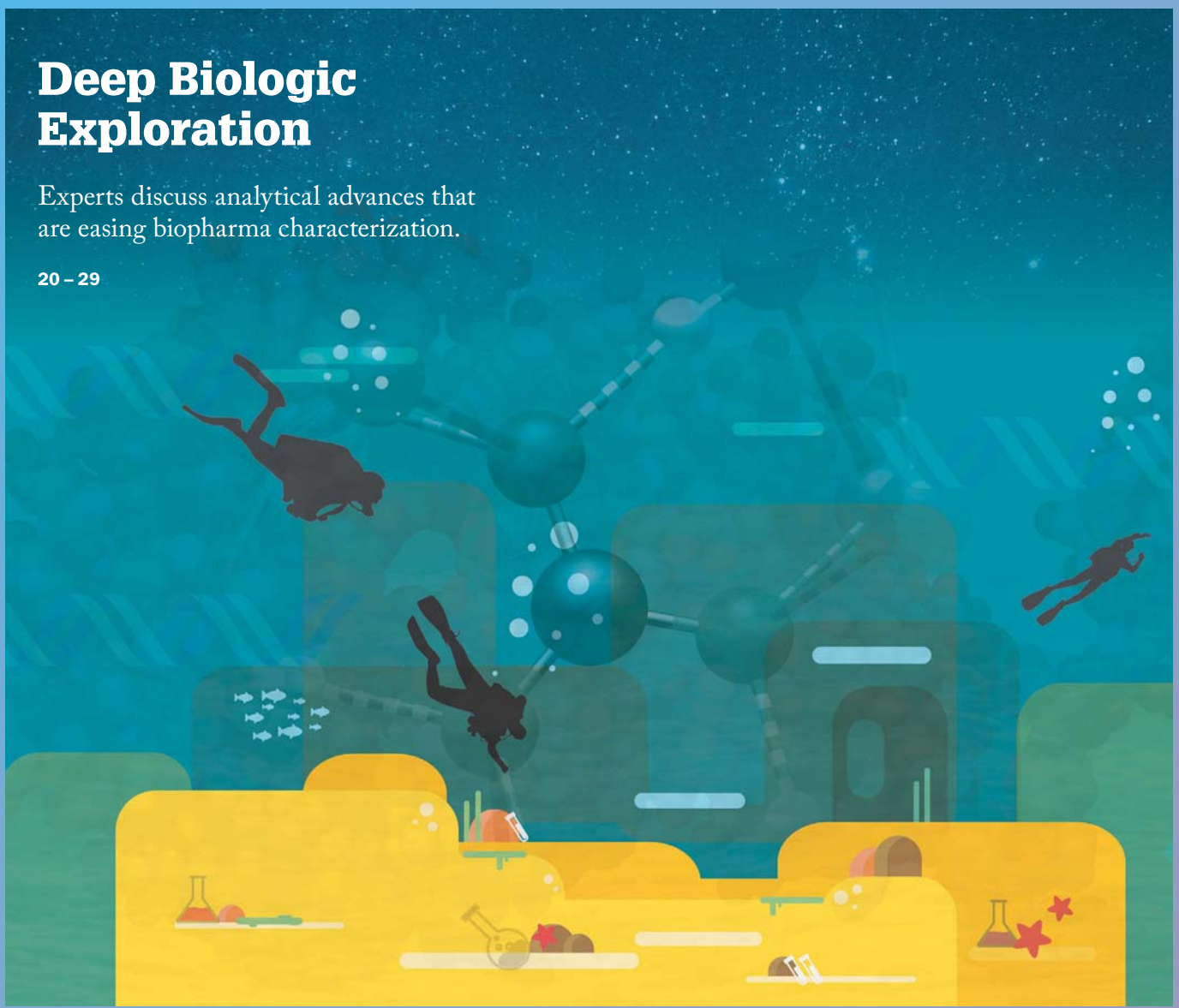
FEBRUARY 2018 # 38

the Medicine Maker™

Deep Biologic Exploration

Experts discuss analytical advances that are easing biopharma characterization.



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Online this Month

Dengue Vaccine 101

In November 2017, Sanofi updated the product information about its Dengvaxia vaccine based on long-term data. Differences in vaccine performance were identified based on prior dengue infection; the vaccine was found to provide "persistent protective benefit against dengue fever" in those who had prior infection. Those who had not been previously infected by dengue virus may, in the longer term, experience more cases of severe disease upon dengue infection.

Over 700,000 children in the Philippines were vaccinated with Dengvaxia in 2016, but the vaccination program was suspended after Sanofi's announcement – and there are concerns in the Philippines that a small number of children may have died because of the vaccine.

We examine the controversy on our website. Read more at http://tmm.txp.to/0218/Dengue

Think Fast, Screen Faster

Combinatorial chemistry and other procedures have produced large libraries of chemical compounds – the (re)activity of which needs to be assessed. High throughput screening (HTS) is already an important component of the drug discovery toolbox in that regard, but could it be better? Graham Cooks, Henry B. Hass Distinguished Professor of Analytical Chemistry at Purdue University, Indiana, USA, certainly thinks so.

Read about Cooks' work at http://tmm.txp.to/0218/Cooks

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On The Cover

Diving deep below the surface of biomolecules with analytical technologies.

Upfront

the Medicine Maker

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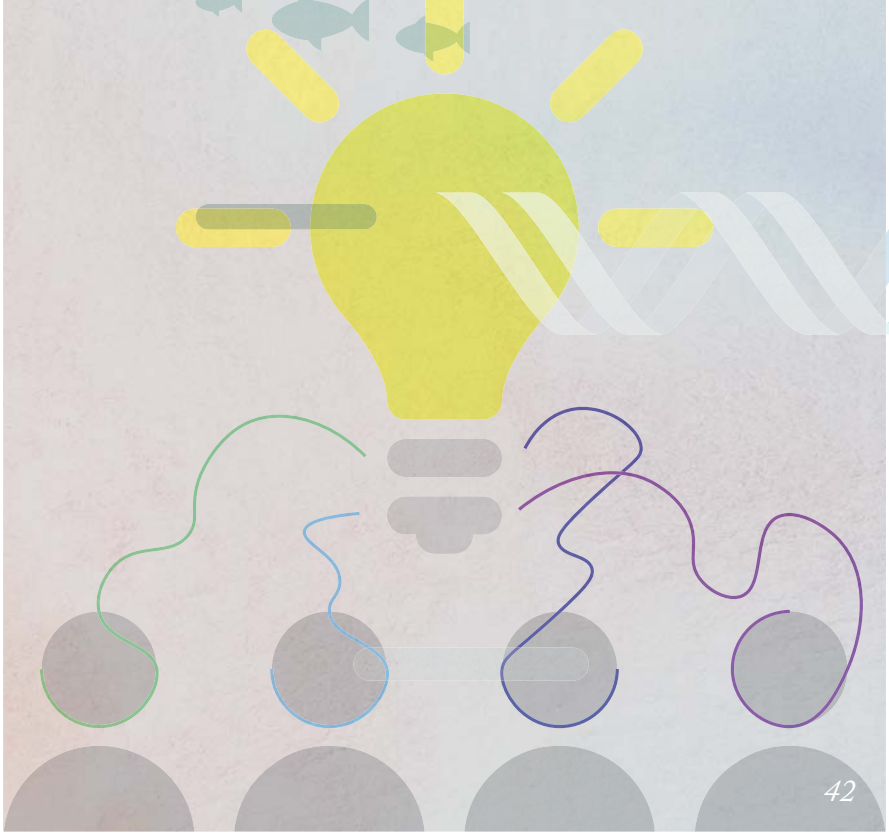


CELEBRATING THREE YEARS OF HUMANITY IN SCIENCE

The Humanity in Science Award recognizes and rewards scientific breakthroughs that aim to have a real impact on humankind's health and wellbeing.

HUMANITY IN SCIENCE AWARD

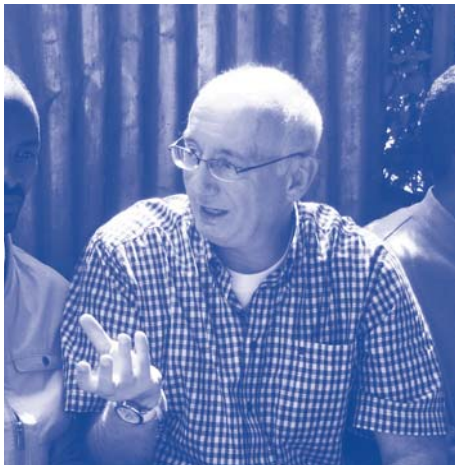
the Analytical Scientist

2015

Peter Seeberger & Andreas Seidel-Morgenstern, Directors at two collaborating Max Planck institutes in Germany, developed an innovative process to manufacture the most effective drugs to treat malaria from plant waste material, air and light.

2016

Waseem Asghar, Assistant Professor at Florida Atlantic University, developed flexible sensors for the rapid and cost-effective diagnosis of HIV – and other infectious diseases – in point-of-care settings.



2017

Richard Jähnke, Global Pharma Health Fund (GPHF), developed and continuously improved GPHF Minilab – a "lab in a suitcase," enabling resource poor countries to rapidly identify substandard and falsified medicines.

Nominations will open soon for the 2018/2019 Humanity in Science Award

www.humanityinscience.com

Are *You* Ready?

Brexit could cause chaos for pharma's fragile supply chains – especially if companies are unprepared.

In January, the EMA launched a survey to learn how (or if!) pharma companies were preparing for Brexit (1). And towards the back end of last year, I spent the best part of an afternoon at CPhI conducting my own straw poll on people's thoughts about Brexit and its potential impact. (No, I'm not a masochist). A number of delegates told me they had plans in place, but a considerable proportion of companies weren't particularly prepared. And some even refused to believe Brexit would happen.

At the show, I also chatted with Sascha Sonnenberg, VP Commercial Operations Americas and EMEA at Marken – a company that specializes in supply chain solutions for clinical trials. Sascha spends much of his time explaining what Brexit might mean for his clients – and what they should be doing about it. Bigger firms tend to be prepared, he says, but smaller companies, particularly those outside of Europe, "do not have Brexit on their radar." (Read more of his views on page 20).

The EMA has been pretty explicit in explaining what Brexit will look like in the absence of an agreement. Although, industry is hoping for mutual recognition agreements, for now, the EMA is assuming the UK will be treated as any other third country – with MAs, orphan designations, batch release, Qualified Person Responsible for Pharmacovigilance, and Pharmacovigilance System Master Files, all needing to be transferred to the European Economic Area before March 30, 2019. Sascha shared his concerns about a bottleneck on the EU side as companies rush to make sure they're ready to carry out batch release, as it could delay or endanger ongoing trials.

But even if the industry gets everything it wants in terms of regulatory equivalence and mutual recognition, pharma companies will be using the same ports and roads as exporters from other industries. Unless there's an agreement that effectively eliminates the need for customs checks across all sectors, pharma companies will inevitably face delays at the border...

Who knows what shape Britain's relationship with the EU will take after Brexit or what the costs/benefits might be in long term? But are you really willing to wager that things won't be any different on Brexit? I feel it's appropriate to quote my countryman, Roger Moore: "It is better to be prepared for illness than to wait for a cure."

James Strachan
Deputy Editor

Reference

1. *EMA, "EMA surveys pharma companies on their preparedness for Brexit", (2018). Available: http://bit.ly/2BsKPX2. Accessed 24 January, 2018.*

Upfront

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

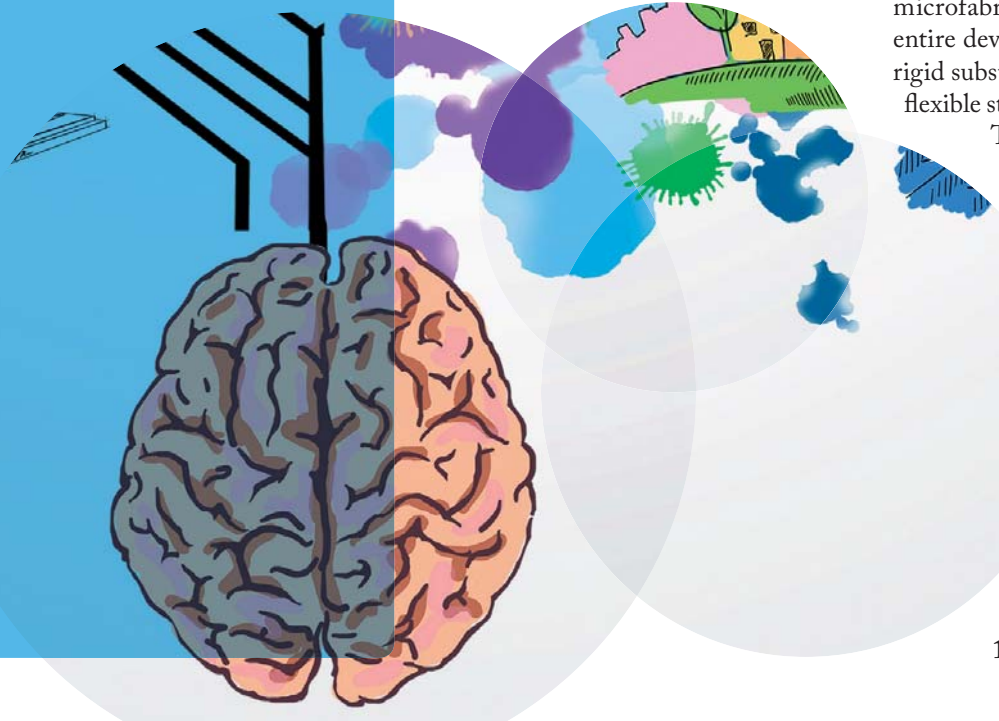
We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com

A Goal in MiNDS

An implantable neural device can deliver drugs to the brain with pinpoint accuracy

A team of researchers from MIT have taken the first steps towards the development of a needle that can deliver drugs to specific parts of the brain (1) – potentially reducing the off-target effects that come with drugs used to treat neurodegenerative conditions. The researchers tested the device – which they call MiNDS – in mice and a rhesus macaque monkey. The results showed that the device could deliver drugs selectively to small deep-brain structures in a controlled manner.

Positron emission tomography imaging showed localized drug delivery with a volume of ~1-mm^3. "This is essential, given that many key neural circuit nodes have such small volumes," says Canan Dagdeviren, assistant professor at MIT and lead author of the study.

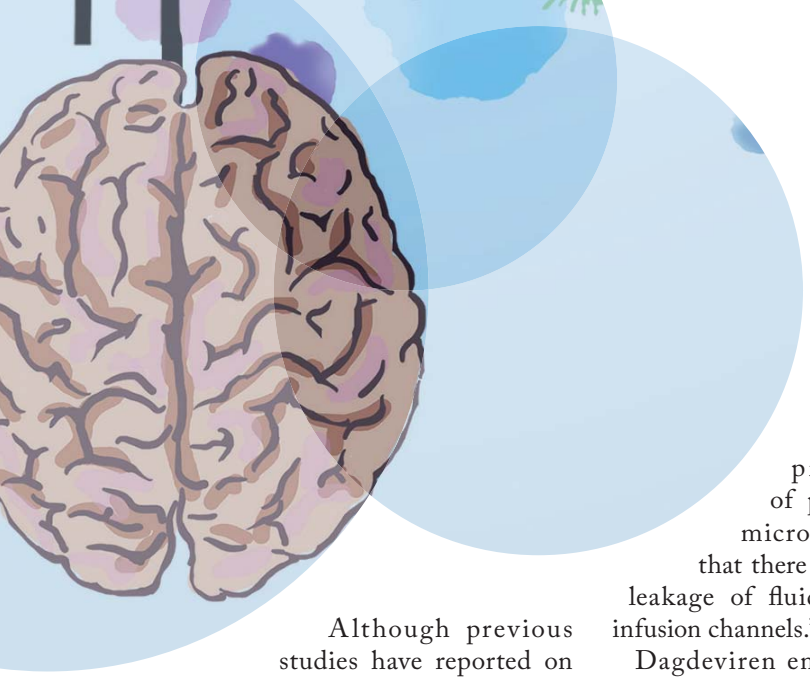


Dagdeviren took her inspiration from an unusual source: Turkish coffee – specifically the fine porcelain cups and plates that are served on a tray in Dagdeviren's home country.

The miniaturized neural drug delivery system has multiple tiny components, including two fluidic channels connected to wireless micropumps for delivering nanoliters of drugs on demand, and an electrode to record neural activity for potential feedback control. "These components are all thinner than a hair fiber and can't be handled with bare hands," says Dagdeviren.

Much like a Turkish coffee tray provides stability to the tiny, fine-featured coffee cups and plates, Dagdeviren microfabricated a polymer tray on a plannar silicon substrate in 2D to support the delicate components. "While the mechanical stability is provided by the polymer tray, I used microfabrication tricks to lift-off the entire device platform from the planar, rigid substrate and encase it in a round, flexible stainless steel needle," she says.

The result is a 3D platform able to reach deep brain structures without the need of an extraneous guide tube to implant in the brain. MiNDS has a diameter of 200 µm – slightly thicker than a hair fiber – and can be scaled: for small animals the team used a small MiNDS with a length of 1 cm, whereas for non-human primates they used a 10 cm one.

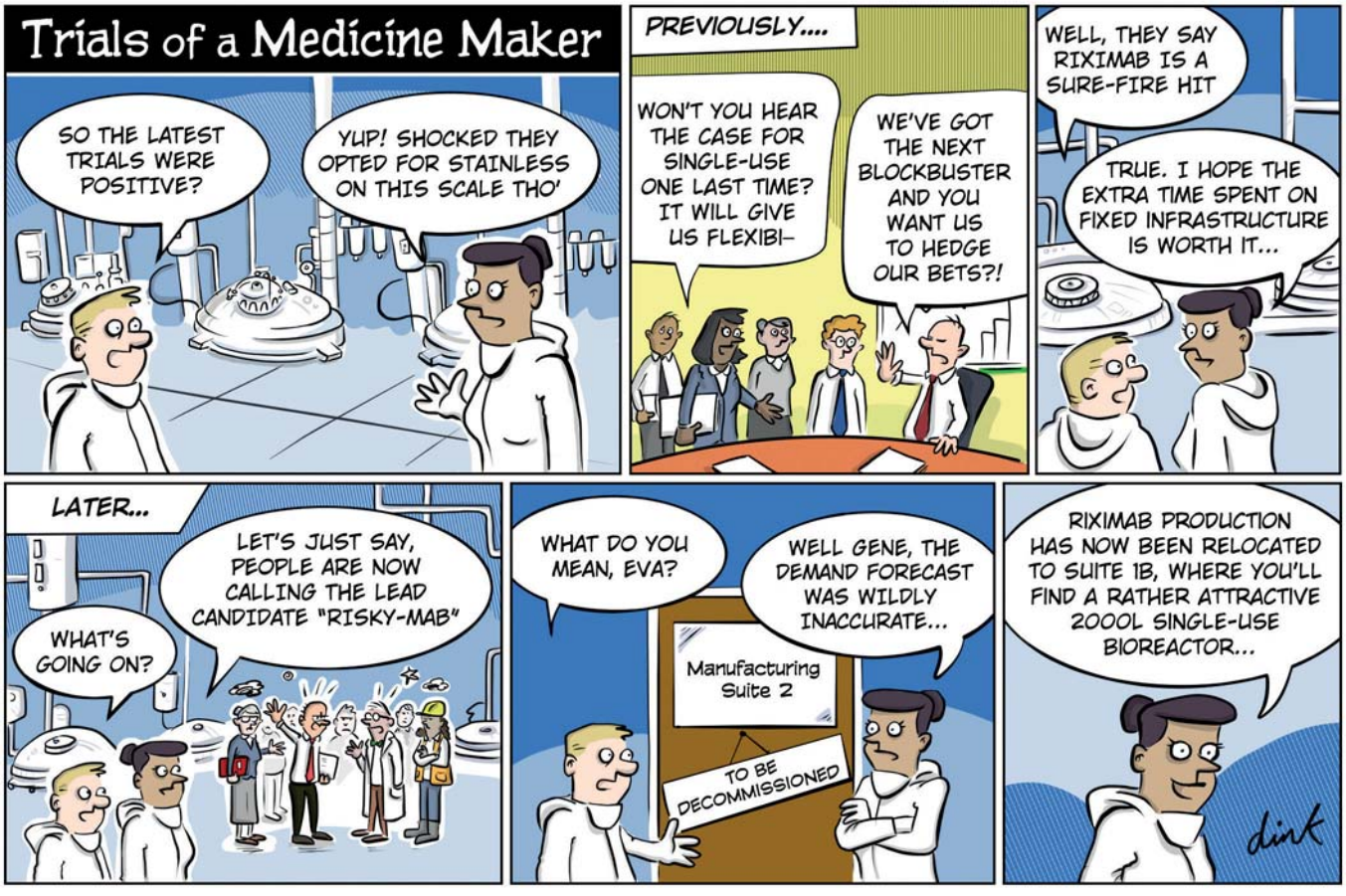


Although previous studies have reported on devices with various sizes, down to 70 µm and infusion volumes as small as 10 nl, Dagdeviren says they suffer from diffusion and leakage problems. "Our infusion micropumps can be refilled, even while implanted, via a septum that can be penetrated using a 31-gauge needle," she says. "Our experimental findings show no infusion past the programmed end of pumping with the micropumps, indicating that there is negligible passive leakage of fluid out of the drug infusion channels."

Dagdeviren envisages additional uses for the device beyond the brain. "Another potential use of MiNDS could be for targeted delivery of chemotherapeutics to tumors in the body," she says. "Such a technique would provide delivery of higher doses without the associated systemic toxicity." She also believes MiNDS could be used to deliver growth factors and stem cells to regions of significant cellular necrosis. "For neurological and cardiovascular diseases, combining growth factor therapy with electrical stimuli might help regenerate electroactive cells. The customizable features of MiNDS could open new routes to deliver not only light but also chemicals and electricity to other organs with pinpoint spatiotemporal resolution," says Dagdeviren.

Reference

1. *Canan Dagdeviren et al., "Miniaturized neural system for chronic, local intracerebral drug delivery", Sci Trans Med, 10, 425 (2018). PMID: 29367347.*



Business-in-Brief

Ongoing bribery investigations, sitting out the Super Bowl, and achieving excellence online… What's new for pharma in business?

Regulation

- The management board of the EMA recently met to discuss their new premises in Amsterdam. A new, tailor-made facility will be built for the EMA in the business district Zuidas, but this will not be ready before the UK leaves the EU at the end of March 2019 (expected completion is November 2019). Temporary premises for the agency are being prepared in the Sloterdijk area of Amsterdam and will be ready by January 1, 2019.
- The UK and China have signed a memorandum of understanding on medicine and device regulation, and expanded on the previous memorandum, with new areas of cooperation outlined, including effective regulation of online trading.
- The European Commission has proposed mandatory future European cooperation on Health Technology Assessments. The legislation, currently being discussed by the European Parliament, covers joint clinical assessments for the innovative health technologies, joint scientific consultations whereby developers can seek advice from HTA authorities and identification of emerging health technologies to identify promising technologies early.

Controversies

- After paying US$2.5 billion to buy the PharMEDium sterile drug compounding pharmacy operation, AmerisourceBergen has run into regulatory problems with its PharMEDium lab in Memphis, USA. In January the company had to recall compounded sterile products due to lack of sterility assurance, and in February it received a Grand Jury subpoena for testing documents on a certain type of syringe.
- In an ongoing bribery probe, GlaxoSmithKline is facing new questions from the UK Serious Fraud Office. GSK has been asked to provide information regarding "third-party advisers engaged by the company in the course of the China Investigations".

Marketing

- Pharma companies sat out the Super Bowl for the second year in a row, despite it being the largest (albeit most expensive) US advertising opportunity of the year. The decision may have been influenced by the backlash three pharma companies faced two years ago for ads than ran during the Super Bowl, with some viewers questioning the timing of discussing fungus and diarrhea during a soccer game.
- GSK has rocketed from number five to number one in an online excellence ranking by Bowen Craggs & Co – the first pharma company to do so in almost ten years. The company's strong homepage, headlines, career section and it's transparency in its online presence all contributed to it moving up the rankings. "GSK turned what was a good site into an excellent one through relentless polish and refinement," said Scott Payton, managing partner at Bowen Craggs.

Rare diseases & Orphan drugs

- Rare Disease Day will take place on February 28, with the aim of raising awareness about rare diseases and the impact on patients' lives. It is believed that 1 in 20 people will live with a rare disease at some point in their life.
- In his first State of the Union address, Donald Trump urged Congress to pass the "Right to Try" Bill, which aims to make it easier to give patients with terminal illnesses access to promising investigational therapies that have not yet been approved by the FDA. Some patients, particularly those suffering from rare diseases, say they would welcome the bill, but the National Organization for Rare Disorders is concerned that there may be "bad actors looking to profit off of false hope".
- The National Institutes of Health is partnering with government, biopharmaceutical and non-profit organizations to help improve drug development successes for Parkinson's disease. The collaboration will focus on identifying and validating disease biomarkers and new biological targets. More than $12 million has been invested as part of the initiative.

What's in a (Brand) Name?

Do patients care about your brand? Not as much as they care about your outcomes

Pharma and healthcare companies spend billions (1) on marketing and promoting their brand – but it may not always be worth it, according to a recent patient survey. The global professional services company Accenture Life Sciences quizzed 8,000 patients from the US, UK, France and Germany on their attitudes to brand loyalty and treatment decisions. Perhaps unsurprisingly, they found that the vast majority of patients (69 percent) consider the benefits of a product more important than its brand. But on the other hand, 25 percent of patients – a significant number – did rate brand loyalty or popularity as a top factor in their healthcare decisions.

Other important factors for patients when considering treatment choice were their relationship with their doctor (66 percent), the ability to maintain their current lifestyle (55 percent) and ease of access to care (53 percent). Of the 14 factors in the survey, product brand came in 12th.

The Accenture survey authors, Jim Cleffi and Boris Bogdan, suggest some key things to bear in mind when launching a new product.

Bring an outcome to market, not just a product

Begin focusing on outcomes at the clinical trial stage, and focus on launching evidence-based solutions rather than just products. Use this mindset to inform your launch strategies and commercialization plans.

When you launch a product, lead with the evidence

Demonstrate that your product can provide better outcomes, and consider how you can best communicate this to different patients – what evidence matters, and to who? Data-sharing and analytics are crucial to understand what and how to communicate with healthcare providers and patients. Also, remember that patients might not speak your "language" – speak to patients in a relevant and understandable way.

Tailor your product launches to match the needs, preferences and motivations of patient sub-segments, considering factors such as, geography and the specific disease

Consider who your patient is; for example, younger patients are generally more likely to switch if they think there is a better option available, whereas many baby boomers reported that their treatment decisions are affected by a lack of knowledge about what's available. The location of patients has just as much impact as their age, making local launch teams are crucial.

Consider whether allocation of resources is optimal

The authors also question whether some of the resources and expenditure currently dedicated to brand promotion might be better used to fund things that really matter more to patients, such as more real world evidence for your product, or patient access programs.

"Our research makes it abundantly clear that product launch strategies must evolve from one-size-fits-all approaches," says Accenture Life Sciences Managing Director Boris Bogdan. "Understanding how patient sub-segments behave differently will fundamentally shift promotional decision-making and the development of supporting services."

References

1. *Kantar Media, eMarketer calculations.*
2. *Accenture, "Product launch: the patient has spoken", (2018). Available at: http://bit.ly/pharmabranding. Accessed February 1, 2018.*

Cherchez la Femme?

A recent review of FDA data suggests that women are now better represented in clinical trials

It is now widely accepted that biological sex can affect a person's reaction to a drug. But historically, the standard clinical trial participant has been male. Is this still the case, or have things improved? Some recent studies and reviews report that barriers still remain, and that women continue to be underserved by clinical trials (1, 2).

However, an analysis of FDA clinical trial registration data for frequently prescribed drug classes found that the inclusion of women increases from 22 percent in phase I trials to nearly 50 percent for phase II – III trials (3).

"The results of this investigation show that drug trials are appropriately designed regarding inclusion of men and women. Furthermore, the underrepresentation of women in trials as observed in the 1980s and before seems to be resolved for most drug trials that we investigated," reports study co-author Robert Rissmann (4).

But there is still some way to go. The authors acknowledge that the scope of their study is limited, and may not cover all the disease areas in which women may still be underrepresented. Other researchers have also reported that there is still room for improvement in our understanding of sex differences in response to some drugs (1) and some racial minorities continue to be underrepresented in various areas (3).

References

1. *KA Liu, NA Mager, "Women's involvement in clinical trials: historical perspective and future implications", Pharm Pract, 14, 708 (2016). PMID: 27011778.*
2. *S Pal, "Inclusion of women in clinical trials of new drugs and devices", US Pharm, 40, 21 (2015).*
3. *A Chen et al., "Representation of women and minorities in clinical trials for new molecular entities and original therapeutic biologics approved by FDA CDER from 2013 to 2015", J Womens Health, [Epub ahead of print] (2017). PMID: 29048983.*
4. *EurekAlert!, "Are women really under-represented in clinical trials?", (2017). Available at: http://bit.ly/wmntrials. Last accessed February 1, 2017.*

PUTTING NUMBERS TO CLINICAL TRIAL INCLUSION

WHAT?

102 *new drugs approved by the FDA Center for Drug Evaluation and Research between 2013 and 2015 (new molecular entities and original therapeutic biologics)*

2,455 *clinical trials*

60 *indications*

13 *therapeutic groupings*

WHO?

484,896 *total participants*:*

40.4% *were women*

77.2% *were White*

12.2% *were Asian*

6.4% *were Black/ African American*

70.9% *were aged under 65 years of age*

**Sex was reported for over 99.9 percent of trial participants, race for approximately 97.5 percent of participants, and age for 72.2 percent of participants.*

Innovation: Your Way

Register your vote in The Medicine Maker Innovation Awards!

The Medicine Maker ended 2017 with a celebration of innovation in industry drug development technologies by compiling a list of the 15 top technologies to hit the market in 2017.

All of these winning innovations can make a mark on drug development and manufacturing activities, but which is the most ground breaking?

We will give one of our winners the chance to showcase the full development story behind their innovation in a future issue of The Medicine Maker. And we want you to choose!

Vote for the innovation you would like to read more about at: http://tmm.txp.to/2017/innovationwinner.
Voting closes on March 1, 2018.

the Medicine Maker *Innovation Awards* 2017

Winners

- AFG 5000
- Cadence Inline Diafiltration Module
- Eshmuno P anti-A & Eshmuno P anti-B resins
- HakoBio
- H3N2 Challenge Virus
- iQ
- KLV 1360
- MabSelect PrismA
- MicroCal PEAQ-DSC
- Prodigi
- Q Exactive HF-X Hybrid Quadrupole Orbitrap Mass Spectrometer
- Valor Glass
- VarioSys Move
- VHP DC-A Decontamination Chamber Atmospheric
- X500B QTOF

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

Software: The Best of Jugglers

As pharma companies attempt to keep too many balls in the air – drug costs, regulatory demands, consumer perception, return on investment – they will increasingly turn to software that can harness data in new and interesting ways.

By David Harty, Head of Professional Services, Adents, France

Modern software companies rarely look past three-to-five-year planning cycles because of the rapid change of technology and, of course, the immediacy of many business requirements. However, when we consider a variety of factors – including the current change in pace of automation, regulatory requirements, and consumer demands – it's clear that the role of software in manufacturing is exponentially increasing. Exciting times lie ahead! And not just for vendors who stand to profit of course, but also for pharma customers who will benefit from increasing software innovation.

Privacy is perhaps one of the biggest issues in the new era of data and software, especially when it comes to pharmacovigilance. The introduction of patient involvement and the accompanying data can open privacy concerns both from a regulatory perspective and a consumer privacy standpoint, which can have dramatic brand protection concerns. That said, changing regulations, even more stringent ones, can have advantages. Regulatory changes force companies to seek out more flexible and comprehensive solutions – in the process abandoning many of the silo or stovepipe solutions previously prevalent. Ultimately, companies have the opportunity to become more efficient and profitable.

The world is growing smaller as we become increasingly connected by growing mountains of data. As pharma companies attempt to balance multiple markets, different geographies and increasing regulatory requirements, advanced software systems can be a huge help. By reducing errors and ensuring that the correct requirements are followed, software can have a far-reaching impact from initial planning and algorithms that support sales efforts across the marketplace, to the most granular operational tasks needed to fulfill production requirements.

"The world is growing smaller as we become increasingly connected by growing mountains of data."

"We will be able to challenge and verify those medicines' authenticity – the crux of regulations currently being rolled out across the globe."

I believe software's ability to increase quality and support "right-the-first-time" production goals will only be surpassed by the power to provide lifecycle management for all products, even immediate consumable medications. Powerful management tools will allow us to fully understand a particular medication. We will know when and where source components were produced for recall purposes; we'll be able to witness medicines' journeys across supply chain networks to ensure compliance in handling and storage conditions; and we will be able to challenge and verify those medicines' authenticity – the crux of regulations currently being rolled out across the globe.

The pharma market is under increasing pressures to balance shareholder values and rights with regulatory requirements, global marketplace competitiveness, consumer perception, intellectual property protection, and return on investment. Most research does not yield a marketable, profitable product, but there is an increasing viewpoint – a false one, in my opinion – that big pharma is a purely profit-driven machine. I believe that as more information is made available and as transparency increases – driven by software that can make better use of data – consumers and patients will be better informed about the inner workings of the world of pharma. In time, the public will hopefully begin to see the complexities of producing and delivering the medicines they need, shining a more positive light on the pharma industry.

The Next (Air)Wave of Inhalables

The inhaler is an important drug delivery device, but for the technology to evolve, questions about efficacy must be answered.

By David Lewis, Director of Aerosol Research, Chiesi Ltd, UK.

Since they were first developed in the 1950s, advances in inhaler drug delivery technology have been substantial. But compared with tablets, the technology it still in its infancy. Inhaled drugs are delivered directly to the target tissue where they can act immediately, in contrast to systemic delivery methods. This localized delivery is a widely recognized benefit of inhalables, as a lower dose is generally needed to achieve therapeutic effect. Since their initial design, inhaler devices and formulations have undergone rapid innovations; most notably the introduction of hydrofluoroalkane as a propellant in metered dose inhalers, which improved the degree of drug deposition in the lung. Despite this, more improvements in inhaled delivery methods are required to further increase the drug dose reaching the lung by manipulating particle properties and therefore improving the treatment of prevalent respiratory diseases, such as chronic obstructive pulmonary disease.

The defining focus of research in the inhalable drug area has, until now, been aimed at learning how to disperse formulations efficiently enough to deliver a clinically efficacious dose – and, in particular, how to create and disperse particles of a size that facilitates deposition in the lung. The importance of this work should not be overlooked, but there are important challenges yet to be tackled. To reach new levels of performance, and to better meet patient requirements, I would argue that we now need to start asking new questions. There are three key questions that the field must address:

i. How can we develop a better understanding of aerosolization performance by extending current research?
ii. How can we better understand particle behavior on the way to the lung (especially the influence of humidity on particle properties)?
iii. How can we improve drug uptake within the lung?

The aerodynamic particle size distribution (APSD) of the therapeutic aerosol produced by an inhaler plays a key role in the physical mechanics of particle deposition in the airways – which means it directly affects the efficacy of the treatment. Understanding the dynamics of dose dispersion is therefore a critical first step towards better drug delivery control. For pressurized metered dose inhalers (pMDIs), we require a detailed understanding of the atomization and evaporation processes that determine the size of particles delivered – a major challenge, but it potentially opens up a route to higher performance efficiency. The use of innovative imaging technology to investigate the aerosol plume, in combination with the intelligent application of computational fluid dynamics, is helping to pave the way towards increasing our understanding. New knowledge will be particularly valuable as the focus of research activity shifts to the potential of extra-fine particles (those less than two microns in size), which increasingly appear to offer both clinical and product performance benefits.

"Understanding the dynamics of dose dispersion is therefore a critical first step towards better drug delivery control."

Next, it is important to establish a better understanding of the patient response to inhaled particles (and vice versa), ultimately allowing researchers and clinicians to understand why patients may respond differently to the same product, according to their age or disease state. For example, during drug development and manufacture, the aerodynamic particle size distribution of inhaled drug particles is usually measured in a low humidity environment, using the technique of cascade impaction. But there's a problem: the route the drug particles follow is close to a saturated water environment, meaning that test data may not accurately represent what is going to happen in vivo. Fine particles tend to be hygroscopic, which means that when they are subject to high humidity they will absorb water relatively rapidly because of the high surface-area-to-volume ratio, becoming larger than they were when they entered the body. In the past, inhaler testing may

not have taken this into consideration. But now, researchers are paying more attention to the effects this can have on the deposition behavior of the drug, and the resulting dose received by the patient.

Oxygen levels in the lung are also known to affect the uptake and behavior of inhaled particles, as shown by research into the impact of pollutants (1). Within the lung, the steady state concentration of oxygen is significantly lower than the 21 percent used for many experiments. Once particles have deposited (frequently in an unpredictable manner), it is the respiratory tract lining fluid (RTLF) that has a defining influence on the uptake of inhaled molecules, and particle transportation at the air-lung interface. RTLF changes with age and with disease state, and therefore plays a role in the variable lung response in different patients.

Additionally, the composition of the RTLF changes depending on the region of the lung, so when particles transverse the lining, the dissolution, cellular uptake and therapeutic efficacy all depend partly upon where the drug particles reach. And that's one reason why dissolution testing has become an important theme. Once an inhaled drug has deposited, the absorption –and, therefore, the therapeutic effectiveness of the drug – depends on the active drug dissolving in the fluid available at the target site. As it stands, there are no dissolution test methods specified for inhaled products; however, FDA grants have been released to investigate this aspect of performance.

Improved understanding of in vivo particle behavior will allow us to more closely tailor inhaled products to meet the needs of specific patient groups in a more efficient way. There is potential to be explored by developing more efficient technologies that use formulations with reduced active pharmaceutical ingredient loading. Respiratory diseases represent a huge burden on healthcare services across the globe, with developing countries in particular struggling with the associated financial weight of such conditions. By improving inhaled drug delivery uptake within the body, we have the opportunity to improve the patient experience, and at the same time reduce healthcare costs.

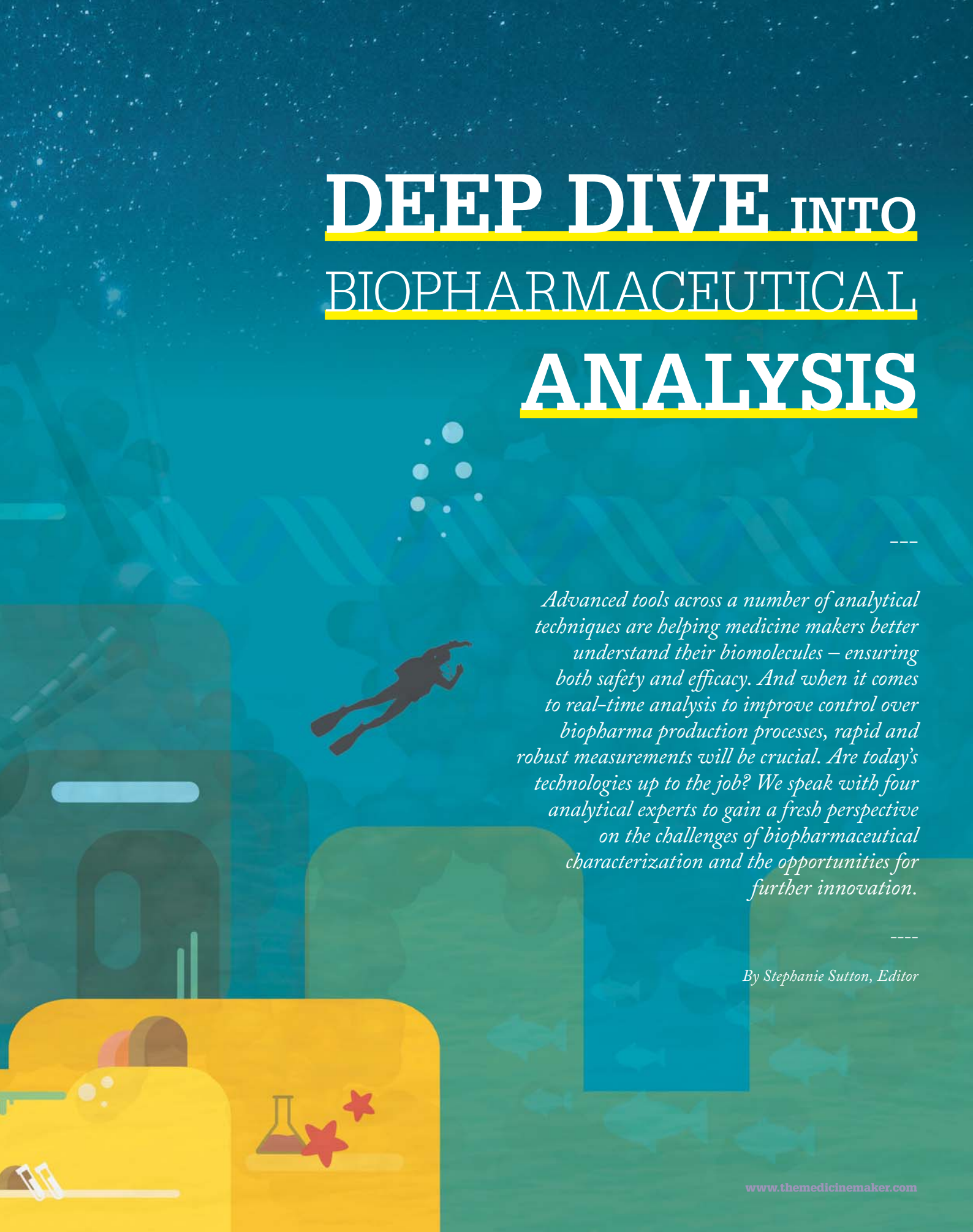
Reference

1. *I Mudway, "'Learnings' about the lung – small particle interactions from environmental science", Presented at the Innovation in Inhalation Meeting, July 9, 2016; Newport, UK.*

DEEP DIVE INTO BIOPHARMACEUTICAL ANALYSIS

Advanced tools across a number of analytical techniques are helping medicine makers better understand their biomolecules – ensuring both safety and efficacy. And when it comes to real-time analysis to improve control over biopharma production processes, rapid and robust measurements will be crucial. Are today's technologies up to the job? We speak with four analytical experts to gain a fresh perspective on the challenges of biopharmaceutical characterization and the opportunities for further innovation.

By Stephanie Sutton, Editor



Why is deep biopharma characterization so important for the discovery, development, and manufacture of new biologic drugs?

Anurag Rathore: The importance, as well as significance, of characterization for biopharma arises from the complexity of the product. Biotherapeutics are complex nano-machines, designed to work at a specific rate, for a specific function. This specificity can only be assured if all the parts of the nano-machines are intact and aligned accurately. For this, it is important to first understand how different stresses impact the assembly. Moreover, as it is a product used in bulk (millions of molecules per dose), the range of contaminants and their effect on product function will vary.

Characterization helps define all of the above features in minute detail – and this understanding can then be used in all aspects of development and manufacturing as a signature of the molecule's behavior. In the drug discovery phase, anomalies identified during characterization of a biotherapeutic for a certain target might also help identify treatments for other disorders. Characterization to some extent also helps understand and manage the risk involved with manufacturing, and can help alleviate the cost attached to clinical trials. In my opinion, there are very few industries where quality of the product matters so much to the consumers. Ultimately, regulation of this quality comes down to efficient and accurate characterization.

Koen Sandra: Anurag summed that up very nicely. Biopharmaceutical products come with enormous structural complexity. The molecules are large (monoclonal antibodies have a molecular weight of 150,000 Da) and heterogeneous as a result of the biosynthetic process and subsequent manufacturing steps and final storage. Despite the fact that typically only one product is cloned, the final drug substance or drug product is composed of a mixture of hundreds of variants that differ in post-translational modifications and higher order structure. These different variants can have an impact on function, stability, efficacy, as well as safety. During development, these characteristics need to be determined in great detail using state-of-the-art methodologies and closely monitored prior to clinical or commercial release. For that, a wide range of analytical techniques and methodologies must be used.

What analytical advances have had the biggest impact in terms of developing biologics?

AR: The field of analytical characterization of biotherapeutics has definitely been a recipient of major developments in the last decade; there are two significant advances I would highlight. The first is mass spectrometry (MS). When hyphenated with separation tools such as electrophoresis and chromatography, MS has made it possible to probe the molecular structure of complex biomolecules in previously uncharted ways. Combinations such as LC-MS-MS (liquid chromatography-tandem mass spectrometry) allow us to accurately identify the mass of a molecule to the fifth decimal place and pin-point not only the type but also the exact location of a range of chemical and enzymatic modifications. Even modifications as complex as glycosylation are now being increasingly profiled using characterization tools. If there is a modification that can be separated via a specific mode of chromatography, it can be identified by mass spectrometry.

The second set of tools that are becoming increasingly promising are surface plasmon resonance (SPR) and biolayer interferometry (BLI). These tools have made it easier to perform binding assays and have significantly boosted productivity. They are gradually becoming the industry gold standard for measuring drug specificity and kinetics.

> *"The ability to hyphenate charge-based separations, such as ion exchange chromatography, with MS also enables manufacturers to better understand protein structure and protein-protein interactions in the native form."*

Kyle D'Silva: I agree that MS is one of the biggest advances. MS has given drug manufacturers a greater level of structural insight into their products than any other technique in recent years. The ability to hyphenate charge-based separations,

such as ion exchange chromatography, with MS also enables manufacturers to better understand protein structure and protein-protein interactions in the native form, delivering a deeper understanding of the drug and its mode of action.

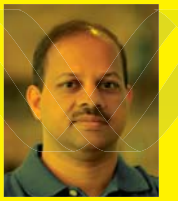
KS: New mass analyzers have been introduced with improved robustness, sensitivity, resolution and mass accuracy. Today, you can use MS to study primary structural features, such as amino acid sequence and post-translational modifications, as well as higher order structures. All of this results in enormous amounts of data for which new powerful software tools have been developed. However, it is important to point out that, despite the significant progress made in software algorithms, data analysis still requires substantial manual intervention. Interpreting all the different spectra to this day remains somewhat of an art, and finding people with the right expertise is very challenging.

Many advances have also been made in chromatography, such as the introduction of highly efficient columns (with chemistries tailored towards the analysis of biopharmaceuticals) and instrumentation capable of successfully operating these columns. Separations nowadays are even performed in multiple dimensions to gain in resolution – two-dimensional liquid chromatography (2D-LC) is a good example.

Looking back to the characterization of the first recombinant therapeutic protein (insulin) in the late 1970s/early 1980s, chromatography and mass spectrometry were of modest performance compared with the current state-of-the-art. Though fast atom bombardment was used to introduce insulin into low resolution mass spectrometers, today the Nobel Prize awarded technology, electrospray ionization, has become the standard to introduce small peptides and large proteins into high-resolution mass spectrometers equipped with a variety of fragmentation modes, providing sequence information and allowing modifications to be detected and localized at very low levels. HPLC separations used to be performed on columns packed with 5-10 µm porous particles and pumps operated at 400 bar, but we now have sub 2 µm porous and superficially porous particles and system pressures up to 1500 bar, allowing us to resolve minor structural differences in a short analysis time.

There was a time when scientists had to identify all peaks in a peptide map using Edman degradation – a very lengthy task – but now we can easily acquire and process 24 peptide maps a day thanks to the many developments in chromatography, mass spectrometry and accompanying software tools.

Hermann Wätzig: We are constantly improving our understanding about the quality of the biologics being



Anurag S Rathore

Anurag is familiar with both academic and industry perspectives in biopharma characterization. Today, he is Professor in the Department of Chemical Engineering at the Indian Institute of Technology in New Delhi, but he has previously held roles at Amgen and Pharmacia Corp. His main areas of interest include process development, scale-up, technology transfer, process validation, biosimilars, continuous processing, process analytical technology and quality by design.

Kyle D'Silva

Kyle offers insight from the point of view of a technology provider. Following a PhD in applied ultra-trace mass spectrometry, he held roles as a mass spectrometrist and applications chemist before deciding to move into product marketing at Thermo Fisher Scientific. Today, he focuses on technologies for both pharma and biopharma applications.

Koen Sandra

Koen is currently the Scientific Director of the Research Institute for Chromatography (RIC). He is also the co-founder and co-owner of anaRIC biologics and of Metablys, an institute performing metabolomics and lipidomics research. As a non-academic scientist, he is the author of over 40 highly cited scientific papers and has presented his work at numerous conferences as an invited speaker.

Hermann Wätzig

Hermann has spent his career in academia and is today Professor at the Technische Universitat Braunschweig in Germany. Since 2001, he has been the chair of the pharmaceutical analysis/quality control division of the German Pharmaceutical Society. He is a scientific committee member of Germany's Federal Institute for Drugs and Medical Devices (BfArM) and an expert of the European Pharmacopoeia.

produced and how aspects such as charge variance and size variance play an important role. I think this is mainly because of chromatography and electrophoresis – (U)HPLC ((ultra-) high-performance liquid chromatography) and capillary electrophoresis in particular. These technologies continue to deliver better separations. MS, of course, is a much newer technology; many interesting things are happening there and I must admit that it continues to surprise me! Chromatography and electrophoresis are older techniques that are very well understood so naturally the advances are smaller – but still very important.

How has biopharma characterization affected the development of biosimilars?

AR: Analytical technologies have made the cost of biotherapeutic production more manageable. Newer guidelines for biotherapeutics across the globe seem to be highlighting the trend of increased reliance on detailed characterization as opposed to clinical trials, which has direct repercussions in terms of drug costs – the reduction in cost of clinical trials allows for cost-effective pricing of the final product.

KD: Advances in analytical techniques enable biosimilar manufacturers to identify potential product differences compared with the reference innovator product that may affect the purity, safety, and efficacy of the biosimilar candidate. It is incumbent upon biosimilar manufacturers to exhaustively characterize both the innovator molecule together with their own biosimilar version. Modern analytical technologies can provide biosimilar manufacturers with even greater knowledge about the microheterogeneity of an innovator biologic than the reference product manufacturer themselves.

KS: Regulatory agencies evaluate biosimilars based on their level of similarity to the originator. In demonstrating similarity, an enormous weight is placed on analytics – and both the biosimilar and originator need to be characterized and compared in extensive detail. The analytical package for a biosimilar submission is considerably larger than that of an originator. During the development of an originator product, the major goal is to show a clinical effect, but for a biosimilar developer the goal is to demonstrate similarity. The structural differences highlighted define the amount of clinical studies required. When biosimilar developers re-characterize blockbuster products developed 20 years ago using the current state-of-the-art analytical tools, many more details are revealed that pose enormous challenges to position a product within the originator specifications.

"When biosimilar developers re-characterize blockbuster products developed 20 years ago using current state-of-the-art analytical tools, many more details are revealed that pose enormous challenges to position a product within the originator specifications."

What are the biggest discussion points in biopharma characterization? Where are there clear gaps or unmet needs?

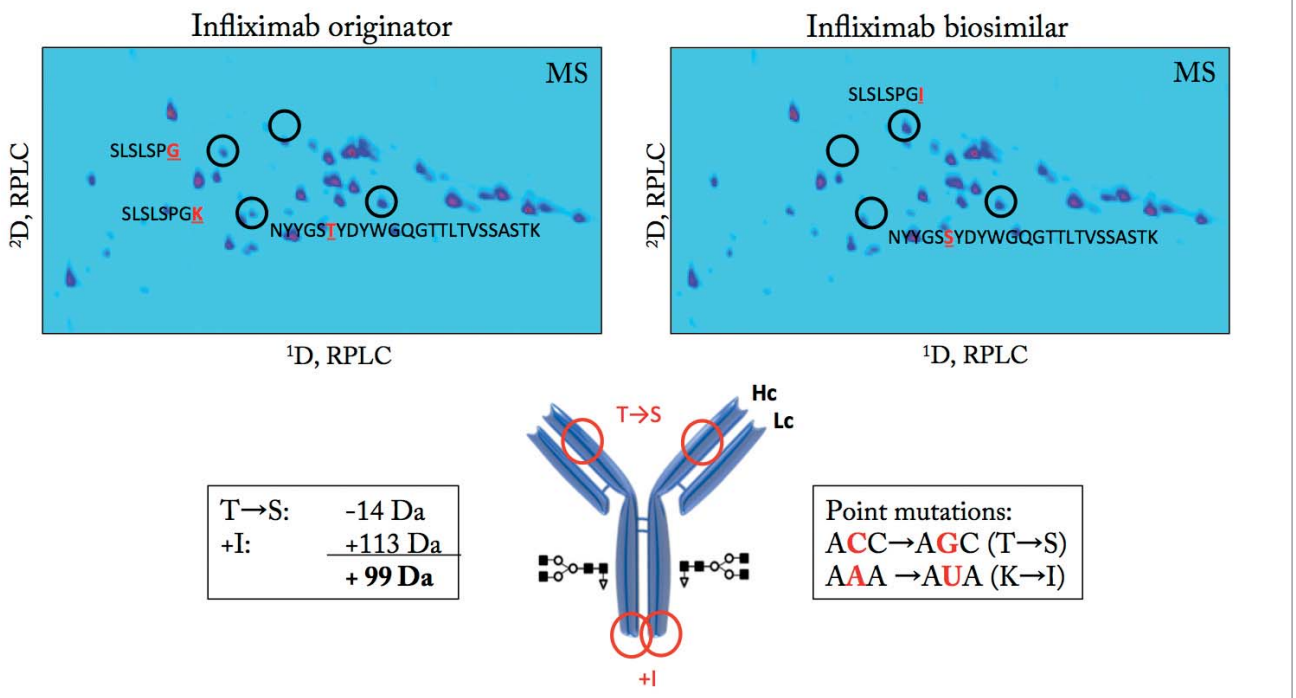
AR: We have come a long way in understanding protein molecules as products – but this understanding has also led us to appreciate the limitations of our knowledge. When we talk about "quality attributes," there are some cases where an understanding of the "cause and effect" is still lacking. In most cases, these gaps in our understanding are because of current technical limitations, which I am certain will be resolved in the near future. One example is aggregation; there are already established immunogenic effects of the presence of this class of contaminant, making it a Critical Quality Attribute (CQA), but we still need to understand, in greater detail, the specific effects of individual aggregate species on immune profiles. The mechanism of anti-drug antibody formation is poorly understood; whether the response pathway is generic to aggregates or species specific still needs to be resolved. Understanding this would greatly help in defining specific ranges for this class of contaminants. It would also help in predicting drug behavior more accurately during storage

conditions and, ultimately, the quality of the product at the time of patient-administration.

A similar gap exists in our mapping of the glycan profile of complex biomolecules, such as monoclonal antibodies. Given the wide range of possible combinations of glycans that can attach to the antibody backbone, complete profiling of these variants becomes a technical challenge. Moreover, given the acute sensitivity of biotherapeutics to their environment, it becomes even harder to ascertain how true a given profile is and what changes have been introduced because of the analysis itself.

KD: One of the key trends we see discussed is the advancement of MS from the development arena further down the product pipeline into manufacturing and quality control. Here, we see a great desire for companies to consolidate several chromatographic characterization tests that monitor for CQAs, into a single multi-attribute-monitoring workflow using high resolution accurate mass MS in the quality control lab. Based on a peptide mapping approach, such tools enable the parallel monitoring of several CQAs in a single run, meaning that several orthogonal methods can be replaced by biotherapeutic quality control.

HW: I see room for improvement in terms of the setting of proper specifications – at the moment, I feel as if there are compromises. Biopharma products are incredibly sophisticated and widely available to patients in different therapeutic areas – but because the product is so sophisticated, there are still byproducts. It is not completely understood which of these byproducts will give unwanted side effects and which will not. And right now I think there is a



The power of advanced analytical tools. RPLC×RPLC-QTOF-MS analysis of infliximab originator and candidate biosimilar. Drawing of the mAb with annotation of the modifications. Courtesy of the Research Institute of Chromatography (www.richrom.com).

compromise on the amount of impurities that are allowed in a biopharma product.

For example, there may be an impurity specification of eight percent for a biologic versus one or two percent for a small molecule drug. Gradually over time, eight percent should perhaps drop to five percent, and then three percent and so on. The need for lower levels of impurities will drive further advances in analytical and purification technologies.

The specifications are set via the ICH – which does a very good job – but there are a lot of mutual recognition agreements about which specifications are necessary versus those that are actually obtainable. Once again: it is a compromise. One would really love to have tighter specifications, but everybody understands – myself included – that it may be too difficult at the present time.

Have you noted any different trends or priorities in industry as opposed to academia?

AR: Academia and industry research goals are mostly well aligned to each other with their primary focus on societal welfare, but the priorities of the two are not always superimposed. Academic research is driven by the impact it will have on the global research community, and the measures of success are largely based on publications. Industry, on the other hand, is driven by the impact it will have on day-to-day activities, and the measures of success are largely based on the long- and short-term value it creates for the company. Though the industry aims to comply with the regulatory guidelines for approval, academicians constantly look to evolve any set norms. For example, a decade ago, charge heterogeneity of a monoclonal antibody based therapeutic was not considered to be a CQA, as the acidic and basic variants were believed to have the a similar safety and efficacy profile as the main product. However, after numerous interesting publications from both industry and academia, charge heterogeneities are now considered significant to a product's safety and efficacy.

"While researchers and equipment manufacturers are continuously pushing the bar on improving sensitivity, I feel where we lack in our understanding is how the different tools compare with each other – and which of them are redundant."

KD: Industry and academia actually make very effective partners. There is certainly a trend for large bio/pharma manufacturers to outsource discovery to academia, which is full of new thinking, and we see greater migration of pharma research hubs around academic sites, such as those in Cambridge, MA (USA), and Cambridge, UK, because of the availability of knowledge. To ensure success though, I think it's important to use a bridging organization that has a keen understanding of both languages and the needs of academic and industrial partners – because ultimately both parties are very different! One good example is the charity LifeArc in the UK – they act as a keystone in the bridge to spanning the divide between academic research and drug developers. These types of organizations usually have the latest technology in drug characterization to ensure that quality is maintained as a concept moves from the academic arena to commercial drug development.

HW: As Anurag says, the goals of each side are ultimately the same, but I think there is more freedom in academia to try out new ideas and new techniques. Findings are very important in academia so you embrace the latest, sophisticated equipment for proper characterization to gain greater knowledge. Academia can also dwell on projects for longer than industry (where time is a constant pressure) and so can more thoroughly investigate a molecule and gain a deep understanding.

Many technological advances and new instruments offer increased sensitivity. Should sensitivity always be a priority?

AR: Manufacturers have been continuously challenged to develop analytical methods for timely and accurate product determination, as well as potential contaminants throughout the manufacturing process, from raw material selection to process analysis, formulation development, and release testing. Analytical technology advances that offer increased sensitivity and shorter analysis time are always welcome, but this is application specific. For instance, MS-based methods and next-generation sequencing are addressing greater sensitivity, dynamic range, resolution, mass accuracy, and user-friendliness in less time, and pharmacokinetic/pharmacodynamic analysis requires high sensitivity methods for detecting pico/nanomoles of target drug in the presence of multiple interfering compounds.

While researchers and equipment manufacturers are continuously pushing the bar on improving sensitivity, I feel where we lack in our understanding is how the different tools compare with each other – and which of them are redundant.

KD: Companies need to understand their products, but although sensitivity gives greater confidence in results, on its own it doesn't deliver knowledge. Every step that takes the customer from sample to knowledge must be as simple as possible, including sample preparation, simplified acquisition, automated data processing and interpretation, and robust reporting of results. It is incumbent on instrument manufacturers to provide tools that deliver knowledge to the end user, not just performance. However, confidence in the result often comes from the foundation of high performance instrumentation and high quality data. Without this foundation, poor data quality can lead to misinterpreted results, with huge time and cost implications.

KS: Better sensitivity is not necessarily what biopharma companies want, but it is a consequence of the recent advancements in analytical tools. Today, it is remarkable that we can detect individual host cell proteins (HCPs) at 0.1 ppm levels and product variants at levels below 0.1 percent. In project meetings, we often hear the comment "we don't want to know about all these low level variants" or "we hope you have not found new liabilities." As analytical scientists, we

feel it is our duty to reveal all the details of the molecules we are studying. At the HPLC 2016 meeting in San Francisco, Reed Harris (Genentech) showed an interesting graph plotting the number of modifications revealed in a molecule versus popularity within the project team. When discovering the first set of modifications, the popularity within the team increases substantially. After having shared yet another set of modifications, popularity declines – and at a certain point you are Doctor Doom because of the consequences that your findings can have on the timeliness of a project.

In the development of new techniques and technologies, I think priority should lie in robustness. We need to obtain the same results over and over again.

HW: Being from academia, my opinion is that sensitivity is always beneficial! Sensitivity allows you to see and understand more – and I think scientists from commercial biopharma should share this view. Sensitivity, however, is not the only important feature of a system – separation efficiency and robustness are equally important, depending on what you are trying to achieve. If you are looking for a certain minor component, you need sensitivity, but if you have a more complicated process that you are looking to control then you perhaps need separation efficiency. System reliability is also crucial. Interestingly, I think that standard analytical equipment can sometimes be more reliable than newer, sophisticated instruments. For example, I find that standard HPLC equipment can be a little more reliable than highly sophisticated HPLC, electrophoresis or MS systems. I am sure that all the instrument vendors are addressing this though – and most definitely there is considerable progress being made.

Could you explain the challenge of developing systems for real-time analysis during biomanufacture?

AR: One area that is ripe for future development is real-time monitoring of product attributes through all stages of development and manufacturing. Typically, the different manufacturers of process equipment and analytical equipment each use their proprietary software for equipment control. And that creates significant challenges when one tries to integrate the process and analytical equipment to get real-time information during manufacturing. Another major challenge is the mismatch between the time that is available for analysis and the decision making required during processing. For example, typical chromatographic elution occurs in 15-30 minutes, and a typical HPLC assay takes 30-60 minutes to do a single analysis.

KD: The complexity of biopharmaceuticals requires advanced technologies to analyze them. More technologies are now being developed with greater automation for routine process-analytical and quality control environments. Do we have high-resolution mass spectrometry sitting next to the bioreactor for real-time monitoring? Not routinely. But multi-attribute monitoring using high resolution accurate mass MS are already being deployed at scale in biopharma quality control departments, and the production environment of the near future will almost certainly be adopting such techniques too.

KS: This has everything to do with the complexity of biomolecules. Measuring oxygen levels, pH, and so on, can readily be performed using sensors, but studying the biopharmaceutical in situ demands more sophisticated chromatographic or mass spectrometric tools – which very often include tedious sample preparation. As an extreme example, monitoring glycosylation requires glycan release, labeling and chromatographic separation (eventually also incorporating a purification step). Various groups within the biopharmaceutical industry have, nevertheless, made enormous progress in real-time monitoring of CQAs directly from the process.

HW: Most definitely it would be very valuable to have more analytical data during processing, but this is not easy. To start with, there is the issue of fouling of the sensors or the sampling in biopharma production – how do you prevent carryover from one analysis to another? There are many basic challenges like this that must be solved before we can begin to implement analytical systems directly in production.

What emerging characterization tools have potential but are not yet routinely applied?

AR: Improvements in MS have dramatically improved our ability to obtain detailed protein molecular information. In addition, the continued development and deployment of such MS-based applications will enable finer control of bioprocess optimization, allowing for correlation of manufacturing process changes to both molecular structure and yield. Numerous hybrid MS-based analytical techniques, including ion mobility-MS, capillary electrophoresis-MS, hydrogen-deuterium exchange-MS (HDX-MS), and size-exclusion chromatography coupled to native MS are yet to make their way into routine use. Alternatives to conventional cell-based analytical methods and continuous processing requiring process analytical technology for real-time process monitoring are in the pipeline for implementation in industry. Also, real-

time efficacy assessment platforms have been proposed (for example, CANScript technology), which I believe will greatly enhance effective biologic development.

KD: We too see phenomenal growth in HDX-MS, especially in areas such as biosimilarity studies from biosimilar manufacturers, but also innovator companies looking to protect their patents. Top-down or middle-down MS protein characterization is also showing great promise as a simple minimal or preparation-free method for confirmation of protein structure. Historically, the sequence coverage obtained from a top-down fragmentation experiment didn't meet the demands for biopharmaceutical manufacturers, but with advancements in fragmentation methods we see great interest in this technique because it can achieve near-full coverage, providing confirmation of primary structure, localization of post-translational modifications and the intact or subunit mass of a biologic. Intact and subunit analysis of biologics is also becoming more information rich due to the coupling of chromatographic separations with MS, and the clarity and accuracy of intact protein mass spectra on the latest MS platforms.

KS: I think it is a very exciting time to be involved in biopharmaceutical analysis given the enormous advances in instrumentation. Mass spectrometry, the workhorse in R&D, is slowly finding its way into routine environments as a release tool. We also have high hopes for 2D-LC, where two different separation mechanisms are combined, with the aim of increasing overall resolution and thereby providing the next level of product detail.

HW: I expect considerable progress to come from automation, particularly sample preparation steps. Less error by dilution or extraction steps will certainly improve analytical precision. Miniaturization also has great potential to speed up analyses, and improve precision by multiple measurements and using the obtained average values as reportable results. Improved surface technologies can reduce the fouling of the analytical instrumentation, enabling the very much desirable process analysis of biopharma products and their impurity profiles during production and clean up.

Getting on the Fast Track: Manufacturing Training for Cell Therapies

Looking to advance in the exciting area of cell therapy? The new CELLT1 course is here to help bring staff up to scratch.

By Trevor Smith

Cell therapy is one of the hottest topics right now in the biopharma industry, with ambitious goals for making patients with no other treatment options well again. New developments are reported every day, and more and more companies are looking to expand into this area.

My background lies in microbiology and immunology, so I'm familiar with dendritic cells, T cells and so on. Today, I focus on cell therapy at GE Healthcare – in particular, on the validation of new technologies for producing cell therapies. I also work on developing new intellectual property for future products. Recently, I was asked to help write the course for GE Healthcare's CELLT1 training course for advanced cell therapy technology, which falls under our Fast Trak training and education services.

Why does the industry need a training course for cell therapies? Similarly to working with other biological drugs, consistency, cleanliness and a suitable background knowledge of the field are critical. Anyone comfortable with traditional cell culture for bioprocessing can learn to work with cell therapies, but there are some specific challenges that require new training – and the equipment is specialized and very much at the cutting edge.

The stakes are also very high, so companies cannot afford errors or time delays. Safety is paramount, so due care and attention must be paid to manufacture and scale up – but, at the same time, there is a push for faster turnaround times and reduced costs. To achieve both, the industry needs innovation around process optimization. GE Healthcare's Enterprise Solutions, which includes equipment, integrated services and staff training, are designed to help address the challenges associated with scale up and manufacturing site expansion, with a focus on flexibility and efficiency. And one of the latest additions to our offerings is the aforementioned CELLT1 training course. Other training courses tend to be limited to singular components of the process when it comes to cell therapy – yes, there is training for individual pieces of equipment and individual types of operations, but we felt that there was a lack of cohesive, end-to-end manufacturing training courses.

"Ultimately, you need a variety of different systems and you need to be able to coordinate the whole process."

Class is in session

When developing new systems and technologies, you gain a unique insight that can be very valuable. We weren't satisfied with simply training users on individual pieces of equipment because, ultimately, manufacturers need a variety of different systems and need to be able to coordinate the whole process. In general, the hardware aspect of the cell therapy process is locked down – our Enterprise Solutions can demonstrate the full line of equipment and an optimized floor plan. But instrumentation only gets you so far; companies need reliable, well-trained staff and cross-site alignment to ensure consistency and product safety.

CELLT1 is designed for research and development scientists, process engineers, and manufacturing technicians. It addresses the full cell therapy workflow – from the isolation of target cells, to harvesting, to final formulation for patient administration. It includes training on instruments and standard operating procedures, as well as tips and tricks that we have learnt along the way. Examples of the topics covered are listed in the sidebar, CELLT1 Topics. Obviously, the cell therapy field is still evolving, so the course will evolve over time too. It can also be tailored to individual needs.

One common challenge in the cell therapy manufacturing process is cell expansion – this is one of the longest process steps. Our bioreactor systems are very flexible in terms of programing, which is useful because they can be adapted to any user process, but new users can find new, robust equipment a bit daunting and it is often one of the biggest fear factors during manufacturing. This topic is covered in detail within CELLT1 – and it is also the most customizable aspect of the course; everyone will have different processes and expectations for how cells are to be cultured and expanded.

We also discuss the idea of digitalizing manufacturing processes, which is something we find companies are increasingly interested in. We are working to ensure that our equipment can be integrated into a digital platform that allows users to see the whole scale of the process, such as setting up instruments using the digital cloud and showing potential warning errors as they pop up, which you can access both inside and outside of the laboratory. In doing so, we hope to increase usability and control.

New Ways of Thinking

Changes in the market demand new ways of thinking. How do you scale up to manufacture the new treatments patients need? And how do you satisfy regulators, while minimizing both financial and production risks? GE Healthcare's Enterprise Solutions bring together a range of services and products, with the aim of supporting companies from process development through to commercialization for biopharmaceuticals and cell therapies. It is based on modular approaches designed to help manufacturers be more flexible and efficient. For example, we offer process development services that can help customers move from open to closed processes that are also scalable. Concurrently, customers can take advantage of our Fast Trak training courses so that staff are trained while process development is being done. GE Healthcare also offers the FlexFactory production platform – a closed, semi-automated solution predominantly using single-use and scalable technology – that can be set up in new or existing manufacturing plants.

There is also KUBio, which is built for the customer with the whole project managed by GE Healthcare. We can help a company break into new markets and take away the stress of figuring out how to get the right permits to break ground – GE Healthcare is a global company so we are accustomed to operating in diverse markets. KUBio is a turnkey solution that can be built out over different phases. It helps minimize business and finance risks by allowing you to adapt more readily to changes in product demand. The KuBio design for cell therapies can produce up to 3,000 doses a year, based on the specific process.

Enterprise Solutions is all about supporting customers from A to Z, from process development, to training staff during the construction of a new facility, to setting up the equipment. The equipment does not necessarily all have to be from GE Healthcare – our goal is to get customers to market faster, and we can work with other suppliers to make that possible. Within 22 months, it's possible for us to build and qualify a company's entire manufacturing facility – from closing processes, to training teams, and then handing over the keys to the new facility.

CELLT1 Topics

- Overview of cell therapy workflows and cell types
- Tube welding and aseptic fluid transfer
- Cell counting
- Isolation technologies
- Transduction and vectors
- Activation process and technologies
- Cell culture media development and design
- Cell expansion and perfusion applications
- Harvesting platforms
- Final formulation and cryopreservation
- Scale-up and scale-out
- Development of standard operating procedures
- Process evaluation and optimization

The course will include two different formats. One will be styled like a lecture or presentation, with the aim of teaching the principles behind the technologies. The second format will be "hands on" in the lab, showing students the equipment in action and testing the knowledge they have learned in the lectures.

Graduation day

CELLT1 has been developed to pair with our Enterprise Solutions, so "graduates" should be able to walk out of training and straight into one of their Enterprise suites – and be confident with managing the processes. After the course, students should be able to:

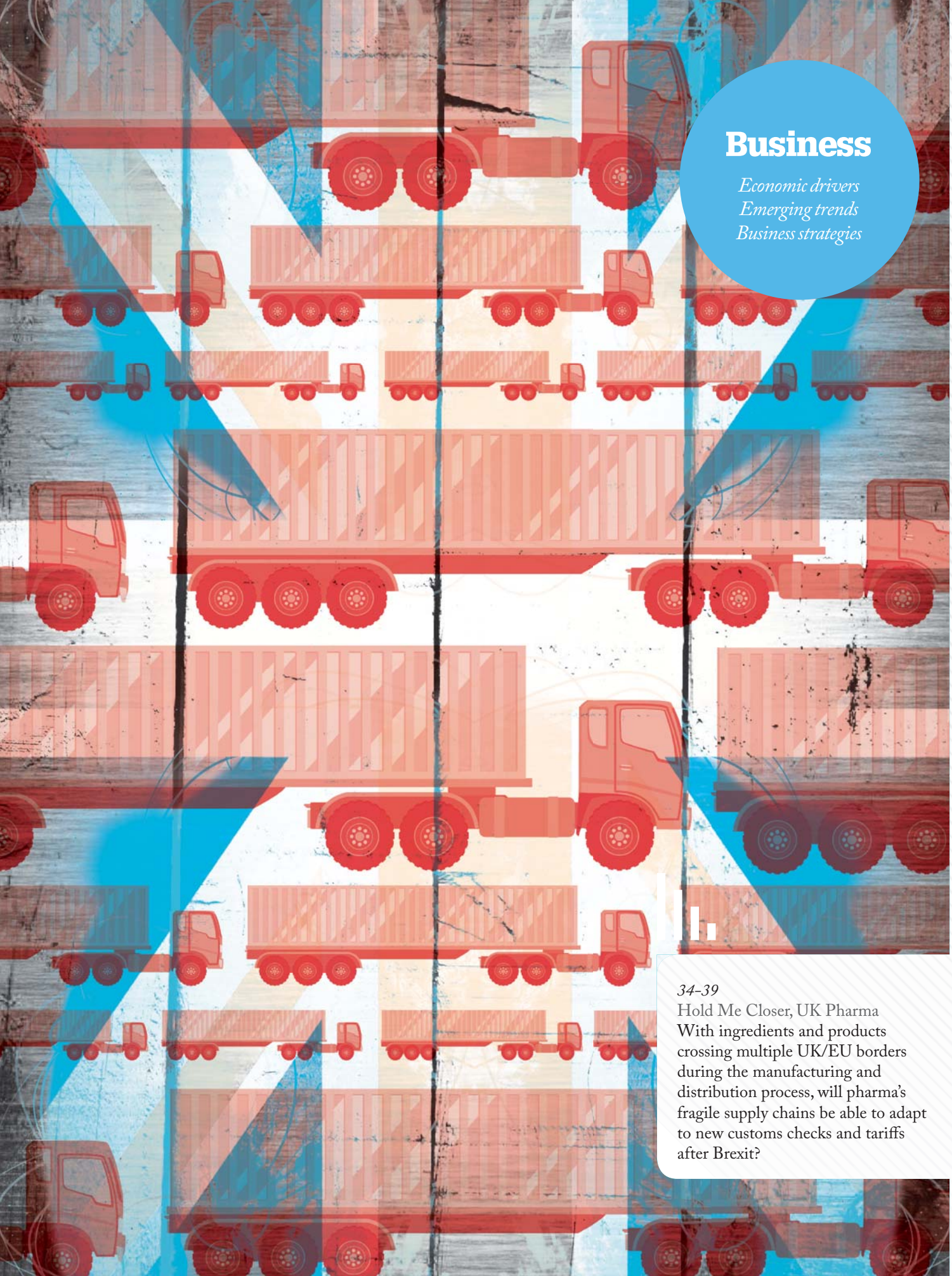
- apply detailed theoretical cell therapy process knowledge to applications across the manufacturing workflow
- identify bottlenecks and troubleshoot specific processes
- perform industry standard techniques related to cell therapy manufacturing
- implement strategies used for process optimization and evaluation.

It may seem easy to overlook the need for a truly skilled workforce, but cell therapy manufacturing requires many people. The flexibility of our Enterprise Solutions is that it allows users to easily scale out into multiple manufacturing suites – companies will need trained staff to work in those suites and standardization to ensure that processes are reproducible anywhere in the world.

Cell therapy is an important component towards a future of personalized medicine; it has long been a goal of the healthcare industry, and to see it unfolding in our lifetime is incredible. Now that the industry has a better grasp of cell therapies and their manufacturing processes, we can really push forward with developing more specific technology platforms. In time, standardization and optimization of the manufacturing process will bolster the field further by reducing costs, accelerating processes, and shortening the turnaround times. At the moment, it is a massive undertaking for companies to develop a cell therapy, but recent speedy FDA approvals have given the industry greater momentum to continue advancing technology to ultimately provide lifesaving therapies to patients who need them.

Seeing our work having a direct impact on patients is really what drives me in all of this. I see products launch – I know they optimize a customer process and this optimization will generate more effective therapies for patients… it's work we can all feel proud of. I think this is the time for companies to work together and to recognize any success as a success for the field as a whole.

Trevor Smith is an R&D Leader at GE Healthcare Life Sciences, based in Marlborough, MA, USA.



Business

Economic drivers
Emerging trends
Business strategies

Hold Me Closer, UK Pharma

Pharma calls for close cooperation and clarity as soon as possible.

By James Strachan, Deputy Editor

Brexit negotiations between the UK and the European Union have moved onto phase two after the EU Council concluded that "sufficient progress" has been made on the three main issues: citizens' rights, the Irish border, and the financial settlement. Despite this, we still know little about what the future arrangement will actually look like. A soft landing – continued membership of the single market via the European Economic Area (EEA) – has been repeatedly ruled out by the British government, but there's been little talk of walking away without a deal in recent months, perhaps signaling that the hardest possible Brexit is "incredibly unlikely," as UK Brexit negotiator, David Davis, said in January (1).

A key feature of the phase one agreement was the UK government's commitment to avoiding a "hard border" in Ireland, including "physical infrastructure or related checks and controls" (2). Critically, the UK committed, in the absence of agreed solutions, to fully "align" its regulations with the EU's so as to avoid such a border. Exactly what "full alignment" means should become clearer once the phase one agreement is transposed into law. As it stands, if the UK is serious about eliminating the need for physical

Operation Stack

The Channel Tunnel and the Port of Dover handle 90 percent of freight traffic between the UK and mainland Europe. Around £119 billion of goods pass through Dover every year – about one sixth of British trade by value. On average, around 10,000 freight vehicles pass through Kent every day and the demand is predicted to rise by over 50 percent in the next decade.

There is a real concern that new customs checks at the border could cause lengthy delays, with severe consequences for pharma supply chains. The flow of goods through the busiest ferry terminal in Europe is currently "frictionless," yet delays are not uncommon. Bad weather, operational problems, industrial action, and more recently, migrant action at Calais, have caused delays. And in cases of severe disruption, Operation Stack is implemented.

Operation Stack is a procedure used to park (or "stack") lorries on the M20 motorway in South East Kent. The system has been implemented 74 times in the past 20 years. On 24 June 2015 Operation Stack was enacted due to industrial action taken by French employees of the MyFerryLink company. This was the first time "Phase 4" of Operation Stack was used, which involved clearing 30 miles of parked Heavy Goods Vehicles. Between January and November 2015 Operation Stack was implemented on a record 32 days, including three five-day stints.

The UK Freight Transport Association (FTA) estimated the cost of the delays to the UK International Road Freight industry at £750,000 per day. The FTA has estimated, based on Border Force KPIs, that passport checks alone cost £1 per minute. "It is therefore highly probable that costs related to customs checks being performed at the border would be much greater due to time spent by customs officials to check goods against documentation," they said (1).

In an interview with The Times, Tim Waggott, the Port of Dover chief executive said, "We will see [Operation Stack] every day of the year in perpetuity if we don't get this sorted" (2).

References

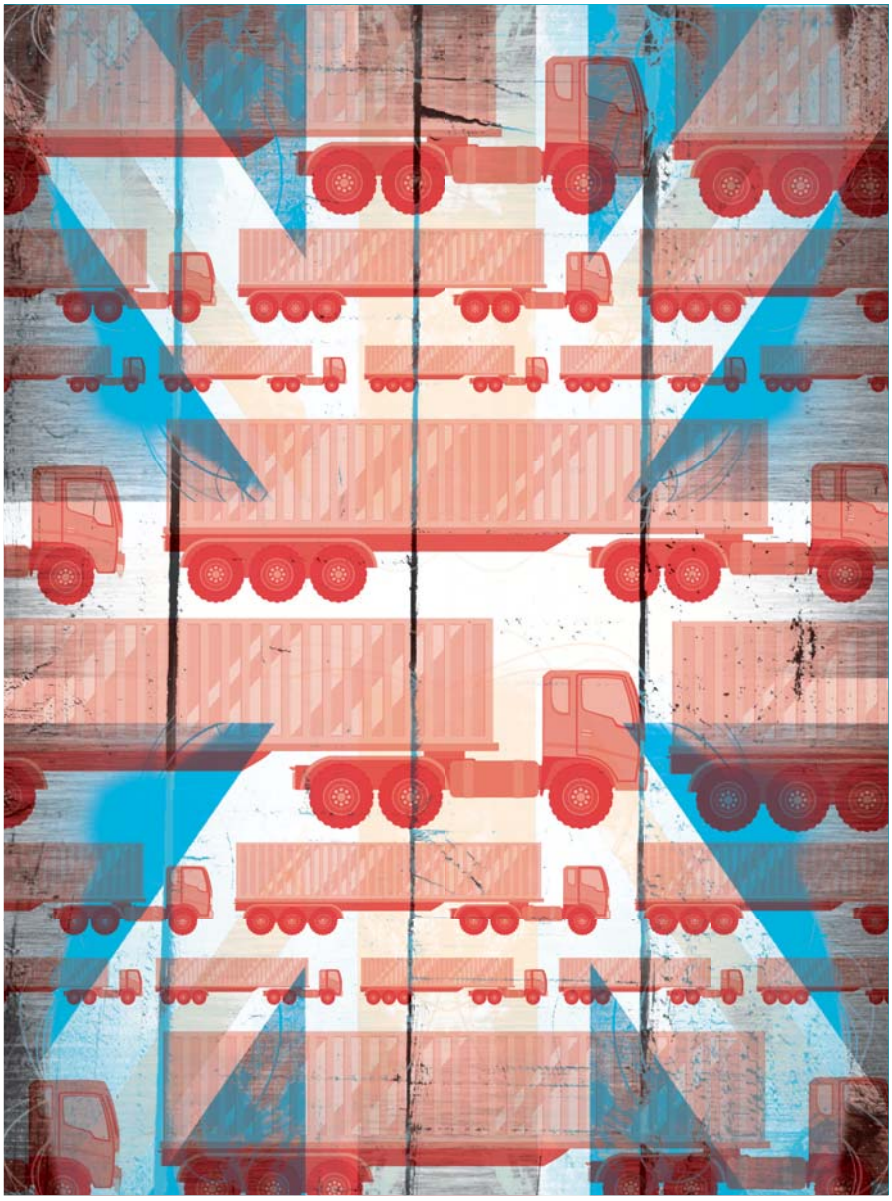
1. *FTA, "Written Evidence submitted by the Freight Transport Association (UKT0033)", (2017). Available: http://bit.ly/2EqEvCr. Accessed 24 January, 2018.*
2. *The Times, "Dover fears hard Brexit as election approaches", (2017). Available: http://bit.ly/2EqEvCr. Accessed 24 January, 2018.*

"Importantly, any delays at borders run the risk of disrupting patient supply of medicines."

infrastructure at the Irish border, while simultaneously ruling out trade barriers between Northern Ireland and the rest of the UK (which the government also did as part of the phase one agreement), the final relationship will likely be very close – which will be a relief for the European pharma industry. "The closer the better!" was the call that came from several global pharmaceutical companies and industry organizations in their submissions to the UK Business, Energy and Industrial Strategy Committee's recent inquiry into Brexit and the implications for UK business (3). The industry was united in its desire for Brexit negotiators to agree a deal that would keep the UK closely aligned to the EMA's regulatory sphere – and, if possible, continuing to participate in the agency.

Save our supply chains

The number one concern for pharma companies is being able to deliver medicines to patients, without delays, after the UK leaves the EU. Pharma supply chains are fragile and highly dependent on frictionless trade, a point



well made by many of the submissions to the Committee. For example, according to Merck KGaA, around 12 percent of their products are "dropshipped" directly to customers from Germany "within 24 hours of an order being placed," so any delays at UK ports would have a "significant impact" on the company's ability to meet the needs of its clients. Merck KGaA also highlighted that products that must be kept cold during transportation; they point out that the refrigeration system is maintained by the running engine of the vehicle in which they are transported. "If delays at ports become consistent, the whole sector will have to develop new ways of transporting and storing goods and medicines to mitigate the risk of a product overheating and becoming unusable," said Merck KGaA. They went on to explain that several customers have "already stated their intention to seek alternative suppliers based in the EU."

Johnson & Johnson raised similar concerns, warning that "ingredients and products can cross the border multiple times in the manufacturing and distribution process [...] Systems must be put in place to ensure that this can continue without the need for Border Inspection Post Personnel checks and tariffs."

As one example, a company that manufactures products in the North West of England identified four occasions where its products cross UK/EU borders before reaching the end user. They added, "Currently this is frictionless, so there is a high risk that any new arrangements will add cost and/or bureaucracy, changing decision-making about both ongoing and future manufacturing."

Eli Lilly's Kinsale site in Ireland is one of the company's major centers for API manufacturing. "As a measure of the integrated nature of our supply routes, products manufactured in Kinsale cross the border from Ireland into the UK before being exported to Europe and beyond," says Chris Lowry, Public Affairs Manager at Eli Lilly. "The fact that these products cross between the UK and the EU multiple times evidently leaves them particularly exposed to any potential customs and border controls. We would be extremely dismayed to see such impediments put in place. Importantly, any delays at borders run the risk of disrupting patient supply of medicines."

"We are a global industry, and Merck Sharpe & Dohme (MSD) is a great example of a multinational operation, working across complex environments that change over time," says Virgina Acha, Executive Director of Global Regulatory Policy at MSD. "Biopharma discovery, development, manufacture and supply chain arrangements take many years to undertake and many years to change. There are long cycles in

planning schedules, with some speciality biological products, for example, only having a production run every one to two years. Supply is carefully allocated in this global planning. The relatively sudden, exceptional and across the board changes that Brexit seems likely to generate will profoundly challenge biopharmaceutical businesses."

Lowry concurs, adding, "Imposing barriers would levy substantial cash flow costs to companies and disrupt the close intertwining of trade and regulation. Mitigating these impacts may require us to explore and validate new supply routes, which given the distribution and storage requirements of some products, is not a simple task."

The Association of the British Pharmaceutical Industry pointed out the challenges associated with cell and gene therapies, which tend to be extremely time sensitive. Novartis' Kymriah, for example, is set to launch in the EU next year. The therapy involves removing the patient's own white blood cells, freezing them, and shipping them to a Novartis site within 24 hours. The T-cells are then treated, before being transported back to the patient for reinjection, again within 24 hours. "The turnaround time is very tight," says Sascha Sonnenberg, VP Commercial Operations Americas and EMEA at Marken – a company that specializes in supply chain solutions for clinical trials. "These are life-saving medicines, and any customs delays – even a six hour delay at the border – could mean you miss the turnaround time and the treatment cannot be used. We're talking about late-stage cancer treatments where the patient might not be in a position to donate additional cells."

To prevent customs delays, the pharma industry is relying on Brexit negotiators to agree a deal that covers the entire economy – delays for other industries could indirectly impact the pharma industry. The Institute for Government, a UK-based think-tank, published a report on Brexit and customs (4); one of if its senior researchers, Joe Owen, points out that the need for new customs checks could severely disrupt the flow of traffic from the UK to the EU, and vice versa. "If the UK is treated in the same way as any other third country, there could be severe border delays. Take Agri-food for example: between 20 and 50 percent of shipments of beef and lamb imported from outside the EEA must be checked at the border. The capacity is not there to cope with the volume of beef and lamb that would need to be checked," he says. Not only is capacity lacking, but there also isn't enough space to build the capacity, argues Owen. The result could be queues of traffic in motorways leading up to the UK's borders with the EU. Not only would this impact exports from the UK to the EU, but any EU to UK exporters would end up stuck in the same queue when trying to get back to the continent – a nightmare scenario for pharma supply chains.

"We're actually in the countdown phase to the rocket launch now and there comes a point where we're beyond the no-go period. For matters like batch release, we need to make decisions relatively soon – but we're already spending money."

Calls for clarity

Though the UK has committed to doing what is required to avoid customs checks between the UK and EU – allowing pharma supply chains to operate as-is post Brexit – nothing is set in stone. The uncertainty over the future relationship means that companies must take action now to ensure their medicines can continue to reach their destination post-Brexit – regardless of what happens in April 2019.

When the UK leaves the EU, it will become a "third country." And so, aside from supply chain issues, another area of concern for UK-based pharma companies is the impact of Brexit on current quality control testing and Qualified Person (QP) batch release systems. Each production batch of medicinal products imported from third countries must undergo "qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorization," in an EU Member State (5). In other words, companies exporting from the UK to the EU after Brexit would, therefore, have to carry out additional batch release testing in an EU member state.

"You're looking at new premises and distribution; and when you add in the possibility of having to transfer your marketing authorizations to the EU, for us the overall cost will be in the region of £5 million," says David Jefferys, Senior Vice President for Global Regulatory, Healthcare Policy and Corporate Affairs for Eisai Europe, and Chairman of Eisai's Global Regulatory Council. "We're actually in the countdown phase to the rocket launch now and there comes a

The Keys to Frictionless Trade

Regulatory alignment

Preserving the integrity of its internal market is of vital importance to the EU. If the UK is able to diverge from single market standards, there is a risk it might loosen its regulations and begin importing faulty toys, diseased animals, or counterfeit medicines from other countries, which could then make their way from the UK to the EU. The EU cannot allow the free movement of goods with the UK to continue after Brexit without an agreement on regulatory alignment – at least for product standards.

Surveillance and dispute resolution

Any agreement on regulatory alignment will have to include appropriate surveillance mechanisms and dispute resolution procedures to ensure that the UK continues to align its regulations with those of the single market. The EFTA court, via the EEA Joint Committee, performs this function for Norway, Liechtenstein and Iceland. Whereas for Switzerland's bilateral agreements with the EU, a Joint Committee (made up of Swiss and EU officials) resolves disputes diplomatically – not legally. It remains to be seen whether a third way can be found.

A customs agreement

The UK and EU will need to enter into a customs agreement if Rules of Origin checks are to be avoided. Rules of Origin are used to determine the national source of a product. To take advantage of preferential tariffs agreed in trade agreements, for example, UK exporters must prove that their goods come from the UK or have had sufficient work – any amount of processing above a certain threshold – done on them in the UK. Border officials check Origin documents at the border, which requires physical infrastructure. Such checks will allow the EU to ensure that countries trading with the UK after Brexit – perhaps with lower tariffs on certain goods – do not use the UK as a means of circumventing the EU's Common External Tariff. The UK could agree to maintain the Common External Tariff or enter into a customs union agreement with the EU to eliminate need for Rules of Origin checks. And though such checks are unlikely to be a direct issue for the pharmaceutical industry (the WTO Pharmaceutical Tariff Elimination Agreement reduces tariffs to zero percent for many pharmaceutical products), the effect on other products could indirectly impact pharma supply chains, if only by causing port and road congestion.

point where we're beyond the no-go period. For matters like batch release, we need to make decisions relatively soon – but we're already spending money."

Jefferys' concerns were mirrored by Lisa Anson, president of the ABPI and chairman of AstraZeneca. "If we look at the frictionless trade, AstraZeneca is already looking at contingencies to duplicate the quality control release processes in the UK and in Europe, because we can't afford to wait to know if there's going to be customs tariffs or any other sort of barrier," (6).

In their submission to the Business, Energy and Industrial Strategy Committee, J&J estimated that the company would have to conduct 50,000 additional tests every year, with a combined cost of almost £1 million per year.

A Mutual Recognition Agreement (MRA) between the UK and the EU would allow companies to base their contract testing laboratories in the UK, but that isn't the default – and there are some concerns over whether an MRA would do what it's supposed to do in practice. "We see that the MRAs between Switzerland or the US and the EU are supposed to eliminate the need for QP testing on the EU side for imports from these countries," says Sonnenberg. "But what I have seen in clinical supply is that there tends to be a simplified release by an EU-based QP in addition to the testing done in the exporting country – even with an MRA in place."

There are also concerns that the EU won't be able to cope with the demand for testing facilities, post-Brexit. "Today, 1,300 products produced by EFPIA members are batch released or tested in the UK," says Acha. "Forty percent of these EFPIA members anticipate challenges to ensure that there is sufficient capacity in the EU27 to replace this infrastructure."

The scale of the work that would need to be done is significant. The EFPIA also revealed that 70 percent of all investigational medicinal products (IMPs) in ongoing EU trials are QP-released from the UK; and more than half of EFPIA members have 100 percent of their IMPs in ongoing EU trials QP released from the UK.

"We see major companies already investing in the EU, building up additional

storage and lab capabilities – the larger companies are quite well prepared," says Sonnenberg. "But some smaller companies, especially Asian and American companies, do not have Brexit on their radar. I worry about a bottleneck on the EU side – especially human resources like QPs – as companies rush to make sure they're ready to carry out QP in the EU once the UK leaves. This could potentially delay or endanger ongoing trials."

Hope for the best, plan for the worst

Companies are optimistic that the final deal will facilitate the continued free movement of goods post-Brexit (see our sidebar for the main elements of such an agreement), but that doesn't (and perhaps shouldn't) stop them preparing for the worst. "We need to be prepared for all eventualities, and this includes a 'no deal' scenario," says Acha. "Our objective is to undertake the investment and changes needed to ensure that following Brexit, regardless of the outcomes of the negotiations, on March 30, 2019, MSD can provide its medicines to patients across Europe as if it were any other day. We are working across our business to meet this objective. However, industry cannot resolve all of the issues on its own."

In phase two, UK and EU negotiators will begin discussions over the transition period. The European Council is proposing a period of two years, in which the UK would lose all EU voting rights, but would continue to participate in the Customs Union and Single Market (7) – potentially providing some continuity for businesses.

"We welcome the recent agreement to progress to phase two of the talks," says Laura Collister, the UK Bioindustry Association's (BIA's) Brexit Lead. "It is now crucial that the UK and EU agree a transition period to ensure that the supply of medicines to patients in the UK and across Europe is not affected." Collister's initial reading of the proposals put forward by both sides is that medicinal products that have been tested and released prior to the Brexit date should continue to be freely available in the EU even if that testing and release is carried out in the UK and the goods are shipped to other EU countries after the UK withdraws. "This is an important detail for global companies deciding how, and crucially when, to progress existing Brexit contingency plans," she says.

Another important factor is whether or not the UK will have access to the EU's trade and mutual recognition agreements during the transition period. As things stand, unless Article 50 is extended, the UK will leave the EU on March 30, 2019 and drop out of several hundred EU agreements – including free trade agreements with Canada, Switzerland and Turkey (7). However, if the UK is bound by the rules of the single market and the customs union during the transition, it will likely be bound by the obligations of the EU's trade deals. Canadian or Korean exporters should be able to sell to the UK as though it was an EU member during the transition, but UK-based exporters would not be able to benefit from the EU-Canada or EU-Korea FTAs (8).

Could the UK roll over the EU agreements on March 30, 2019 or agree a legal fudge whereby the UK continues to be covered by the EU's external trade policy as a non-EU member for the transition period (the so-called "Guernsey option," 8)? Well, that remains to be seen. And the uncertainty, both over the nature and length of any transitional arrangements, as well as the future relationship, is an ongoing problem for pharma – forcing companies to defer investment decisions.

"When companies are thinking about investing in the UK, the uncertainty is definitely having a negative impact," says Jefferys. "And I would say the choice isn't just between London and Frankfurt or Milan, for example. It's London versus New York versus Singapore versus Tokyo, and so on."

When it comes to the final arrangement, Sonnenberg just hopes the negotiators understand what is at stake for those who rely on the life-saving medicines produced by pharma industry. "We are talking about patients' lives," says Sonnenberg. "Particularly when it comes to clinical trials, oftentimes these drugs are the only option for patients. There are so many uncontrollable events that could lead to drug shortages; if we make Brexit one of those, then I think we all fail."

References

1. *Exiting the European Union Committee, "The progress of the UK's negotiations on EU withdrawal", (2018). Available: http://bit.ly/2DtYnDj. Accessed 24 January, 2018.*
2. *EU Commission, "On Progress during phase 1 of negotiations under article 50 TEU on the United Kingdom orderly withdrawal from the European Union", (2018). Available: http://bit.ly/2iGFODe. Accessed 24 January, 2018.*
3. *Business, Energy and Industrial Strategy Committee, "Brexit and the implications for UK business: Pharmaceuticals inquiry – publications" (2018). Available: http://bit.ly/2GbJU0D. Accessed 24 January, 2018.*
4. *Institute for Government, "Implementing Brexit: Customs", (2017). Available: http://bit.ly/2gZ6nGb. Accessed 24 January, 2018.*
5. *EU Commission, "EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 16: Certification by a Qualified Person and Batch Release", (2015). Available: http://bit.ly/2BqrtBP. Accessed 24 January, 2018.*
6. *Sky News, "Pharma sector warns of 'dire' consequences without Europe regulation deal", (2018). Available: http://bit.ly/2rDBf3M. Accessed 24 January, 2018.*
7. *EU Commission, "Annex to the Recommendation for a Council Decision", (2018). Available: http://bit.ly/2kuG0a3. Accessed 24 January, 2018.*
8. *CER, "Of transition and trade deals", (2018). Available: http://bit.ly/2nbrK6n. Accessed 24 January, 2018.*

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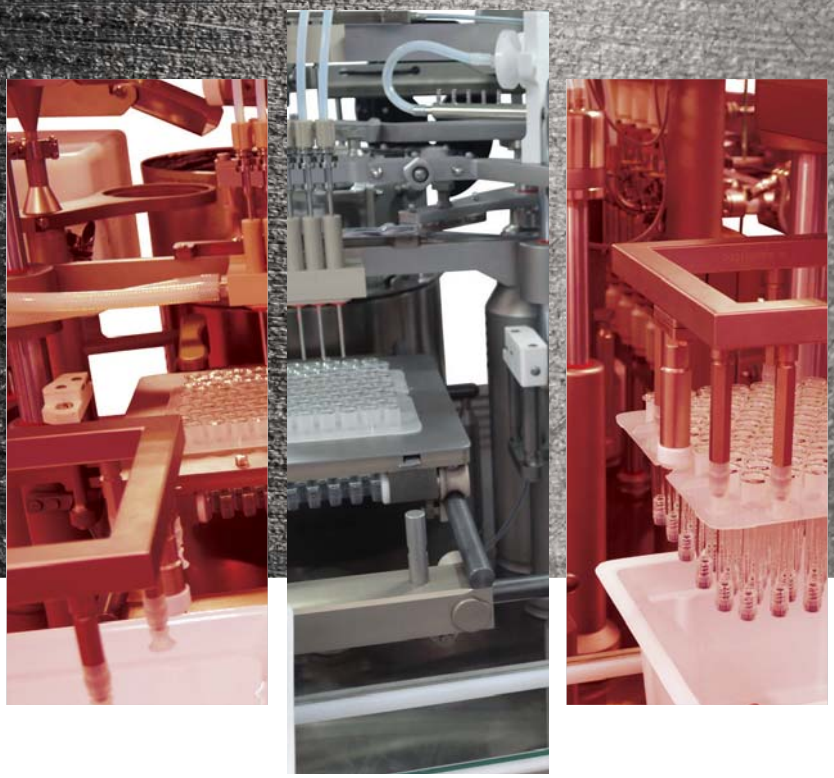

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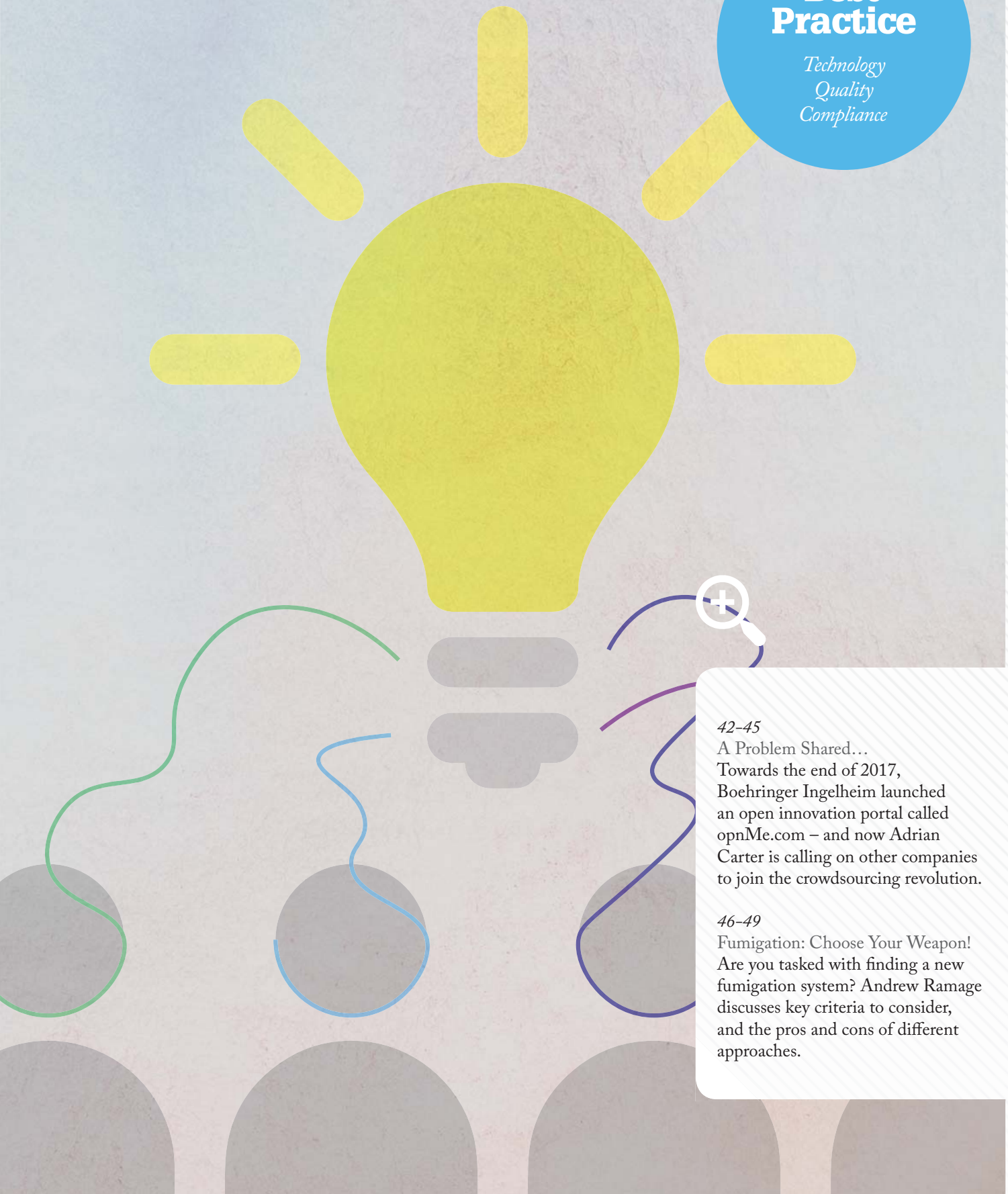
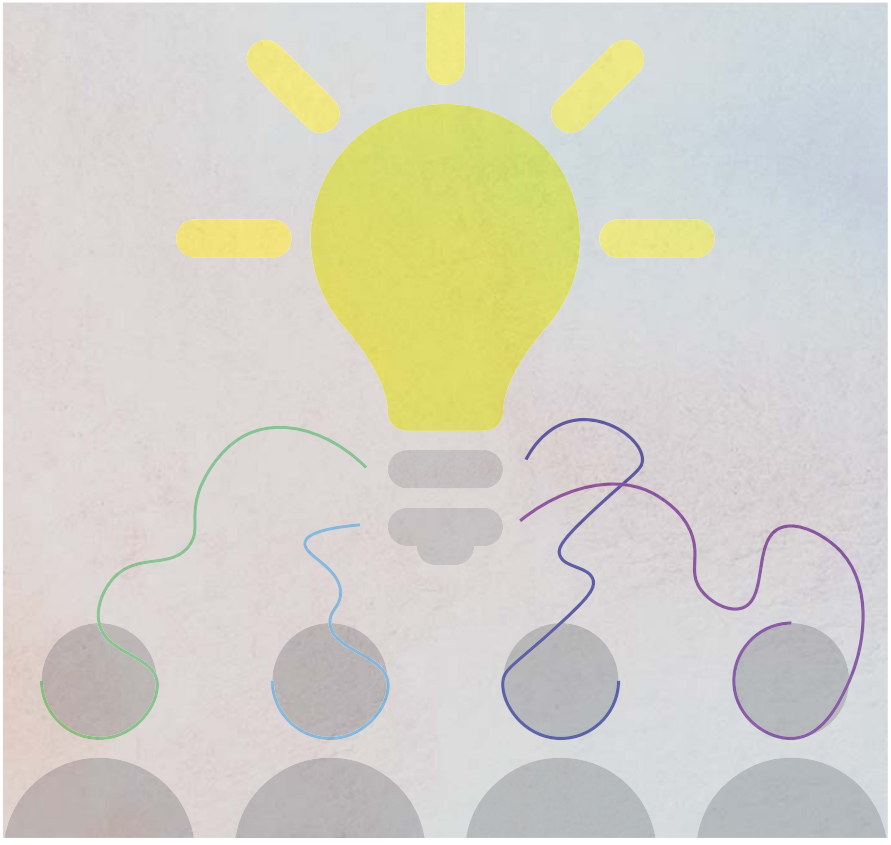


A Problem Shared...

It's time for pharma to join the crowdsourcing revolution. Open access science may seem counterintuitive to some objectives but by joining forces with the broader scientific community, we will be far stronger together than we are alone.

By Roisin McGuigan, Deputy Editor



The ways in which individuals, organizations and companies can find solutions on the Internet is constantly expanding – from naming a new polar research vessel using an online vote (the Royal Research Ship Sir David Attenborough, if you're interested) to funding innovative projects in art, science and technology through crowdfunding platforms like Kickstarter. But how can the crowdsourcing revolution benefit pharma? And how can companies strike the right balance between sharing their own data and protecting intellectual property? We spoke with Adrian Carter, Corporate Vice President and Global Head Discovery Research Coordination at Boehringer Ingelheim, Germany, to find out why he believes open innovation is important for securing a better future for pharma research and discovery.

How did you become interested in open innovation?

I "grew up" in discovery research – I'm a pharmacologist by training. But when I moved from the UK to Germany for a postdoctoral position in the research organization at Boehringer Ingelheim, I quickly developed an interest for neurobiology and spent 15 years working in that area. And then I crossed to the "dark side" – I moved into business development and spent 10 years there. In 2011, I moved back to research in a networking and coordination role at Boehringer Ingelheim that allowed me to bring together these two different parts of the collaboration puzzle. My broad aims were to examine how the pharmaceutical industry and academia could best work together, what advantages that brings, and also what needs to be done from the operational side to make it work well. It made me realize that, as an industry, we need to look further afield for new ideas.

It's important to recognize that many discoveries in a pharma company do not actually come from inside their own four walls; to be successful in research and discovery, you need to seek out creative ideas from elsewhere. With this in mind, we developed a strategy document that assessed not only where and how we could find innovative ideas and approaches, but also how we could turn them into new medicines. One concept we hit upon was the idea of "opening up" the innovation process and inviting contributions from the scientific community to help solve current research puzzles.

This idea has its pros and cons: on the one side, you have the opportunity to tap into the creative power of scientific minds from all around the globe – someone might just hold the answer to the conundrum. The downside? You have to share some of your own hard-won knowledge. Some people within industry will balk at the idea of sharing propriety information with the public, but if you do it right, the pros far outweigh the cons.

The practice of opening up collaboration and publicizing data has

its roots in the software industry in the 1980s. The industry was revolutionized by Richard Stallman, who used the open source approach to create an alternative to Unix, the operating software that large mainframe computers ran on at the time. He encouraged software programmers around the world to work together to develop operating software for mainframe computers that wasn't tied to Unix's developer, AT&T, who subsequently licensed it to IBM. The effort resulted in an alternative called Gnu, a recurring acronym "Gnu is not Unix", which was combined with another open source software kernel, Linux – eventually going on to enormous success. Most of the computers in the world now run on Gnu/Linux software – and huge brands like Amazon, Google and Android, and many more, all use this open access software as the basis for their large servers. I think many people don't fully appreciate how much of our modern technology is driven by this open access source material. And if an open access approach can have such a far-reaching impact on the software industry, just imagine what it could do for pharma!

What does open innovation mean to you?

"Open innovation" is a term that has evolved over the years. As it's taken off, we've developed a variety of terms to describe the free movement of ideas and data (see "Behind the Buzzwords"). Science is seeing the effects too – many scientific journals today require scientists to make their data public so that others can use it, and more journals are making their papers open access. Large commercial publishers may prefer to keep their content behind a pay wall, but public funders are challenging the idea and demanding that the research they pay for is made publicly available. An open approach to science means that everyone gets to participate in the scientific process – but don't let that put you off! You don't have to give everything away for free to participate in open innovation. Different degrees of openness in the forms of project participation, scope and access may be appropriate, depending on your goals.

Open innovation has clear benefits for both pharma and academia. Developing new drugs is an expensive business model with a high failure rate. I call it the rule of 10: by the time you get a molecule to the preclinical development stage (which takes a huge amount of work), the chance it will make it from there to market is around 10 percent – and if it does, it will take around ten years on average. Despite all the effort, there's no guarantee of success. I believe this is down to a lack of efficacy – candidate drugs often tick all the safety boxes, but fail because they don't exhibit the desired improvements for patients. Why? One theory is that we simply don't understand enough about human biology, and I believe that increasing our knowledge will help us overcome the efficacy wall we keep hitting.

Meanwhile, many academic institutions worldwide, which are filled with brilliant scientific minds, are lacking research funding and resources. Collaboration with the private sector is an attractive prospect in this climate – as long as both parties benefit and as long as researchers are not subjected to hidden and unnecessary "strings attached."

How did opnMe come to be?

Boehringer Ingelheim's open innovation portal – opnMe.com – started with our work with the Structural Genomics Consortium (SGC), a public/private partnership involving nine pharma companies. The idea was to encourage the scientific community to work on particular proteins that may be of interest by providing them with new

Adrian Carter's Key Messages

- Open innovation is evolving. Originally used to describe a closed collaboration between two organizations, today it covers much more – from crowdsourcing problems to open access data.
- Pharma must embrace a more open way of working; fresh approaches will improve our understanding of human biology and lead to new drug targets, ultimately helping us provide novel therapies for patients in need.
- There are challenges ahead but, with the right approach, we can create trust and foster true collaboration between companies, research institutes and individuals.
- There is strength in numbers – the more we all buy into open innovation and the more we share resources, tools, and knowledge, the more we all stand to benefit.
- Boehringer Ingelheim has recently launched its open innovation portal opnMe.com to provide access to scientists from all around the world to a unique selection of well-characterized, pre-clinical probe compounds.

Behind the Buzzwords

Open innovation: Originally defined by Henry Chesbrough as a closed collaboration between two organizations, the meaning has evolved to include a variety of strategies and practices that allow ideas to flow between businesses, research organizations and the scientific community.

Crowdsourcing: A way to elicit ideas and services from the scientific community at large, usually via the Internet.

Bilateral collaboration: The traditional way in which pharma often collaborates, involving a closed partnership between one company and one academic investigator or institution.

Precompetitive public/private partnership: A partnership in which private and public funders identify an area of research and share their ideas, protocols, and tools.

Selective revealing: The practice of revealing some proprietary information in return for insights and ideas, while keeping other information private.

Open source: An idea pioneered in software development, which aims to make the results of collaborative projects free for anyone to access.

Open data: Data that anyone can access, use and share.

Open science: The practice of sharing lab notes, methods, data, and research outcomes with the scientific community, allowing others to benefit from or contribute to the work you are doing.

tools. One such tool was a chemical probe for the bromodomain (BRD) family member BRD4; making it freely available catalyzed a great deal of research, thereby leading to a number of clinical programs and new biological knowledge on BRD4 (1).

Our work with the SGC helped us to understand the potentially huge advantages of making our chemical tools available to a wider scientific audience. We also learned that you get much better uptake if you provide the tools free of charge – and without any catches. The minute you start charging and adding caveats to the use of the tools you're offering, people lose interest.

The success we saw with BRD4 led us to launch opnMe.com, a project with two main aspects: "molecules to order (M2O)" and "molecules for collaboration (M4C)". M2O are chemical probes freely available to the academic world. These are molecules we're no longer pursuing, for various reasons. Instead of having them sit in our vaults, gathering dust, we have made them available for other people to experiment with. And this option is truly free – no intellectual property restrictions, and no usage restrictions other than requiring that people don't do anything irresponsible or dangerous, such as using an unapproved molecule in humans. We'd like nothing better than to have someone take one of these molecules, develop a new mechanism or make a discovery, and publish that in a high quality journal. Using this approach, we can advance scientific knowledge and provide helpful tools to researchers, at very little cost to the company.

We've taken a different approach with our M4C, which are still part of our ongoing programs. For organizations interested in working with us on these molecules, we provide them under a standard material transfer agreement, and this forms the basis for a more traditional collaboration. Providing these two options in our portal allows us to monitor what information we're sharing, and how we share it. opnMe.com launched in mid-November 2017 – we are still working to spread the word and seek feedback from our users to help us improve the portal. Nevertheless, we have been pleased to see that the site has been frequently accessed thus far, and we have already received a steady stream of new orders. Embracing open collaboration is a process and I believe pharma will go through a similar transformation to the software industry as we seek new and better ways to work together. I would encourage other companies to follow suit and look at what information they could afford to share to help move science forward.

What's your top advice for other companies wanting to establish an open innovation initiative?

Internally, you may face resistance: our industry is traditionally a conservative one, and some people may view sharing proprietary information as a big risk. You'll need to develop a release procedure and criteria for choosing what you want to share, and how you'll share it. The most important external consideration is how you're going to connect with the people you need to crowdsource the answer to your problem. In short, you need a reliable Internet portal that functions well; people won't be interested in what you're offering if it is difficult to access.

Trust is also crucial. Academics can be wary of industry, so you may need to take the brave step of making the data or tools you want to share truly free – if you try and retrain too much control or place too many restrictions, people will be reluctant. Remember: the more you share, the more you stand to learn!

There are many passionate scientists in both industry and academia. And

On the Open Road

Many companies and organizations already have some form of open innovation platform, but restrictions, confidentiality, and intellectual property rights can vary. Some notable examples include:

- *LEO Pharma Open Innovation:* an open drug research platform that makes research tools available to external partners. LEO Pharma tests compounds for free, but the partner will receive full scientific insight into the assays used and will own the produced data. Partners do not have to disclose the structure of their compounds, which helps maintain confidentiality. Read more at http://bit.ly/1pHh4M1
- *Eli Lilly* – Open Innovation Drug Discovery: A platform focused on neglected and tropical diseases, diabetes and oncology. Researchers get access to computational design tools and can submit compounds for screening.
- *AstraZeneca Innovative Medicines and Early Development biotech unit*: The company gives partners access to compounds, compound libraries, technologies and services.
- *Merck Mini Library:* Organizations and individuals can apply for free access to a collection of former R&D compounds.
- *The European Lead Factory:* A public/private partnership that provides free access to up to 500,000 novel compounds.
- *Structural Genomics Consortium:* A project that aims to accelerate research by making its output available to the scientific community without restrictions, and create an open network of scientists and pharmaceutical companies.

when you bring them together, the energy and enthusiasm you can generate is incredible. If we pursue the right environment of openness and collaboration to bring people together, I believe we can begin to push the boundaries of biological knowledge and see some truly exciting progress. To do that, we need the courage to do things differently. Some companies are already joining in (see "On the Open Road"), but I want to see everyone getting involved! The more we can get industry, academia and individual scientists to participate, the more we all reap the rewards.

Reference

1. *AJ Carter et al., "Establishing a reliable framework for harnessing the creative power of the scientific crowd", PLoS Biol, 15, e2001387 (2017). PMID: 28199324.*

Further Reading
Boehringer Ingelheim has written extensively about open innovation. Read more at http://go.nature.com/1YuLb5l

Fumigation: Choose Your Weapon!

Do you want to replace a fumigation system that is no longer up to scratch? Are you looking to switch out formaldehyde – before it's phased out? As a former site fumigation lead, here is how I would go about it.

By Andrew Ramage

Previously in The Medicine Maker, I recognized the challenges of selecting the right fumigant for microbiological safety cabinets, high containment level areas, and cleanrooms (1). I noted my relief that it was no longer my job to choose a new fumigation system (I'm now based on the vendor side), but for the purpose of this article, I am going to put myself back into the shoes of a site fumigation lead and think about how I would approach the task of replacing an existing system.

From a formaldehyde user's perspective, at the time of writing, we are still waiting for the Biocidal Products Committee to decide whether they will approve or reject its use in the EU Biocidal Product Regulation (EU-BPR) usage classification PT2 category. A decision on formaldehyde usage was originally expected in the summer of 2016 (2), but there is still no news. The British Health and Safety Executive (HSE) document, "Biological agents - The principles, design and operation of Containment Level (CL) 4 facilities" (3), has a whole appendix related to fumigation advice. At the very end of the appendix, it quotes, "Further guidance on the use of alternatives to formaldehyde as a fumigant is currently in preparation and will be available from the HSE website." The HSE has released nothing yet, so formaldehyde is still the recommended fumigant – backed up by a study from the HSE's Health and Safety Laboratory (HSL) (4).

Factors to consider

When it comes to choosing your fumigant, there are a number of criteria to consider. Here is my list, based on order of importance:

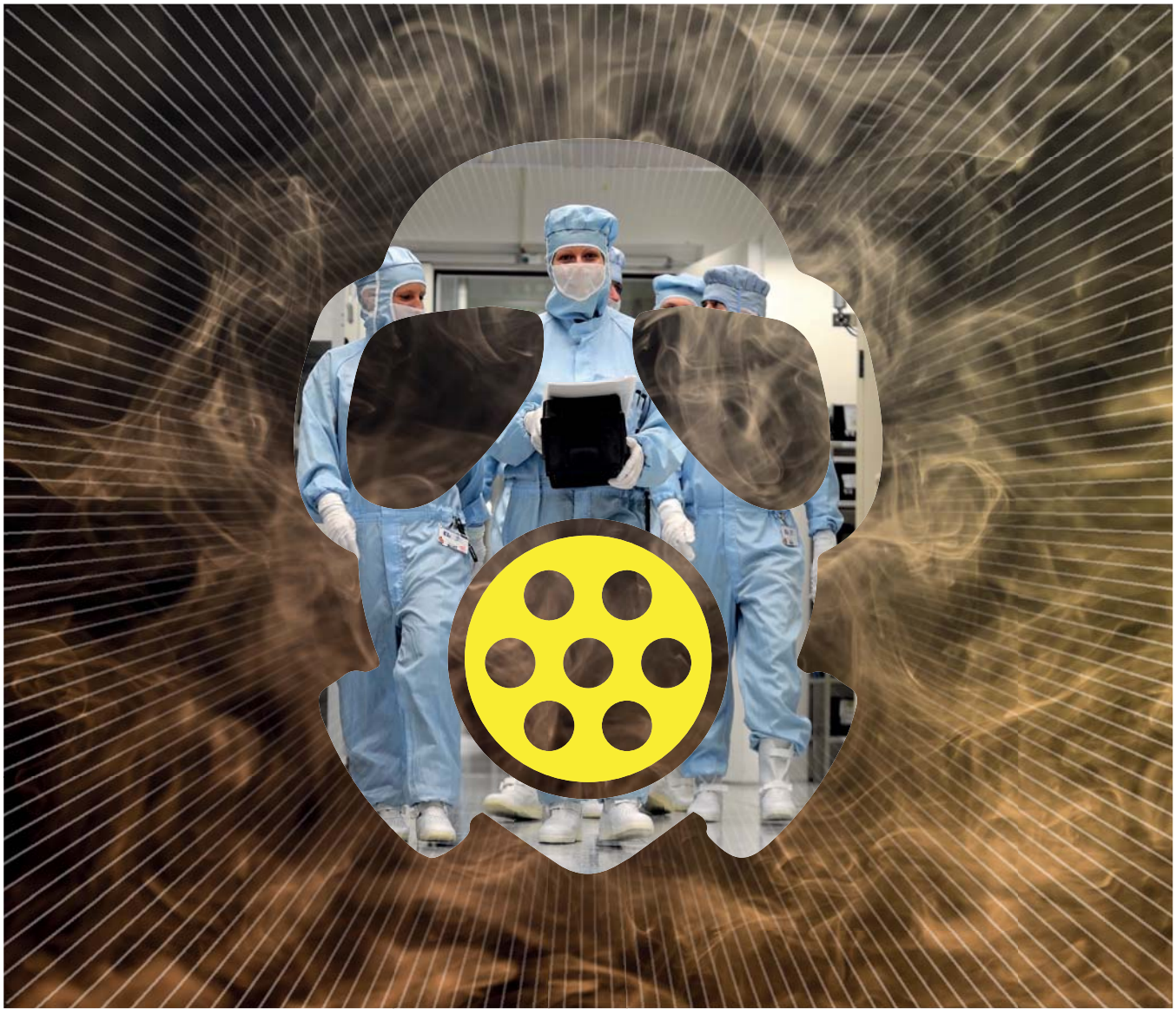
1. Active substance registered in or exempt from Biocidal Products Regulation (BPR) category PT2
2. Repeatable process
3. Efficacy of the fumigant/biocide
4. Penetration of spills
5. Ease of use
6. Corrosiveness of biocide to fixtures, fittings and equipment
7. Chemical incompatibilities of the fumigant
8. Cost
9. Downtime from fumigation process

As soon as you start looking at a new fumigation system, make sure the active ingredient is registered as a PT2 biocide – or exempt from that classification. Exempt disinfectants (or more precisely the active ingredient) will be registered under the EU Medical Devices Regulations. If it isn't, then you are breaking the law by using it as a fumigant. If you are not based in the EU, you will need to check what regulations you should be adhering to. Arguably the next two criteria (repeatability and efficacy) are equal in their importance with CL3 and CL4, but in the end whatever fumigation system you choose must be robust – and you must have total confidence that it works every time.

Penetration is very important when decontaminating spillages, and it has been a requirement for many years in the HSE advice – and in many other countries – on the management, design and operation of microbiology labs, with specific advice in appendix 3 (5). Ease of use is vital, as most operators will not perform fumigations on a regular basis; in short, the easier the better. Corrosiveness is a greater issue in areas where there are frequent fumigations. Chemical incompatibilities can be managed by removing or isolating the incompatible chemical. For example, with formaldehyde as the fumigant, any chemical containing chlorine needs to be removed from the area before fumigation begins. The amount of downtime for the fumigation process must be sensible, but isn't crucial. The cost also has to represent value, and there is often a prudent limit on what can be spent. Notably, most of the cost comes from the setup and validation rather than actual future usage.

There are other factors that will affect the relative importance of the above criteria. For example, choosing a new system for a clean room where pathogens are not handled will mean a number of the above criteria need not be considered at all. Also, in areas where there is no chance of spillages, efficacy in most cases need only be demonstrated against the recommended biological indicator for that biocide, so will come lower

"Ease of use is vital, as most operators will not perform fumigations on a regular basis."



down the list. Certainly in the private sector, cost and downtime will be of greater importance, where other factors such as chemical incompatibilities and corrosiveness can be controlled, or are less of an issue because of fumigation infrequency.

Weighing up the options

The basis for my search for an alternative to formaldehyde began with the HSL fumigation study (4), in which hydrogen peroxide (H_2O_2), chlorine dioxide and ozone based fumigation systems were assessed. Starting with H_2O_2, two systems (where H_2O_2 is the active substance) were assessed in the HSL study – either can be provided as a service offered by the manufacturer, or the equipment can be bought. H_2O_2 is registered as a PT2 biocide so can be legally used as a fumigant (6). The fumigation service is usually a cost-effective solution to users who do not require frequent fumigations and do not have the expertise internally to perform the task in house; however, should you purchase either of the systems assessed in the study, then the initial setup costs are considerable. The amount of H_2O_2 required and the cycle length is calculated by the equipment based on a number of factors such as room volume

"The fast turn-around time is clearly an advantage, but it does leave a slight acetic acid odor after fumigation."

and pre-conditioning stages.

Both of the assessed H_2O_2 systems have been in use for many years and arguably are the most mature of the formaldehyde alternatives on the market. One system generates a layer of micro-condensation (above the dew point) and the other maintains the vapor level below the dew point. An independent study from the HSE does acknowledge that both H_2O_2 systems frequently gave good results against all pathogens (4).

Chlorine dioxide (ClO_2) is gaining in popularity. Although its anti-microbial properties have long been known (it is commonly used as a disinfectant in other areas), ClO_2 struggled to be accepted initially as a fumigant because of fears over its potential corrosiveness and toxicity. It is not considered a substance of concern by the ECHA, so is exempt from BPR PT2. ClO_2 fumigations are actually not corrosive, but a controlled study by the US EPA showed it can be corrosive inside functioning computers due to the heat from the CPU (7).

The HSL study gives this system the thumbs up in terms of its efficacy and reliability in comparison with formaldehyde against a range of tough-to-kill pathogens and spores. It is also excellent at inactivating beta-lactams and, thus, ideal for decontamination of those facilities (8). The cycle starts with a pre-conditioning step, which increases the humidity in the room to 60-75 percent where ClO_2 is most effective. The humidity is then held for 30 minutes, and then ClO_2 is generated and delivered into the room and controlled at the appropriate level. The final stage is aeration (extraction). It should be noted that the ClO_2 system is operated externally, so any connections to the control system must pass through an aperture into the room. Also, as a true gas system that can penetrate most crevices, you must be able to guarantee sealability of the area to prevent leakage.

Another system to be considered uses hydrogen peroxide/peracetic acid, although not assessed in the HSL study, it has a number of existing customers in the pharmaceutical sector. The proprietary chemical – 22 percent H_2O_2 and 4.5 percent Peracetic acid – which is diluted down for use as a 10 percent solution, claims a broad range of efficacy against all types of microorganisms. The delivery system uses compressed air to pressurize the unit, forcing out ultrafine, atomized droplets into the atmosphere (fogging).

The amount of the chemical to use is easily calculated based on the room volume. Fogging starts as soon as the compressed air is switched on and following a one-hour hold time the

fumigant is vented – the whole process takes around 2-5 hours from start to finish. The fast turn-around time is clearly an advantage, but it does leave a slight acetic acid odor after fumigation (which should clear fairly quickly). The other main advantages of this system are that the room humidity does not need to be raised pre-fumigation, so there is little chance of the chemical pooling in cooler areas. It is also considerably cheaper than H_2O_2 systems. My main concern for this system is that the chemical might corrode copper over multiple fumigations. But in cleanrooms with predominantly stainless steel and plastics, this will not be an issue. The proprietary chemical is registered as a medical device and so is exempt from the EU-BPR.

Ozone fumigation systems are another alternative. Although aimed more at the food, water treatment and clinical sectors to reduce bioburden and undesirable microorganisms, such systems were also tested by the HSL study. However, I could not find the system described in the report. Also, although the anti-microbial properties of ozone are well documented (9), I have not found any ozone fumigation system being marketed for the fumigation of laboratories or cleanrooms in the pharmaceutical sector (if you know of any then I'd be interested to know more).

Drawing from the results of his findings, in a presentation to the Annual Biological Safety Conference in 2012 (10), Alan Beswick, principal author of the HSL study, offers advice to both end user and manufacturer. To the end user, he emphasizes the importance of validation, especially against target organisms where high containment laboratories are concerned; to the manufacturer, he asks for both reliability in terms of the consistency of fumigation cycles and technical reliability of the equipment provided. It is sound advice!

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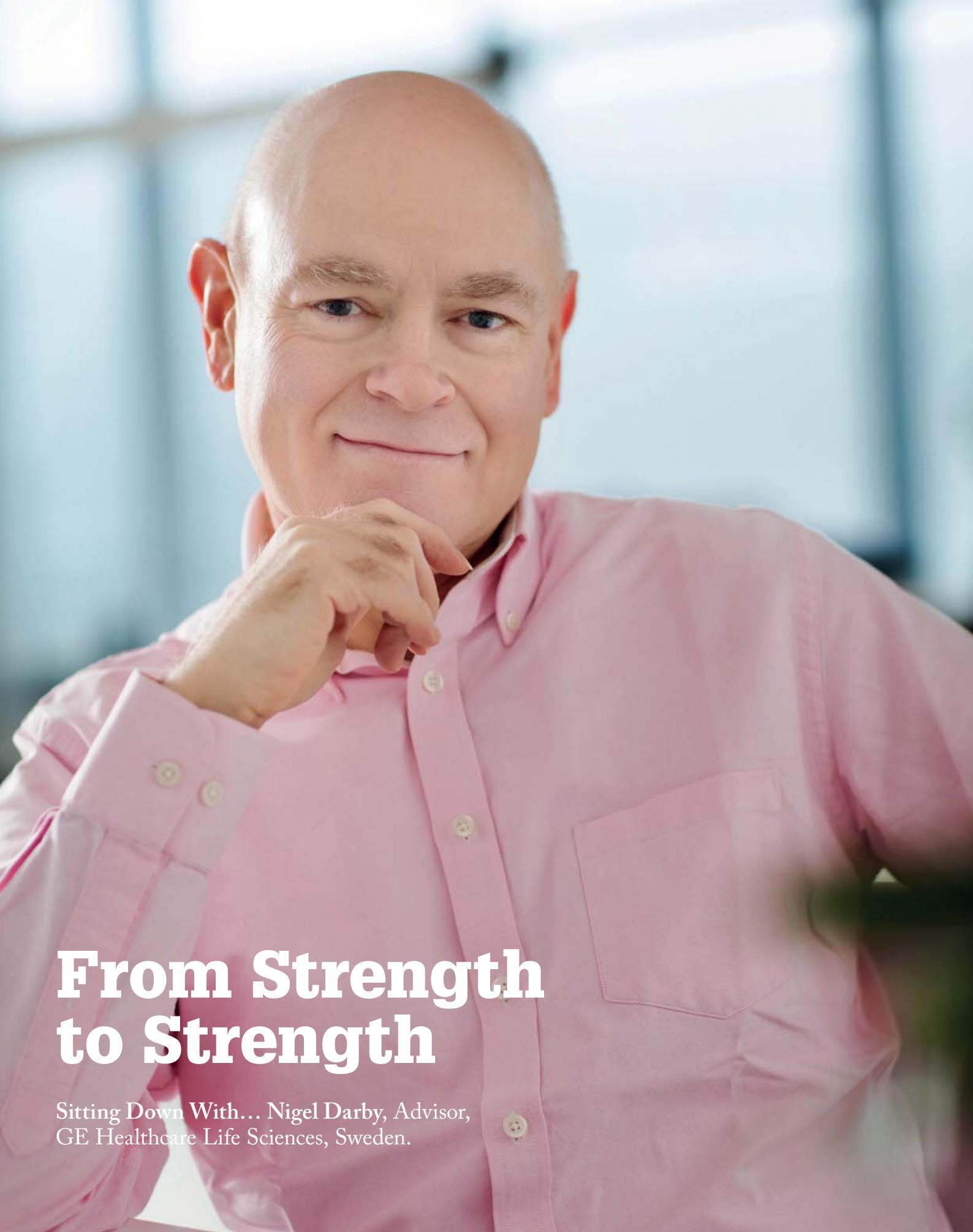
References

1. *A Ramage, "Finding a Fumigant", The Medicine Maker, (2016). Available at: http://bit.ly/2zSSQru.*
2. *J Chewins, "Is this the death of formaldehyde?" Laboratory News, 37-38 (2016).*
3. *The Health and Safety Executive, "The Principles, Design and Operation of Containment Level 4 Facilities", 2006, Available at: http://bit.ly/2jFXMcK. Last accessed November 20, 2017.*
4. *A Beswick et al. "Comparison of Multiple Systems for Laboratory Whole Room Fumigation", Applied Biosafety, Vol 16, No.3, pp.139-157 (2011).*
5. *The Health and Safety Executive, "The management, design and operation of microbiological containment laboratories Guidance", HSE Books 2001 ISBN 0 7176 2034 4. (2001).*
6. *Biocidal Products Committee, "Opinion on the approval of active substance: Hydrogen Peroxide: Product Type: 2 ECHA/ BPC/40/2015", (2015). Available at: http://bit.ly/2zkGLM8. Last accessed November 20, 2017.*
7. *United States Environmental Protection Agency, "Compatibility of Material and Electronic Equipment with Hydrogen Peroxide and Chlorine Dioxide Fumigation – Assessment and Evaluation", (2010). Available at: http://bit.ly/2z4EwIy. Last accessed November 20, 2017.*
8. *K Lorcheim, "Chlorine Dioxide Gas Inactivation of Beta-Lactams", Applied Biosafety Vol 16, No.1, pp34-43. (2011).*
9. *MA, Khadre et al., "Microbiological aspects of ozone applications in food: a review", Journal of Food Science 66, 1242–1252 (2001)*
10. *A Beswick, "Green gas, dry mists and dense vapours: An overview of independent fumigant testing at the UK Health and Safety Laboratory (HSL)", (2012). Available at: http://bit.ly/2zYlF3j. Last accessed November 20, 2017.*



From Strength to Strength

Sitting Down With… Nigel Darby, Advisor, GE Healthcare Life Sciences, Sweden.

Why did you choose science?

I grew up in the 1960s, and there was so much happening in terms of science and technology: the moon landing, the first heart transplant, Concorde... Nowadays, technology is so commonplace and disposable that we take it for granted, but when I was a child, each and every one of these things was a miracle – and that definitely influenced me.

I also think my parents had a big impact. They encouraged my curiosity, and let me do a lot of things that many modern parents would not! I remember performing chemistry experiments on the gas stove – I destroyed a number of my mother's saucepans by melting sulfur and boiling acid in them... I also broke quite a few things around the house by taking them to pieces to see how they worked. But my parents never stopped me or yelled at me for being curious.

How did your pharma career get started?

I spent 18 or 19 years doing academic research, so I didn't enter industry until I was nearly 40, which is a bit unusual. I was fortunate enough to spend time in a number of very good research institutions, which taught me a lot of humility. When you meet so many people who are simply orders of magnitude smarter than you are, you realize you have to figure out what makes you unique, because you can't compete with people on pure cleverness! I learned a lot of lessons from my time in academia.

When I entered industry – AstraZeneca – I originally managed a group of three people working in drug discovery. Three years later, I was heading a group of maybe 500 people all around the world – mainly because of so many changes, mergers and acquisitions and so on. Someone said to me: "Will you have a go at managing this? You always try hard, and perhaps do the things other people don't like doing."

So the advice I give to people is to be patient in times of difficulty, such as when everything is falling apart around your ears... Be the person to stand up and try to fix it, and that will go a long way towards helping you move forward with your career.

How did you find the jump from research to GE?

I used to work in the very early parts of pharmaceutical discovery, so the molecules we discovered would still have at least ten years before they came to the market – and we met with failure probably 99.9 percent of the time. In GE the work has mainly been about developing new biopharmaceutical manufacturing technology. It means I've moved much closer to the customer – product cycles are much shorter, and when you develop a product it goes to the market in two or three years. It's great to actually get to launch products! When I first came to GE we were launching perhaps 20 products a year. In early stage pharmaceutical research, you feel lucky if you participate in one project in your entire lifetime that results in a drug reaching the market.

On the flip side, there's been more commercial pressure in my GE roles. I'm much closer to the financial realities of the business; if something goes out into the market and does not do well, it has consequences. In early stage pharma research, one tends to be more distant from that (or at least we were in my day). When I first joined GE, I didn't even know what a profit margin was! But providing you have an interest you can pick that sort of stuff up.

What trends do you see in technology adoption?

The speed at which the industry adopts new biopharmaceutical manufacturing technology is always a major challenge. The lack of pace means missed opportunities to improve. Right now, the market for individual therapeutic indications is very competitive. If you look at the explosion in immunotherapies, there are many molecules competing for the same or similar indications. The question of how to get to the clinic faster is becoming more important every year. Twenty years ago, there were perhaps one or two molecules for a particular indication. Now, in the immunotherapy market you might see as many as ten different molecules appearing almost simultaneously. Being second on the market might be okay, but being fifth probably isn't – and the time difference between being second and fifth is not large. Time to develop manufacturing processes, deliver molecules to the clinic and build manufacturing infrastructure plays a key role in competitiveness.

When I speak to folks in the industry, I often hear "Yes, we know this new manufacturing technology is great and that it works, but honestly? We just don't have time, we're focusing on getting our product to market as fast as we can." For a blockbuster drug, every day that you lose is costing you millions of dollars – far more than the cost of using slightly older but still adequate technology. People in pharma love new technology – they're scientists, they want the best and latest – but they're also aware of the highly competitive race to market, so they have limited time to explore other considerations. Once you design a process and put products into that process, it's difficult to change it. But given that you'll have to live with the decisions you make today for the next 20 years, you better make sure it's a good decision!

What do you think should be a priority for 2018?

Over my career, I've seen biopharmaceuticals go from a niche interest to a big part of the drug market – and to be a little part of that is so gratifying. We are on a tremendous trajectory: biopharmaceutical sales will probably grow in double digits for the next five years. The big question is how to get enough capacity in terms of manufacturing. There is a very complicated supply chain behind manufacturing, and we need to consider whether it is robust enough to support long-term growth. We need to find a balance between making sure that we build on the strength and security of our past, and embracing new tools and technologies that are going to make us even better tomorrow.

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