstrate and deliver value with specialty medicines. Compounding the problem, is the fact that company units can be scattered around the globe,

CEOs Consider Cost

Remarks made by pharma CEOs in response to President Trump's comments on the industry at the 2017 World Economic Forum (WEF) and during interviews in Davos, Switzerland (1,2).

- "One way of lowering healthcare costs is to have more innovation and more competition." Ian Read, Chairman and CEO of Pfizer
- "Industry has to price in an empathetic way. Just because you can demonstrate value doesn't mean it is affordable." Andrew Witty, CEO of GlaxoSmithKline
- The new administration has been pretty vocal about supporting innovation. They understand that when you spend money on research and you develop intellectual property there needs to be some level of return for that investment." Joe Jimenez, CEO of Novartis
- "Pricing will remain a challenging issue for those of us who are in the research-based pharmaceutical industry, as well as a challenge for the overall healthcare system in terms of what it can afford." Ken Frazier, Chairman and CEO of Merck
- "If you provide true medical differentiation coupled with a strong intellectual property position, I think the US will continue to reward this kind of innovation. If you don't offer that then, frankly, I think it is the right thing that prices should come down." Severin Schwan, CEO of Roche
- "It's very difficult to understand what all those comments and tweets will end up being." Olivier Brandicourt, CEO of Sanofi

which makes interactions difficult. What is needed is greater coordinated decentralization, and more cross-functional teams to better connect units, for example, scientific, clinical, operations, commercial, and health economics and outcomes research (HEOR). Further, just as a brand team in commercial may have a representative from sales or managed markets, this thinking must extend to other relevant parts of the organization instrumental in demonstrating and delivering drug value. Integrator roles could be set up to help instil cross-organizational thinking into identifying, solving, and executing solutions to common issues.

Talent

Companies must seek people with two traits. First, people should value, above all else, the service of pharmaceutical companies to patients and the healthcare system, as opposed to the business of pharmaceuticals. This means hiring people for who financial rewards are not their primary driver, and who are passionate about the good that pharma companies do for society. Second, companies must hire people who can think and operate on cross-functional and trans-organizational teams. They must be willing to adopt new thinking, especially from outside the industry. This also means hiring people who are prudent risk-takers, strive to innovate every day, and are able to engage a broad set of individuals with varying backgrounds. The increasing complexities of the pharma environment will demand the demonstration and delivery of drug value throughout the entire project/product lifecycle.

Process/system

Processes and systems can be used to bring groups together under a common goal to share ideas in solving key challenges – whether it be R&D project portfolio optimization, marketing mix optimization, business planning, lean analysis for production quality control, or public policy risk assessment. For example, a sales force optimization process should take into account not only traditional strategic and operational sales issues, but also views from areas such as marketing and pricing. In addition, the analytics underlying these areas allow for interdisciplinary thinking. Further, and critical for today's pharma environment, data are needed to link commercial and clinical HEOR research to drive insights. This means adding to the current objective of driving physician prescriptions and market share, by also introducing metrics that will be indicators of improvements in future health/economic outcomes. The role of analytics is to connect sales and marketing activities to improvements in health/economic outcomes. This will involve infusing different analytical methods to make these connections.

"Increasing complexities of the pharma environment will demand the demonstration and delivery of drug value."

The importance of analytics

Figure 1 summarizes the potential policy actions of the Trump administration and the anticipated effects on overall pharma industry performance. The role of analytics is to understand both the intended and unintended effects of policy actions on a range of areas in the entire healthcare system. Pharma companies and industry trade groups, such as PhRMA, will need to develop and disseminate empirical evidence to show the expected consequences of policy actions. This is more than just analyzing proposed Trump policy actions – the increasingly complex pharma environment demands companies to become experts in leveraging analytics for key decision-making throughout their organizations if they are to achieve long-term success (6).

The "deal" President Trump is likely to offer pharma CEOs is a promise to strengthen IP protection, enact beneficial corporate tax and financial reforms, and make changes in business regulations and at the FDA to increase pipeline productivity and production efficiency. In exchange for these benefits, however, there is a huge concession on drug pricing, with further potentially negative effects from reforms of the Affordable Care Act and Medicare, international trade, and labor. My opinion is that huge (or as some like to say, "yuge") concessions on drug pricing, coupled with other negative policy actions, will likely offset any offered policy benefits. A combination of commercial, HEOR, financial, and public policy analytics is needed to understand the magnitude of potential policy action effects and to weigh the overall effect of any "deal" proposed by President Trump. For example, large price concessions, even with benefits from "positive" policy actions, will likely mean lower margins, which in turn will reduce R&D investments. Forced lower drug prices will also mean slower diffusion of new technology. Lower prices, in the short-run however, would certainly help drug adherence, which has positive health/economic outcome effects. But in the long-run, a structure of lower drug prices will reduce financial incentives, lower new drug diffusion and innovation, and

Business Area	Policy Action
Drug Prices (-)	Changes in bidding for Medicare price and spillover effects to commercial and Medicaid pricing; Allow US consumers to imports drugs from abroad
Intellectual Property Protection (+)	Strengthen IP protection
Tax and Financial Reforms (+)	Reduce US corporate tax rate and repatriation of US subsidiary unit profits held abroad, reform personal income tax rules on US residents abroad
ACA / Medicare Reform (-/?)	Improve patient access to quality healthcare through ACA reform; Mandate greater Medicare use of generics and biosimilars
FDA / Regulations (+)	Reduce business regs; Rules on operations ex-US; Quality controls on operations in China/India; Increase FDA staffing; Fund 2016 Cures Act
Labor Immigration (-)	Restrictions on number of visas for high-skilled immigrants
International Trade (-)	Promotion of protectionism and possible trade war

Figure 1. Potential Trump policy actions and anticipated effects on overall industry business performance. Positive=green, negative=red, uncertain/mixed=orange.

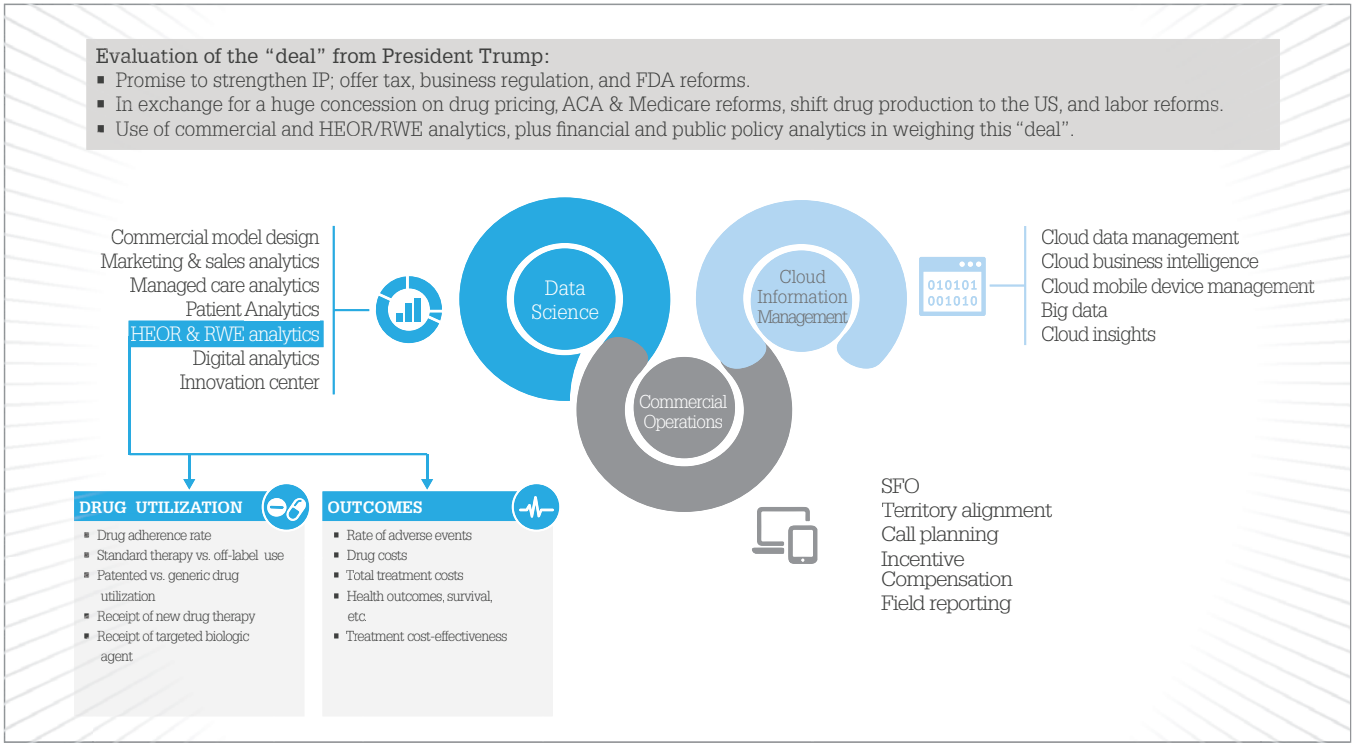

Figure 2. The role of Commercial, HEOR/RWE and other analytics in evaluating a Trump "deal".

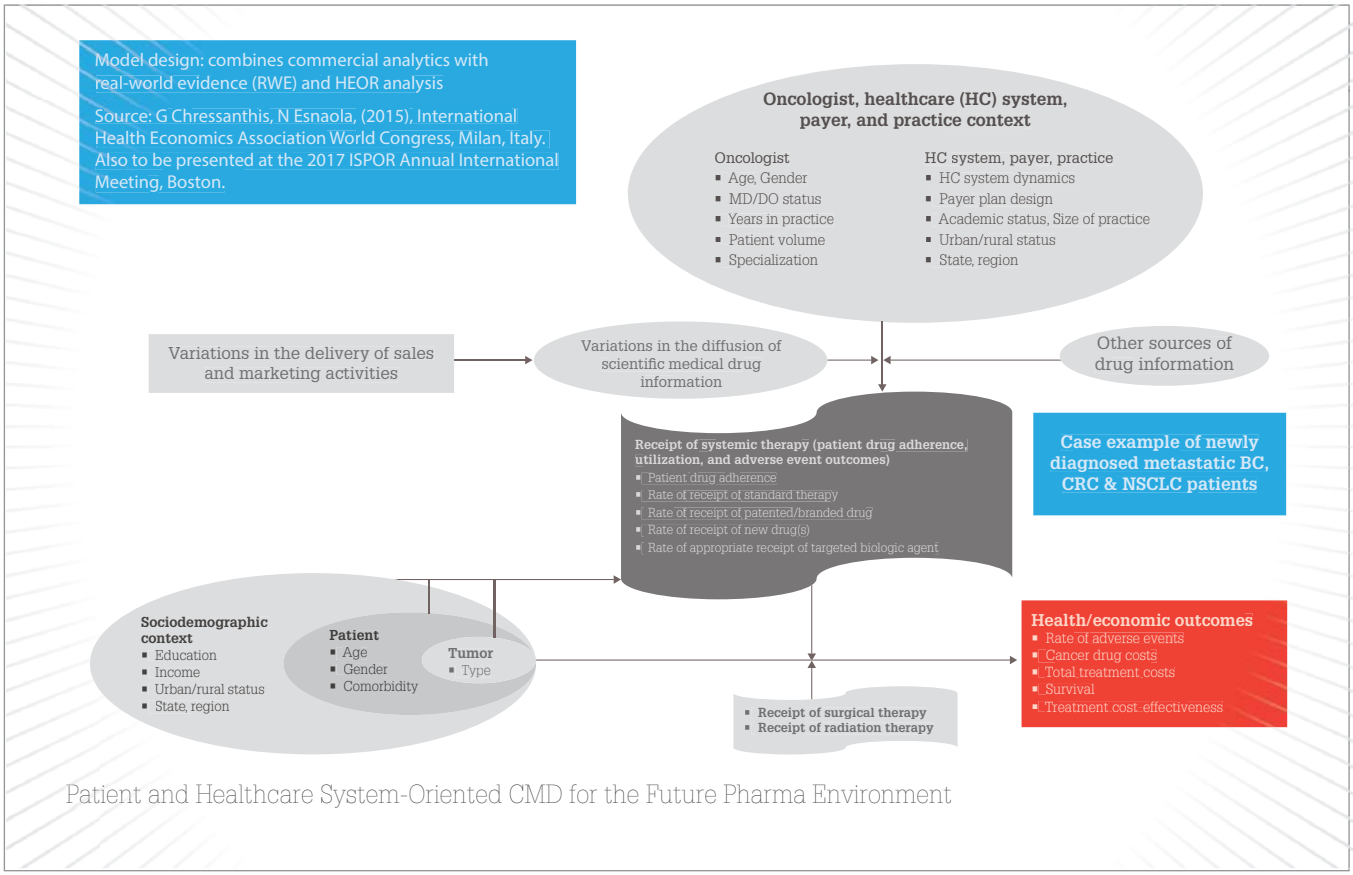

Figure 3. Proposed new commercial model design (CMD): a patient and healthcare system-oriented CMD.

thus create adverse future health and economic outcomes.

Analytics are needed to weigh the net effect of these countervailing forces. **Figure 2** illustrates how these analytics need to be linked to execution, such as in commercial operations with the strategic and tactical allocation of field sales personnel. Similar links can be added to include, for example, other marketing channels, external medical affairs and public policy. In **Figure 3** provides a detailed conceptual commercial model design for the future pharma environment. The case study example involves newly diagnosed metastatic breast cancer (BC), colorectal cancer (CRC), and non-small cell lung cancer (NSCLC) patients (7). A few key insights are outlined that can be applied across all specialty medicine therapy areas:

1. Traditional sales and marketing are primarily vehicles that drive the diffusion of scientific medical drug information rather than the frequency of messaging, resulting in intermediate drug utilization outcomes. This is where typical commercial analytics ends. Recent academic marketing studies show the added effects of including the dissemination of drug scientific evidence in prescription sales response (8-11).
2. Future outcomes needed to demonstrate drug value in a patient and healthcare system-oriented commercial model design are rate of adverse events, cancer drug costs, total treatment costs, survival, and treatment cost-effectiveness.
3. The model design shows how the oncologist, healthcare system, payer, practice context, sociodemographic, patient, and tumor information are all linked to achieve intermediate and final outcomes.
4. Underneath these relationships are commercial and HEOR/RWE statistical analytics to measure relationship effects.
5. Supporting these analytics is a robust and flexible data management process. Traditional commercial along with newer claims and EMR databases are need to be linked in ways not done

"Trump could end up being the kind of change-agent the industry needs."

before in order to demonstrate and deliver drug value to key healthcare system stakeholders.

6. The framework presupposes that a pharma organization is focused on patient and healthcare system outcomes. The interdisciplinary analysis is fostered by a culture, organizational design, talent, and process/system that facilitate the linkages.

Rebuilding pharma

The Trump administration poses new opportunities, but also risks, uncertainties, and challenges for US and global pharma. Regarding opportunities, at the printing of this article, President Trump intends to nominate Dr. Scott Gottlieb to lead the FDA. As a former deputy commissioner of the FDA, physician, and conservative health policy advocate, Dr. Gottlieb will look for ways to reduce industry regulatory burdens and speed up the approval process of new drugs. One way would be to leverage the allowance of observational data, such as HEOR and RWE analysis, for new drug applications, as allowed under the 21st Century Cures Act, to quicken approval times and thus reduce costs. Industry critics, however, are suspicious of this move and will demand caution.

Regarding challenges, the populism fueling Trump's rise and his targeting of the pharma industry highlights the need for the industry to rethink its current commercial model design, internal company orientation, and use of analytics. Trump's proposal for the government to directly negotiate Medicare drug prices may have external global pricing effects. Trump's policy will not only lower Medicare prices, but also commercial and Medicaid pricing as well. The result will be a lower US pricing structure, meaning governments elsewhere, such as in Europe and Canada, will face greater tension with pharma companies to use a even lower structure of US prices to cross-subsidize their policies to extract lower prices. Most European countries use government-imposed external price referencing schemes to lower the structure of drug prices. As noted in a December 2015 European Commission report (12), the result is that pharma companies launch in the highest price country, resulting in drug shortages and/or slowing the diffusion of new drug technology in lower priced markets. As prior academic research has shown, slower access to new drug technology adversely affects patient health outcomes and can increase the cost of healthcare if new drug treatments bring greater cost-effectiveness. Thus, a lower structure of US drug prices caused by President Trump will place greater pricing pressures on European markets if they desire to continue receiving the benefits of the latest new drug technologies.

In short, Trump could end up being the kind of change-agent the industry needs to make necessary internal reforms. I often emphasize that there is a growing gap between the cost/risk to bring innovative medicines to the market, and individual/societal willingness and ability to pay for these medicines. Demonstrating and executing drug value is critical for an individual company's success, as well as the success of the whole industry. The current pharma business model is broken, still focusing on drug utilization as the primary goal, and relying mainly on price increases to sustain revenue and margins. This is not economically sustainable in the long run (13,14). Dramatic changes are needed. Whether you voted for and/or like Trump or not, he is forcing the industry to reshape itself for long-run success. Market forces were already affecting this need for dramatic change. Trump has just accelerated the process.

George A Chressanthis is Principal Scientist at Axtria. This article has been co-published with Axtria: http://bit.ly/2nuZbQO. The references for this article are available in the online version at http://tmm.txp.to/0317/chressanthis.

Calling for Change in the UK

George Chressanthis is not the only one calling for the pharma industry to change. Karim Meeran, professor of endocrinology at Imperial College Healthcare NHS Trust, Charing Cross Hospital, London, also believes that things cannot continue on. His main area of concern is generic drug pricing.

In a letter to the BMJ, Meeran, and his co authors, Sirazum M Choudhury and John Wass, discuss the scandal of generic drug pricing and suggest a radical shake up – developing an arm's length NHS organization to manufacture essential, generic drugs (1). "This would enable the NHS itself to set the market price for generic drugs. Such a company could be run as a non-profit making NHS Trust with the aim of making generic drugs at cost prices, setting prices to ensure solvency, and ploughing profits back to getting approval for other generics," the authors write.

We caught up with Meeran to learn more.

What prompted you to write the letter?

I have been shocked by the huge increase in the price of hydrocortisone (used to treat adrenal insufficiency) over the last 8 years. The pharma industry has an important role to develop new drugs, and there is indeed risk taken on when embarking on new developments. The degree to which innovation and research is undertaken, however, varies – and some companies have no intention of innovating at all and are simply price gouging. The price of hydrocortisone in the UK today is now 12000 percent higher than in 2008 – interestingly, this isn't the case in the rest of Europe, where the drug remains cheap. Drug development should continue to be rewarded with patents, but generic drugs, by their very nature of being generic, should be sold cheaply.

How would the manufacture of generic drugs in-house at the NHS work in practice?

There are several possibilities. One is for the Department of Health, or NHS England, to invest in building a plant in the UK. There is a World Health Organization list of essential drugs that should be available to any person in any healthcare system. Any drug on the list that is overpriced, such as hydrocortison, should be made in the proposed plant. An alternative is for the pharma industry itself to do this. They already have the infrastructure, and if they make all the drugs on the list at cost price for the NHS, and other healthcare systems, it would be a sensible way forward. I think this is a real chance for industry and a conglomerate of industry (such as the British Generic Manufacturers Association or the Association of the British Pharmaceutical Industry) to join the NHS for the greater good.

Creating a specialist body – as what happened with the UK's cost watchdog, the National Institute for Health and Care Excellence (NICE) – that had the authority to review prices and set the drug tariff in an open way could be another way forward.

What would be the main challenges?

The biggest problem is that the Department of Health is too busy trying to run the NHS to actually spend time sorting out this problem… Turning these ideas into action requires will, capital, time to get the MHRA to agree to license the drugs made in the UK, someone to set the drug tariff, and all with the authority of a government, that frankly has bigger worries right now.

Read more at
http://tmm.txp.to/0317/meeran

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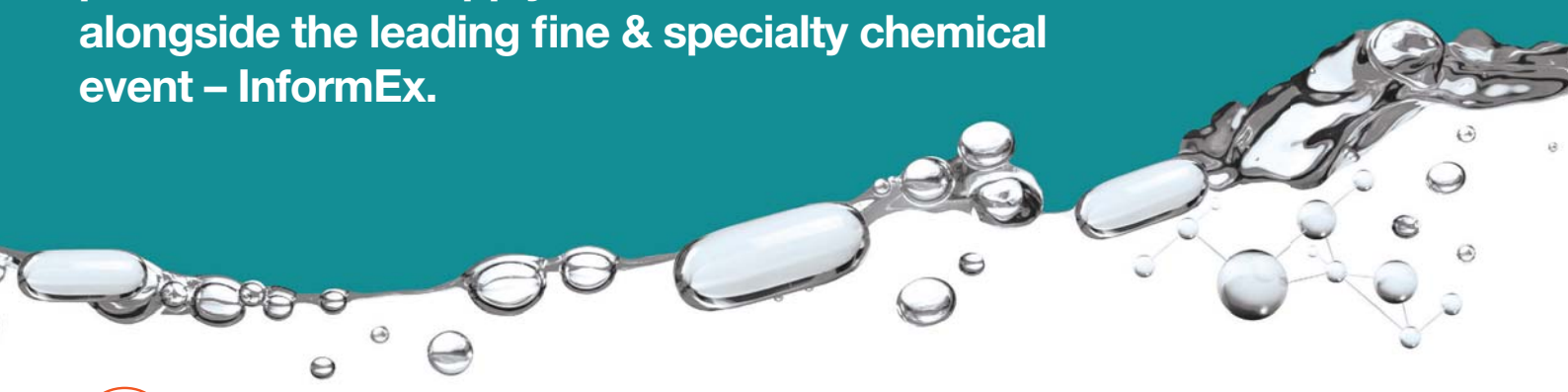

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Chemistry, Conjugation and Management: Lessons Learned with Bernhard Paul

From bench chemist to a general manager, small molecule APIs have always been a strong focus for Bernhard Paul. Here, he describes his career transition, and offers his take on the latest API trends.

The diverse applications of chemistry are inspiring

Chemistry is a subject that always came naturally to me when I was in school – I didn't have to try very hard and yet I seemed to be good at it! I also found chemistry inspiring because there are so many real-world applications. It seemed clear that this was the right subject for me, so I studied chemistry at the Graz University of Technology in Austria, which is where I am from. After graduating, I had the opportunity to do a PhD in Florida – the combination of chemistry and sunshine sounded like a good one!

As I reached the end of my PhD, I came to the turning point that all young scientists face: an academic career or an industrial career? I'd experienced a lot of the academic side during my studies, but what interested me most was the application of chemistry to real-world problems. Medicine is particularly inspiring and rewarding because of the connection with patients and the potential to improve people's lives – this lured me to my first role in industry at a custom research organization (and continues to inspire me today). It was fast paced and exciting, and I was able to contribute to a number of different projects in a very short time span. I worked with many different customers and partners on a diverse set of molecules (both innovator and generic), ranging from early stage process development, all the way through to commercial products. Looking back, I think that working at a custom research organization was the best introduction to – and education of – the pharma industry that I could have asked for.

In a complex world, outsourcing is essential

I later joined a biotech company in the Boston area where I helped oversee API process development and outsourcing. The company focused on a wide range of diseases – among other things we looked at improving the quality of life for patients with chronic diseases. It gave me a great perspective on how outsourcing and manufacturing work. Today, I am the general Manager for Johnson Matthey's European Custom Pharma Solutions business and I often look back on my early experience in Boston, when I was the customer, to think about how we can provide the best customer experience – I think about how I would have felt about certain things at the time and what was important to me.

I joined Johnson Matthey about seven years ago, initially with responsibility for chemistry development and then, later on, developmental manufacturing. Subsequently, I was promoted to the general manager position of the Pharma Services business. It's been interesting to have been on both sides of the fence. Some people talk about biopharma companies and outsourcing providers as different worlds, but ultimately they are linked closely together, while facing different challenges. The most successful relationships I have seen are when outsourcing providers are considered as partners rather than just vendors, which brings a collaborative approach to solving problems and overcoming challenges. Drug development is becoming ever more complex, so having all the right expertise in house can be difficult; outsourcing certain parts makes sense and having a strong partner can make all the difference.

"The majority of therapies in development today are still small molecules and the field is not standing still."

Management is about soft skills

My scientific education gave me the hard skills in science, but management has required a softer skillset. I think that every scientist transitioning from a scientific to a management role has a number of hurdles to overcome. But it's important to remember that although it may seem difficult at first, management and leadership skills can be learned, just as chemistry and physics can be learned.

My interest in management actually stems from a project I worked on as an undergraduate, when I had the opportunity to collaborate with a group of doctoral students who were doing their PhDs. When I first joined

that group they outlined their vision, clearly explained my part of the overall project, and empowered me to make independent decisions. I found myself incredibly motivated and inspired as a result. The experience made a big difference to how I look at management and leadership. The students made a real effort to show me what value my work would have, how it fitted into their research, and how it would help make a research product come to life. Seeing the big picture and how it all fitted together was tremendously inspiring and ever since then I've tried to inspire people in the same way.

For those wanting to move into a management role, I would say it's really important to learn as much as possible about a wide range of areas. Scientists often become experts in a very narrow technical field, but for management you need general expertise in technical and non-technical areas. I also think it's essential to learn about the challenges that other groups within the company are facing, and to look at problems with a much more strategic view.

Finally, the biggest lesson I have learned over my career so far is that people are an organization's most valuable asset. I've had the privilege to work with incredible people and one of my most important roles is to identify talent and ensure that people remain engaged and challenged. This should be a priority for any leader.

Small molecules continue to be a success story for the industry

I have spent most of my career working with small-molecule APIs. At the moment, there is a lot of talk about biologics – and rightly so. There are many exciting advances blossoming in the biopharma field, not to mention the huge growth. But these biologic innovations sit alongside small molecules, which remain hugely important. The majority of therapies in development today are still small molecules and the field is not standing still. Small molecules are becoming larger and increasingly complex, and often show remarkable efficacy. For example, many of the new drugs that treat Hepatitis C are incredibly efficient small molecules and there are many other recent small-molecule success stories in the industry.

However, the increasing complexity of today's small molecules is leading to challenges in bioavailability and solubility. Innovative thinking is needed to overcome these issues and, as a result, there has been a lot more focus on materials science, such as the physical form and properties of an API, and how these can be controlled to ensure bioavailability. A number of new formulation technologies and approaches are being developed that should help in this area. Co-crystals are also receiving a lot of interest, mainly thanks to recent encouragement from regulators.

Over the last few years there has also been a lot of attention paid to drug conjugates. For these types of therapies, one combines a small molecule, which is usually very potent, and a polymer with a targeting ligand or an antibody that helps deliver the molecule to the best place. These products present unique challenges, having highly complex small molecules requirements, yet also needing many of the same advanced analytical techniques applied in large molecule manufacturing. The lines between small and large molecules are becoming more blurred.

Continuous processing is here to stay, but isn't the solution to everything

One of the most exciting advances in terms of API manufacturing is continuous processing – I'm seeing a lot of demand and questions around this. It's not new – the first wave of interest in the pharmaceutical industry was quite a while ago – but we are now seeing a surge thanks to new technologies and the fact that regulatory bodies are encouraging the industry to explore the potential. However, the volumes we work with in the pharma industry are relatively small compared with other industries – and continuous processing has traditionally been associated with high volumes. Being able to adapt continuous processing to the unique needs of our industry will allow us to deal with certain chemistries more effectively, particularly those involving unstable intermediates or hazardous reactions. I think the key is to bear in mind that not every stage of every process is suited for continuous. It's important to be selective about where you use it and to examine where it could have a real impact – and what problems it can potentially solve.

There is growing interest in biocatalysis

Another big trend in small molecule development is green chemistry, particularly biocatalysis, which stems from recent advances in genetic engineering, analytics and molecular biology. Biocatalysts, like all catalysis, increase the speed at which a reaction takes place, but can often require only mild operating conditions and less solvent usage. They also have high selectivity, which can reduce side reactions and make them more environmentally friendly. As with continuous processing, biocatalysts aren't suitable for everything, but are definitely a great tool to have in the toolbox. When it comes to synthesis, the most important factor is to always choose the right solution for a problem – whether it's a biocatalyst, a chemo-catalyst, or something else. It's difficult to argue against the fact that catalysis is the most effective way of doing chemistry, given that a single catalyst molecule can rapidly process thousands or even millions of substrate molecules in each reaction. It's a very efficient way of making or breaking chemical bonds.

Challenging times lie ahead, but the industry must continue to focus on quality

We are experiencing a dynamic time for the industry. Important political events that occurred in Europe and the US in 2016 will certainly have an impact on the drug industry, and there are also increasing conversations and arguments around drug pricing and the cost versus benefit of new drugs. There are definitely some difficult discussions to be had – and I've no doubt that these will continue throughout 2017 and into 2018 and beyond. I also expect the high levels of industry consolidation that we've seen in recent years to continue, both on the innovator side as well as the contract manufacturing side. From the point of view of a contract manufacturing and development organization, I think it will be important for service providers to offer a wide range of solutions, and to be nimble and agile enough to respond to problems quickly.

I also value out-of-the-box thinking – and so I'm very interested in open innovation. There are many challenges in drug development that cannot be faced alone; a platform that allows outsiders to bring in their ideas and encourages collaboration can only be a good thing. At Johnson Matthey, we encourage this with our open innovation program called eXovation. The first round of applications closed recently and I'm looking forward to seeing the results.

Whatever events occur to shape our industry, we shouldn't forget that our main focus should always be on quality since that ultimately assures patient safety. Increasingly, there are companies that are not meeting the necessary quality standards, particularly when it comes to supply chains (although transparency and traceability are on the rise). Only companies that consider safety, quality and compliance as their core values will be successful in the long run – no matter what other changes befall the industry.

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Hopping Aboard the Darjeeling Limited

India has held pharma's interest for decades, but now – more than ever before – there is great interest in setting up regional facilities.

By Dev Ohri

India is a fascinating place when it comes to healthcare and drug development. The country has a large population and a high population density, which contributes to the prevalence of infectious diseases. Add to that inconsistent levels of economic development, and access to effective and affordable healthcare becomes a huge challenge – a challenge that has triggered Indian companies to create cost-based innovations. Generic drugs in India are some of the least expensive in the world and the country is the second largest supplier of generic drugs by value, and the largest supplier by volume. Generic drugs in India include a broad range of small-molecule drugs, over-the-counter products, AIDS antiretrovirals, oncology drugs and more.

One of the largest disadvantages of drug manufacture in India is consistency and quality. Multinational companies with facilities in India usually keep to global quality standards, with integrated global supply chains and global management overview. But this is not the case for the entire market in India – I estimate that around 10 percent of the industry follows global quality norms and the remaining 90 percent does not. However, regulations are now tightening with major regulatory agencies, such as the US FDA and UK MHRA, pushing for stricter norms for pharma companies not only in terms of manufacturing practices, but also where they source their ingredients or components. Manufacturers of both small- and large-molecule drugs are being driven to partner with more reputable suppliers, rather than simply looking solely at price, which also pushes other suppliers in the region to migrate to higher standards to be competitive. Many Indian companies are improving in this area, but I believe there is still a need for global expertise to aid the transition.

"Multinational companies with facilities in India usually keep to global quality standards."

Another important and notable trend in India is the increasing development of large-molecule drugs, and especially generics as more innovative drug products come off patent. Generic small-molecule products are becoming commoditized, leading to increased pressure on profit margins. Only a small fraction of pharma companies in India are investing in research and development, so the "copycat" industry will have a natural lifecycle, especially as it's not easy to copy biologic medicines. Over time, I believe that the differentiating factors for these largely commoditized products in India will be the quality of materials they purchase and produce, and their production processes.

Finally, supply chain reliability is a challenge in India – as well as the majority of Asia Pacific for that matter. The size of the region is vast and the market is growing exponentially. Suppliers to the pharma industry, in particular, are under pressure to get their products to pharma companies quickly – and to this end there is a trend to establish regional facilities. The same is true for pharma manufacturers. In many cases, patients and governments are demanding local production capacity, but establishing a footprint in a new region is certainly not easy and can be very expensive.

Recently, I was involved in developing a new facility in Panoli, India, for producing pharmaceutical chemicals. I'd like to share some of the lessons I learned along the way.

A regional base

In today's globalized industry, I believe that regional facilities are crucial for suppliers because they can reduce the supply chain from months to weeks. Many manufacturers in India or other emerging markets have highly dynamic demands, so if you have a supply chain with a few months' lag, you may find that needs change before you can adapt to them.

Regional facilities are also great for the local community. Once one multinational company has set up a quality facility then others usually have the confidence to follow. In time, a manufacturing and quality hub appears, creating jobs and local benefits for the community – as well as raising standards throughout the region. Panoli is located in the highly-industrialized state of Gujarat; there are about 5000 different kinds of factories nearby and a major international port is only 70 kilometres away. But standards of safety in the area haven't always been consistent.

Our Panoli facility has become a benchmark in the region and the Indian FDA sends representatives from other

plants to look at our facility as an example of how to do things. Two years ago, we were awarded the National Safety Award for our plant operations. A quality plant creates awareness and boosts competition for business – and the best local talent. It seems all boats really are lifted by a higher tide!

The story of the plant goes back nearly 30 years. It started when Ranbaxy created an excipients capability called Ranbaxy Fine Chemicals, with the aim of developing expertise in both excipients and lab-grade materials. The Panoli plant was going to manufacture both lab- and pharma-grade materials, but we (Avantor) acquired Ranbaxy Fine Chemicals in 2011, when the facility was still under construction. We did not want two product lines with different standards of quality being manufactured under the same roof, so all the laboratory-grade and lower-quality requirement products moved out. At the same time, global teams moved in to make sure that the quality and design standards were up to scratch – and it involved a complete redesign of the facility.

When redesigning any facility, the biggest challenge is almost always dealing with existing infrastructure – the challenges (and costs) of retrofitting are well known in the industry. In our case, we already had employees working on some production lines and wanted to keep the retrofit going while also ensuring worker safety. I am very proud to say that, up to today, there have been zero accidents at the plant (touch wood!). Those of you who have worked in different markets will understand how rare this is, especially in an ecosystem like India, which can seem chaotic when compared with developed countries. There's no big secret to this – don't cut corners, and make sure your design teams have both local and global capabilities. I recommend hiring people who have worked for multinational big pharma companies with a good understanding of global standards of quality and safety. Throughout the redesign, you must maintain discipline and high standards.

Finding the right people in India can be perceived as a challenge, but given the country's expanding pharmaceutical market and the number of multinational pharma companies in the country, there are many employees with excellent design, engineering and technical talent.

Images courtesy of Avantor.

Initially, when the Panoli plant was manufacturing both lab- and pharma-grade products, there were a lot of laboratory product packing operations, which led to a floating population of contract workers. Once we removed the lab-grade work, we found that the talents and skills of people who wanted to join us – and their engagement levels – increased, especially after we'd invested in the high purity, low endotoxin sugar wing of the facility.

Working to increase standards does often result in some involuntary exits – simply because not everyone in India is comfortable with the high, rigorous standards demanded in pharma manufacturing and pharma ingredients. Today, I think our attrition rate is a shade below the market norm. In growing economies, such as India, there are multiple options for talented, skilled employees – and you have to be prepared for poaching, especially once workers have experience in a quality facility.

Unexpected disruptions

When retrofitting, it is easy to overshoot your budget and it should be something you are prepared for (within reason) – holding onto a high-quality ecosystem in an environment that could easily be lower quality will always confer a competitive advantage.

Sometimes, you will face unexpected challenges. In one part of our Panoli facility, for example, workers were using mechanical excavators and drilling equipment, which was causing errors in the highly sensitive, quality testing equipment in a neighboring part of the plant. We didn't want to risk compromising our data so we had to make some changes to the work schedule by resorting to manual labor, which increased construction timelines by more than a month. But it meant no vibrations and the rest of the plant ran smoothly – and the construction team did a great job.

"Aim for 'right first time' rather than trying to change things half way through."

Data integrity was a whole different challenge, largely driven by the perception that manufacturers in China and India sometimes fudge data or take shortcuts, which also causes a negative halo affect across the whole emerging market business. For this reason, I recommend getting an international consultant to perform an audit – that's what we did to ensure that we were on the right side of the line.

As we are in the excipients segment, the US FDA has the right to audit our plants, but may choose not to because excipients (unlike APIs) are not on the FDA's core list. The Indian FDA, however, has multiple rules around manufacturing, processing, quality, and the establishment of plants – and they are extra, extra strict when it comes to multinational companies! This is partly because there is a perception – and a legacy among countries that came from colonial rule – that overseas players may take advantage of the local population by exploiting worker safety, for example. In my experience though, if you adhere to the right standards and obtain the right licenses, then the Indian FDA is very supportive.

The global picture

When looking to establish a regional facility in India – or any other emerging region – my advice is to consider it a "global" facility with global standards from the very start. You may be tempted to take a shortcut and create a local facility similar to other nearby players, but you will quickly find yourself crowded out of the market. In addition, aim for "right first time" rather than trying to change things half way through. We experienced a number of delays and inefficiencies when we changed the design of the Panoli facility in 2011. Sometimes a change in design is inevitable (as it was in our case), but it is better to avoid it if possible. Also, draw upon the experiences and expertise of employees from your other facilities. Most plants have made mistakes at some point and have learned to refine processes. And I personally think it is incredibly rewarding to see a global company working together on project with standards shared across all geographies – a positive side effect!

You will need to ensure that you take into account the nuances of the local environment. For example, if you import machinery from countries of low humidity to more humid environments, then you'll find that those machines will need some time adjustment. Employees with local experience, as well as experience in quality plants, can help with achieving the optimal levels of adaptation; for example, we had one piece of equipment where the drying was problematic, but a locally-made design change solved the issue.

It is also very important to keep a close eye on logistics. Is the facility located in a place where it can link in with both the international supply chain and the domestic network? Some locations in India are well networked – others are not... Just following the tax subsidies and putting a plant in the middle of nowhere can cause frustration further down the line! Fortunately, Panoli is in Gujarat, which is perhaps the most developed state in the country. It's also well positioned between the Middle East, Africa and Asia-Pacific.

For suppliers, remember to engage with global customers immediately. When we inaugurated our facility, a number of customers were already aware of what we were doing, but initially we didn't focus on forming an international identity for the facility. This is something we have now given a lot more direction, but I think there are benefits to looking at this early on.

Finally, don't create an insulated facility. To create a facility that really packs a punch, bring in a blend of global and local talent, look to exceed rather than meet local standards, but be mindful to fit in with the community to make your plant the one that everyone wants to work at.

Dev Ohri is Executive Vice President, APAC, Avantor.

Proving Biosimilarity

Sitting Down With... Fiona Greer,
Life Sciences Global Director,
Biopharma Services
Development, SGS.

How did you get into (bio)analytical science?

At school I was always into medicine. I initially wanted to be a surgeon but had second thoughts. I knew I wanted to be involved in science though, and was extremely interested in microbiology, so I went to university to do a degree in Food Science and Microbiology. That was back in the late 1970s – at the start of the biotechnology industry and the use of microbial fermentation. At that point, I got sidetracked into analytical chemistry by a Masters in forensic science, before becoming very interested in analytics and doing a PhD at Aberdeen University in Protein Chemistry. Many years ago, a Bulgarian diplomat was killed with ricin from the castor oil plant. I worked with a similar toxin, a lectin from the kidney bean plant (which is not as potent as ricin); it was very interesting to isolate this toxin and look at its capabilities. I think it was this investigative nature of analytical chemistry that piqued my interest.

My PhD was actually spent between Aberdeen University and the Rowett Institute for Nutrition and Health, where they had one of the first gas phase sequencing instruments – a piece of kit that was revolutionizing protein sequencing at the time. Around the same time, Howard Morris, FRS (professor of biochemistry at Imperial College London) was setting up a company (M-Scan) to use mass spectrometry to sequence proteins – pioneering work. I joined Howard's company in 1984, where we initially used an ionization technique called fast atom bombardment (FAB) to sequence a variety of proteins and glycoproteins from the new biotechnology industry. That was my first foray into applying analytical instrumentation to biotech problems.

Sounds like an exciting field...

It was! But actually, protein science was not very trendy at that point – everybody wanted to be a geneticist or molecular biologist. Up until that time – and even during that time – a lot of the scientific focus had been on genetics, working on constructs that could express proteins. It wasn't until they'd succeeded in engineering and process development that they needed protein science to confirm that the product was the right one. To begin with, we were a small operation, about five or six people in the UK. But by 2010, we had four international sites operating with about 65 people. We had a reputation as the foremost protein and carbohydrate structural lab offering analytical services. At that stage, all four labs were acquired by SGS.

So biosimilar characterization was a natural progression...

Right. You can't proceed onwards with either the FDA or EU pathway until you've shown biosimilarity at the analytical level. And the biosimilar boom has really driven analytical science to apply new techniques, as well as to use techniques that have been around for a while but perhaps needed updating. It's fair to say that things have come on apace since the first biosimilar was given authorization in the EU in 2006! Seven or eight years ago, people didn't think we would ever have biosimilar mAbs – the analytical and clinical challenge appeared too great. The EU now has over 20 biosimilar products, including monoclonal antibodies (mAbs). And we have about 100 different orthogonal techniques that we can use to look at the structure of a biosimilar in a comparative way.

Is staying at the cutting edge important to you?

Very much so. In the beginning, we were a very small, privately funded company; we had to keep driving forward so we could offer new techniques and capabilities to survive. And it wasn't just about running the instrumentation – determining the analytical strategies and interpreting the data were also crucial to solving problems. It's actually a considerable time since I wore a white coat in the lab, but with SGS I'm still focused on pushing forward our capabilities in the laboratories – ensuring that we keep introducing the most up-to-date, properly qualified and validated techniques.

What has kept you in the same company for so long?

The interest and excitement. The field has developed rapidly – driven by the challenges we were given by the biotechnology industry. When I first started, we were using a state-of-the-art high-field magnet mass spectrometer made by VG – now Waters – and the largest intact molecule it could look at was probably 6–7,000 Daltons. We had to drive forward both the instrumentation and the ionization techniques to be able to look at intact proteins at high sensitivity and perform MS/MS sequencing. We picked up electrospray very quickly along with MALDI-TOF and Q-TOF instrumentation. Biotechnology is a global industry and I have worked around the world, interacting with a lot of very bright scientists who were setting up companies, trying to exploit their research and bring it through into a commercial product.

Why do you think you've had such a successful journey?

Sheer bloody-mindedness! Everybody makes their own choices, and maybe I was lucky in that I chose something that I enjoy doing. I get intellectual stimulation from working with very bright people, and it's scientifically rewarding to look at the new techniques that are coming through and to try and introduce them to the labs that I work with.

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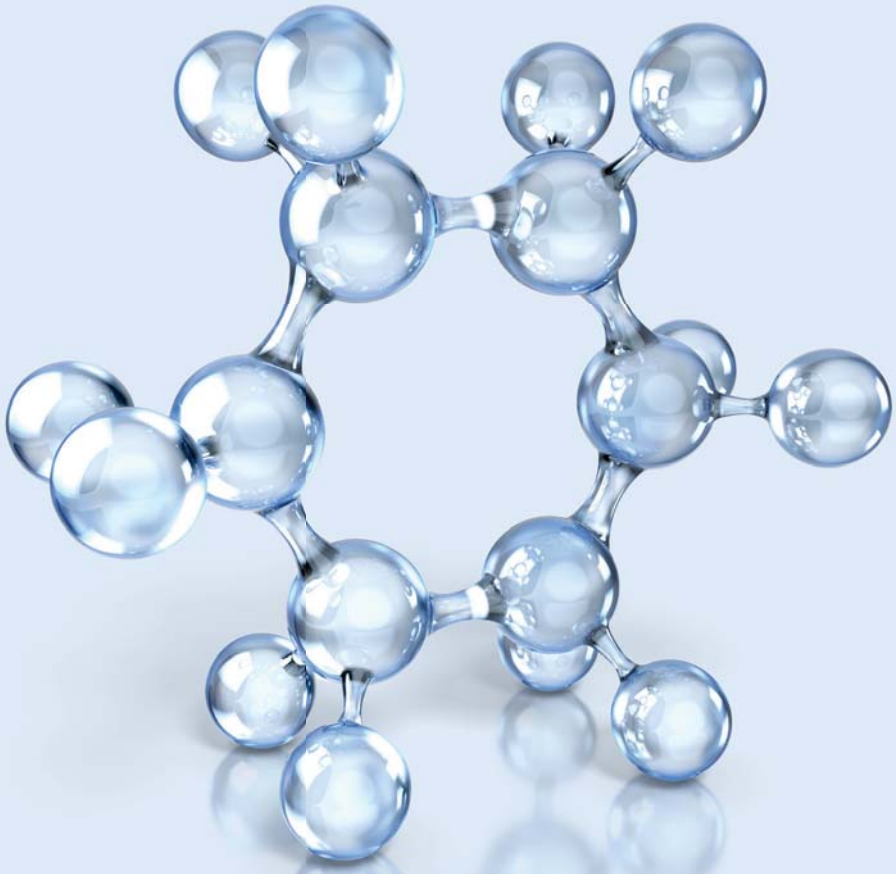

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