SEPTEMBER 2018 # 45

the Medicine Maker™

Towards Industry 4.0

Experts prepare to meet in Ireland to discuss biopharma's tentative steps into the fourth revolution of manufacturing.

Active ingredients Dynamic people

Meet the experts you'll enjoy working with and discover why we're one of the biggest names in small molecule APIs.

Pharma ChemOutsourcing, September 17-19,
Booth 2, New Jersey

CPhI Worldwide, October 9-11,
Hall 5, Booth 5G12, Madrid

www.cambrex.com

Custom development & manufacturing | Generic APIs | Controlled substances

Cambrex

Online this Month

Nominations for the Medicine Maker 2019 Power List Are Now Open!

The Medicine Maker 2019 Power List is on the horizon – and the power to shape it is in your hands! Our annual list of the great and good of pharma will be published in April 2019. From academics and philanthropists, to business leaders and entrepreneurs, to technicians and regulators, everyone involved in pharma is eligible. Nominations for this prestigious list will close in late January 2019. Nominate your pharma heroes for consideration today!

http://tmm.txp.to/2019/powerlist

All Aboard for Biopharma Trends 2018

The Medicine Maker and NIBRT are collaborating on an exciting new conference series focusing on global trends in biopharma and the future of the industry. The inaugural event – Biopharma Trends 2018: Towards Industry 4.0 – will be held on November 13 and 14, 2018, in the Clayton Hotel Silver Springs in Cork, Ireland. You can read more about the conference on page 24.

Registrations are now open, so don't miss your chance to be part of the conversation about the future of biopharma. Sign up for you place at www.biopharmatrends.com

Contents

the Medicine Maker

ISSUE 45 - SEPTEMBER 2018

Editor - Stephanie Sutton
stephanie.sutton@texerepublishing.com

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

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

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

Publisher - Richard Hodson
richard.hodson@texerepublishing.com

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

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

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

Junior Designer - Hannah Ennis
hannah.ennis@texerepublishing.com

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Distribution:
The Medicine Maker (ISSN 2055-8201), is published monthly by Texere Publishing, Haig House, Haig Road, Knutsford, Cheshire WA16 8DX, UK
Single copy sales £15 (plus postage, cost available on request info@texerepublishing.com)
Non-qualified annual subscription cost is £110 plus postage

Reprints & Permissions – tracey.nicholls@texerepublishing.com

The opinions presented within this publication are those of the authors and do not reflect the opinions of The Medicine Maker or its publishers, Texere Publishing. Authors are required to disclose any relevant financial arrangements, which are presented at the end of each article, where relevant.
© 2018 Texere Publishing Limited. All rights reserved. Reproduction in whole or in parts is prohibited.

Available on the App Store

texere publishing ltd

Our Commitment,

The Industry Leading Experience

PCI Pharma Services – a market leader for integrated drug development and commercialization

The foundation of a successful partnership is trust. At PCI, we dedicate our unwavering commitment to provide the industry leading customer experience. This focus enables us to be a trusted partner to 19 of the top 20 pharmaceutical companies in the world. We earn trust by providing our clients flexibility and responsiveness, outstanding operational performance, and the support of uncompromising quality and regulatory standards. By this commitment we deliver our clients an end-to-end development and commercialization solution including drug development and scalable drug manufacturing, integrated clinical trial services, and commercial packaging services. We are trusted to support lifesaving medicines destined to over 100 countries around the world.

We invite you to learn more about what the PCI commitment can do for the success of your business.

pci MANUFACTURING SERVICES pci CLINICAL SERVICES pci COMMERCIAL PACKAGING

Please Join Us at:

CPhI worldwide

9-11 October | Madrid, Spain

Booth 3F10

pci PHARMA SERVICES

pciservices.com

© Copyright 2017 PCI Pharma Services. All Rights Reserved

Unleash your creativity.

Capsugel® | Lonza Pharma & Biotech

Capsugel® Colorista™

All the colors you need, in one capsule.

Cuts development time

Available in Coni-Snap® gelatin and Vcaps® Plus capsules

Wide color selection

Made better. By science. ™

Want to know more?
Visit www.capsugel.com

Science Versus Sensationalism

Don't give journalists an excuse to fuel the hype machine

I was recently invited to speak at the International Society Cell and Gene Therapy's (ISCT's) conference in Florence, Italy, on the communication of cellular therapies. The title of my presentation? "The Journalist's Dilemma: Science Versus Sensationalism." It's clear that cell and gene therapies are incredibly exciting, with "the potential to transform medicine," as FDA Commissioner Scott Gottlieb put it – so we journalists want to talk about them. But we also don't want to sensationalize the research.

I've heard stories of clinics being bombarded with calls from patients wanting to know if they could benefit from a CAR-T cell therapy, despite the fact that only around 300 patients are eligible for treatment. At the same time, we've got the growth of unproven cell therapy clinics, tapping into the hope (or hype) generated by media coverage.

There are often three steps to the science communication process: the journal article, the press release, and the news article – each with incentives to boost the impact of the research and play-down the caveats. Of course, the ultimate responsibility for the claims made in a news story lie with the journalist. But it turns out that a major source of hype in science news originates at the second stage: the university press releases. One study looked at hundreds of papers, press releases, and news articles and found that 33 percent of primary claims in press releases were more strongly deterministic than those present in the journal article (1).

Thankfully, I'm able to check claims and often speak with authors directly – but others are less picky. And when an increasingly busy reporter is confronted with an enticing press release and, perhaps, a less-than-readable journal article (aflush with technical terms and unnecessarily complex language), it's easy to understand where the problem arises.

If we want effective science communication, we need researchers to take more responsibility for how institutions report their research; the whole "story" should be comprehensible to a busy news reporter.

It would appear that there are two types of sensationalizing journalists out there: the unscrupulous/incompetent and the lazy/busy. There isn't a great deal that scientists can do about the former, but they can certainly have an impact on the latter.

Please share science responsibly!

James Strachan
Deputy Editor

Reference

1. *P Sumner et al., "The association between exaggeration in health related science news and academic press releases: retrospective observational study," BMJ 349 (2014).*

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

For Patients, Not Profits

A new not-for-profit company will manufacture important generics in the US

Back in January 2018, "Project Rx" was announced – an ambitious initiative to establish a not-for-profit generic drug company. Further exciting details have now emerged (1). The company will be called Civica Rx and will be headed by Martin Van Trieste, former chief quality officer at Amgen and number 2 on The Medicine Maker's Power List of Industry Influencers (2). More than 120 health organizations – representing a third of national hospitals in the US – have expressed an interest in some sort of participation.

A huge number of generic medicines have been approved in the US, but shortages – and high prices – are still an issue, particularly for sterile, generic medicines considered "foundational" to hospitals (3). The American Society of Health-System Pharmacists has listed hundreds of compounds facing shortages (4) – a clear problem is that demand is outstripping supply.

Van Trieste has described the company as "a public asset with a mission to ensure that generic medications are accessible and affordable." Leading very much from the front, Van Trieste takes on the new role without compensation.

What are the facts?

- Civica Rx will be an FDA-approved manufacturer that will either directly manufacture

generic drugs or sub-contract manufacturing to reputable contract manufacturing organizations.
- The company will seek to stabilize the supply of essential generic medicines administered in hospitals.
- A secondary goal is to boost competition within the generic market to lower the costs of crucial medicines.
- 14 hospital-administered generic drugs will be targeted by the company as an initial focus.
- The first products are expected to be on the market as early as 2019.

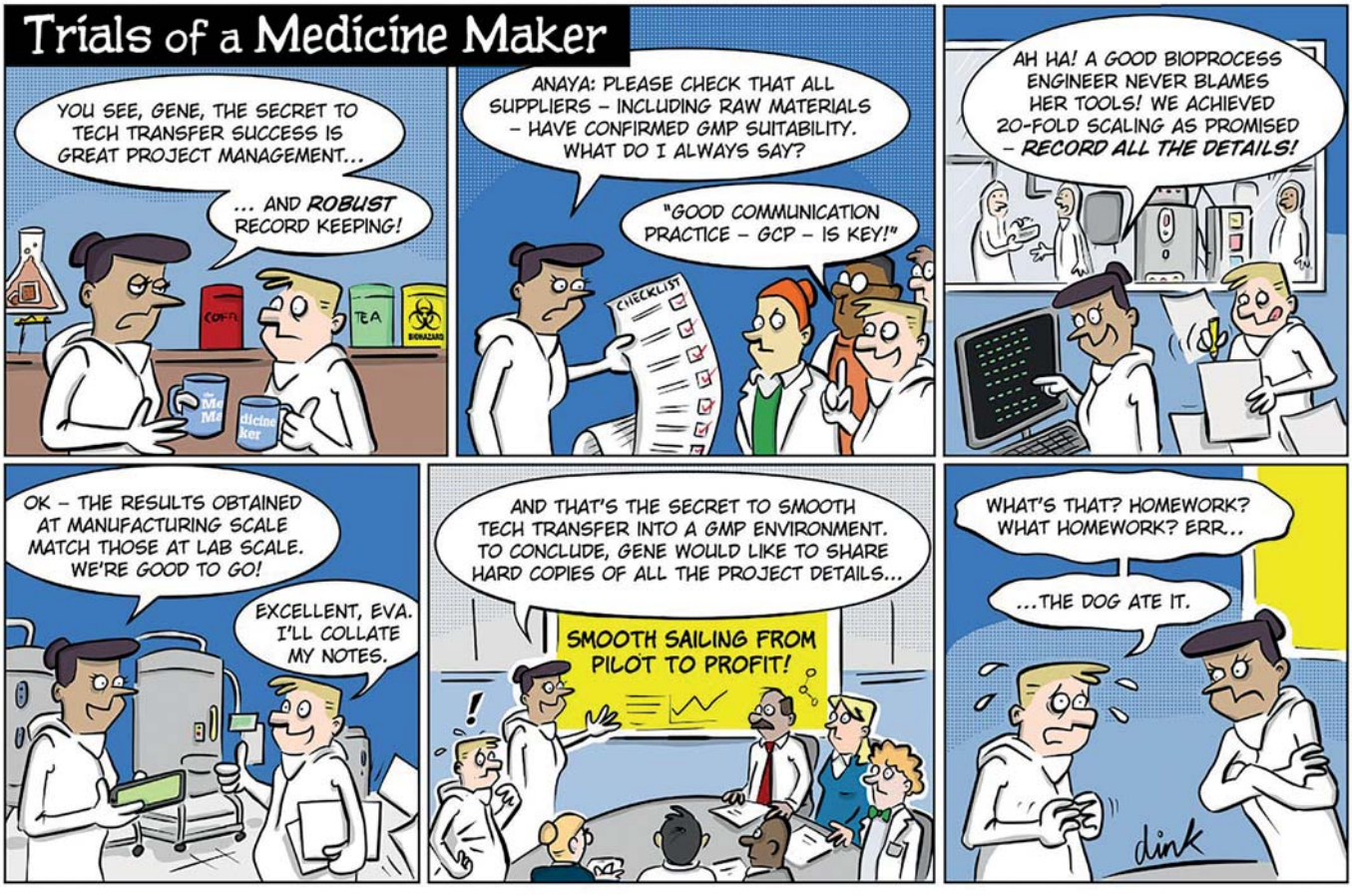
Who's involved?

- Catholic Health Initiatives
- HCA Healthcare
- Intermountain Healthcare
- Mayo Clinic
- Providence St. Joseph Health
- SSM Health
- Trinity Health
- The US Department of Veterans Affairs
- The Laura and John Arnold Foundation
- The Peterson Center on Healthcare
- The Gary and Mary West Foundation

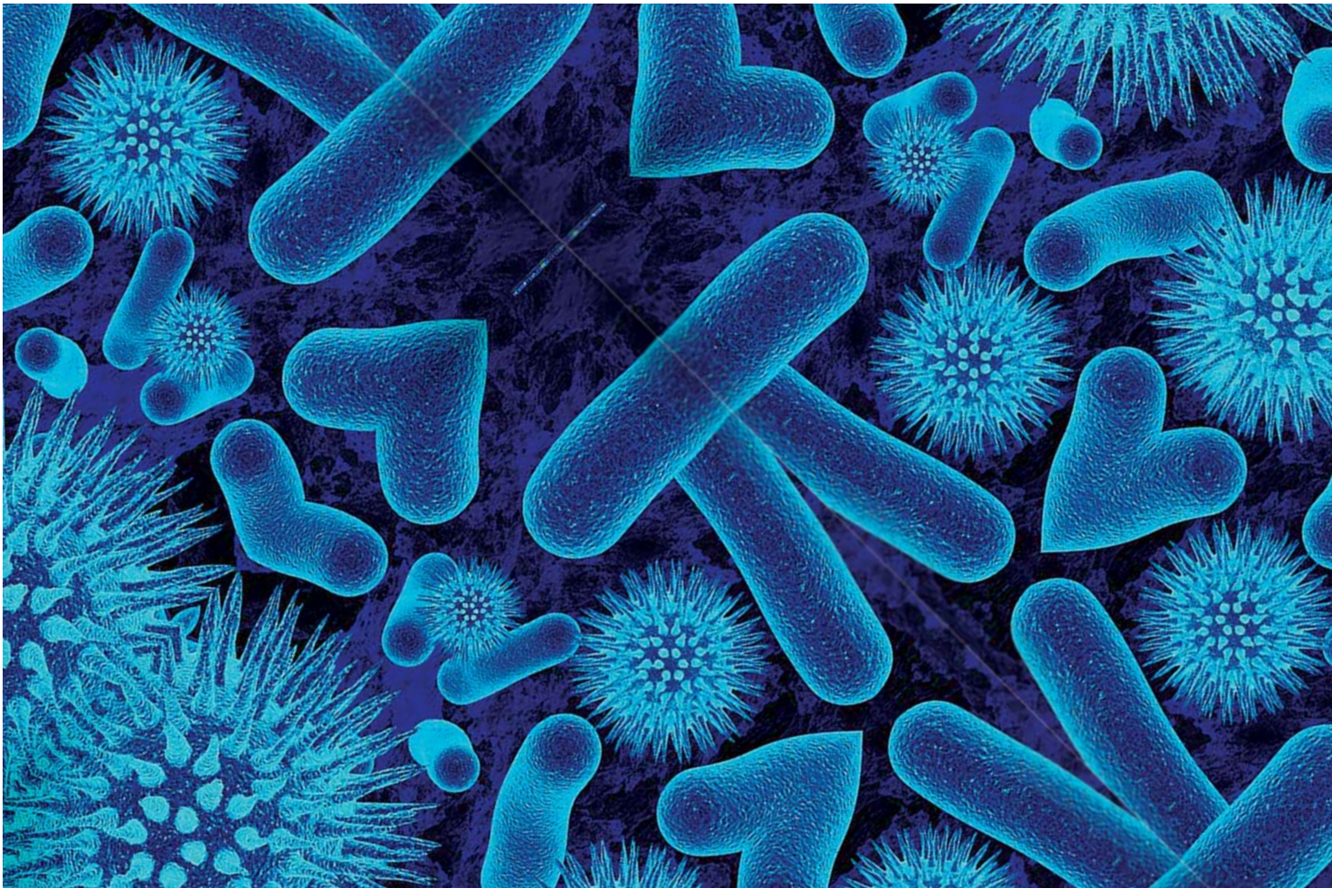
References

1. *P BusinessWire, "Not-for-Profit Generic Drug Company Officially Established, Attracts Interest of More Than 120 Health Organizations," (2018). Available at https://bit.ly/2CvyqHz. Last accessed September, 2018.*
2. *The Medicine Maker, 2018 Power List. Available at https://themedicinemaker.com/power-list/2018/.*
3. *S Barlas, "Frustration Over Generic Drug Shortages and Prices Prompts Federal and Private Actions: Health Systems Take Matters Into Their Own Hands, Pharmacy and Therapeutics, 43 (2018).*
4. *ASHP, "Drug Shortages List". Available at https://bit.ly/2L3zRNv. Last accessed September, 2018.*

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



Brought to you by GE Healthcare



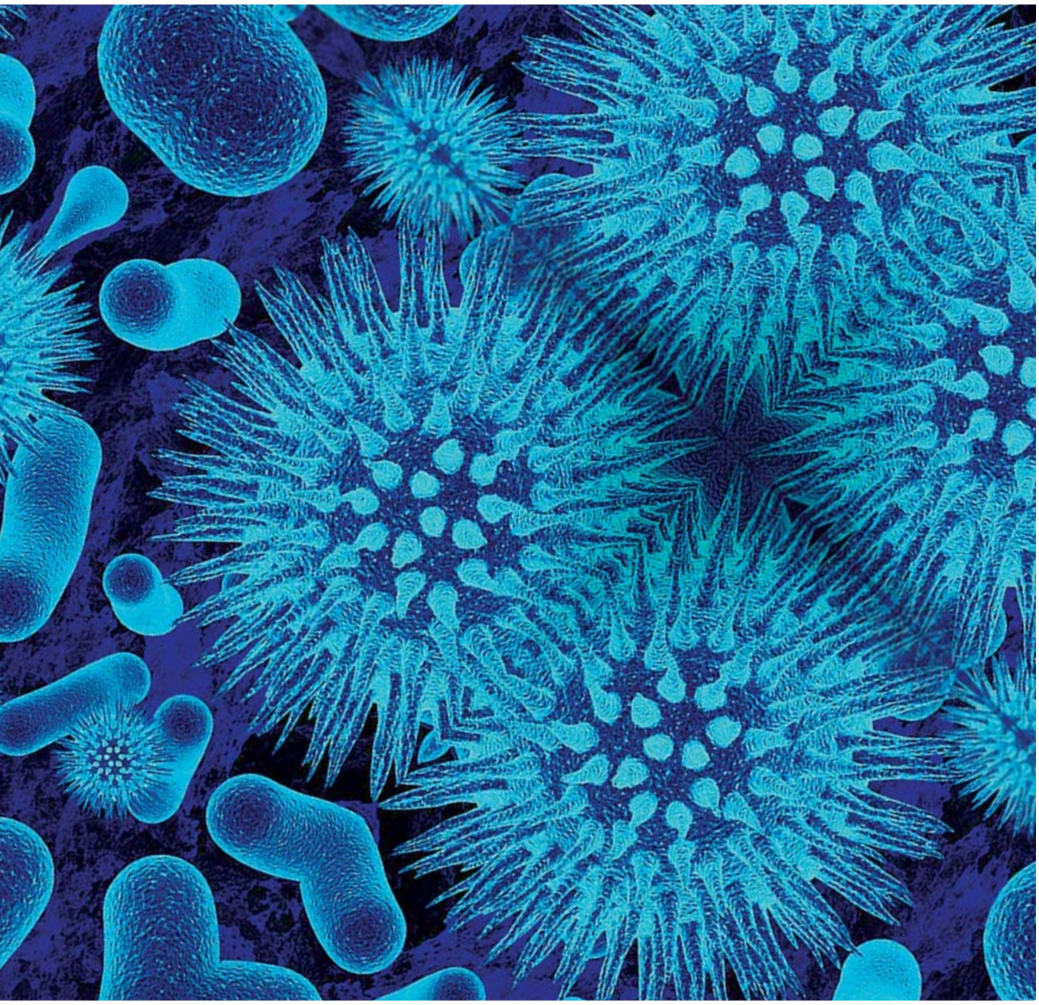
Just One Shot

A vaccine using mRNA demonstrates potential for broad influenza protection

A universal flu vaccine is on the agenda for a research team at the Perelman School of Medicine at the University of Pennsylvania. The team has developed a vaccine that uses mRNA molecules formulated in lipid nanoparticles (mRNA-LNPs) that encode HA proteins to create a strong antibody response.

"Today's flu vaccine is about 60 percent effective, on average, and has to be reformulated every year. This is not really good enough given that flu causes extensive disease and significant mortality," says Drew Weissman, a professor of infectious disease at the university and co-author of the study. "We are hoping to develop a better vaccine. Two things need to be improved; the first is efficacy and the second is durability of protection. We believe that a modified mRNA-LNP vaccine can do both."

Weissman and the team have shown that their vaccine offers protection against distant flu strains in mice and protection in ferrets against homologous and related viruses – and they claim that the magnitude of antibody response has been huge. Once injected, the RNAs are taken up by the immune system and then copied, mimicking a real flu infection and leading to a good antibody response. After immunization, a strong antibody response to the vaccine lasted for thirty weeks. "Many different vaccine platforms have been studied for their ability to develop a universal flu response. Unlike most others, we used a common immunogen, HA, which



is used in almost every flu strain. This resulted in a broadly protective response," explains Weissman.

Other studies have shown that mRNA-based vaccines could offer protection against influenza, but Weissman says that none of these studies have looked at using mRNA-based vaccines to neutralize distinct flu strains with a single shot. The vaccine can also be made quickly. Production of conventional, FDA-approved vaccines for pandemic viruses can take months, but mRNA-LNP vaccines can be made in a matter of weeks once the genetic sequence of the target HA antigen has been identified.

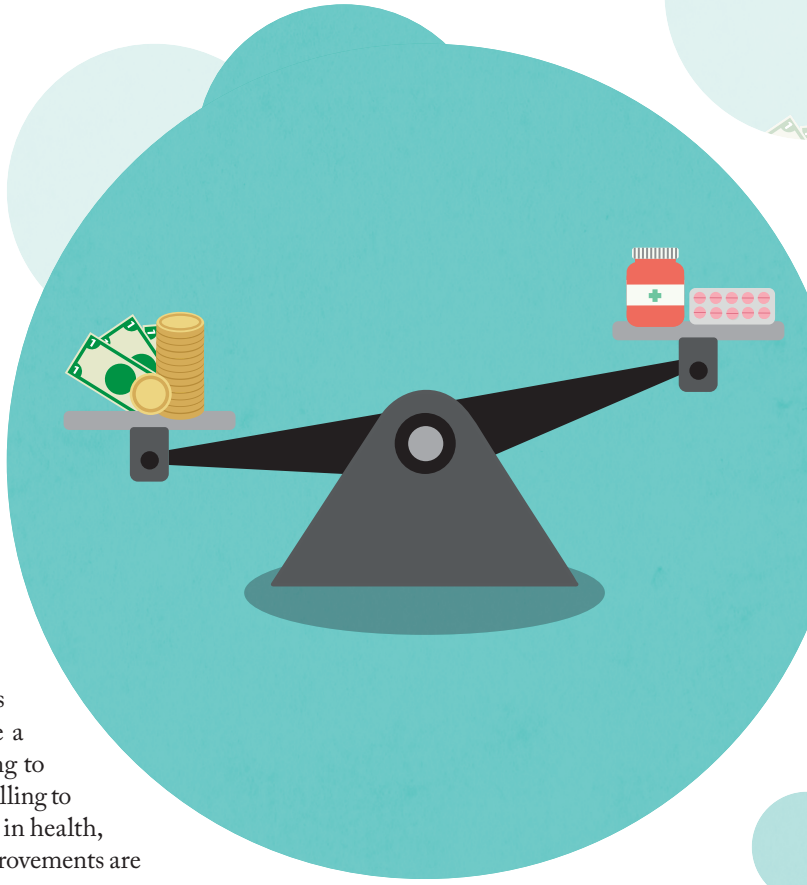
"mRNA-LNP vaccine production is sequence-independent and can be applied to virtually any pathogen," says Weissman. "We are now evaluating improved immunogens to improve both the HA stalk response and broadly protective responses in mice and ferrets."

Reference

1. *N Pardi et al., "Nucleoside-modified mRNA immunization elicits influenza virus hemagglutinin stalk-specific antibodies," Nature Communications, 9 (2018). PMID 30135514*

Knowing Your Values

Does a medicine's price consistently track with its benefits and value? Not in the US, according to a study



Many healthcare authorities place a strong emphasis on value when it comes to deciding which medicines to include in national health programs. Decisions are strongly driven by health technology assessment agencies who closely scrutinize the price and expected health benefits of a new medicine. In other countries, it's more of a blackbox approach. The US appears to fall into the latter category.

Jon Campbell and colleagues at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, in collaboration with international experts, recently took a close look at the healthcare system in the US (1). Even at the outset of the study, Campbell had a hunch about what the final results would show. "As a scientist, I am trained to not put much weight on expected findings so as to lessen the potential for bias related to trying to shape or interpret unexpected findings into expected ones. But as a human with a Bayesian approach to life, I have priors. The prior expectations for this research included the general idea that within the US, the pharmaceutical marketplace and specifically pharmaceutical pricing from the past few decades was likely not heavily influenced by a traditional understanding of the pharmaceutical's health gains or value."

The team used a forecasting model to look at the prices of common cardiovascular drugs in the US, estimate their value in terms of added cost per health outcome achieved, and to find out if there was a common payment threshold. But Campbell's initial expectations were correct – prices of cardiovascular medicines in the US were not consistently aligned with value. The US can pay up to twice as much for branded drugs as other wealthy countries, and Campbell believes that the US has done a "poor job" of signalling to innovators what it is willing to pay for improvements in health, and which health improvements are most important.

The US health care system involves many stakeholders and decision makers, and the transaction price paid for drugs is often masked by rebates and different entities involved in the drug supply, who may take a cut of the price paid in ways that are difficult to track. "Sometimes, the payer receives rebates or kickbacks that are not easy to observe in the market," adds Campbell. "The value of a drug is even more difficult to comprehensively grasp as drugs impact patients differently. Further, such differences may be measured or unmeasured. Metrics such as the quality-adjusted life year, which is used by the UK and elsewhere, attempt to aggregate health signals within a disease and allow for health signal comparisons across diseases. Measuring value is an area of continued research within the field."

Campbell hopes that the study will generate more discussion about fair pricing in the US and how to measure improvements in health. "More targeted and individualized therapies are emerging that have the potential to improve health in big ways, but change is needed to ensure that such therapies reach those who will benefit from them. For example, certain subpopulations may be able to improve their health the most by making behavioral or changes," says Campbell. "Identifying and treating the subpopulations who will benefit from pharmaceuticals and who will achieve good value for money is a way forward toward being wise stewards of our healthcare resources. If we continue to nudge the system toward incentivizing payments for value, we will reduce wasteful spending and continue to make improvements in population health."

First, the US needs to have a more unified vision on what constitutes value in health. Campbell also urges pharma to take an active role toward achieving fair drug pricing, and to support research within methods of assessing value, including multicriteria decision analysis and augmented cost-effectiveness analysis.

Reference

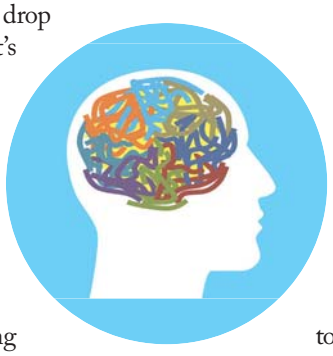
1. *JD Campbell et al., "Prices For Common Cardiovascular Drugs In The US Are Not Consistently Aligned With Value," Health Affairs 37 (2018).*

Let's Talk About Mental Health

A recent survey examined the relationships – or lack thereof – between pharma companies and mental health patient groups

A recent report has ranked the pharma industry's reputation among mental health-focused patient groups. And the findings show that the industry has a long way to go. Nearly half of the patient groups surveyed did not work with any pharma companies, and 11 percent only worked with one or two (1).

"We were quite surprised at the low level of networking between pharma and mental health patient groups," says Alex Wyke, CEO of PatientView, the company behind the report. Of 101 participating patient groups, after quite high scores from the leading companies (Janssen, Lundbeck, and Eli Lilly), the numbers drop substantially. Of course, it's important to remember that companies will not deal with every kind of mental health condition, and some may be extremely specialized and only deal in small areas of the field. But even so, the level of networking was still low when compared to other disease areas, such as cancer."



"Mental health has always been a difficult area for pharma companies to tread. It's important to remember that historically there have been some big issues around how mental health was treated – and it remains an understandably sensitive area for patients and patient groups," says Wyke. "In the past, patient groups have been among the most critical of the industry, but more recently there is an increasing feeling that they have a greater contribution to make".

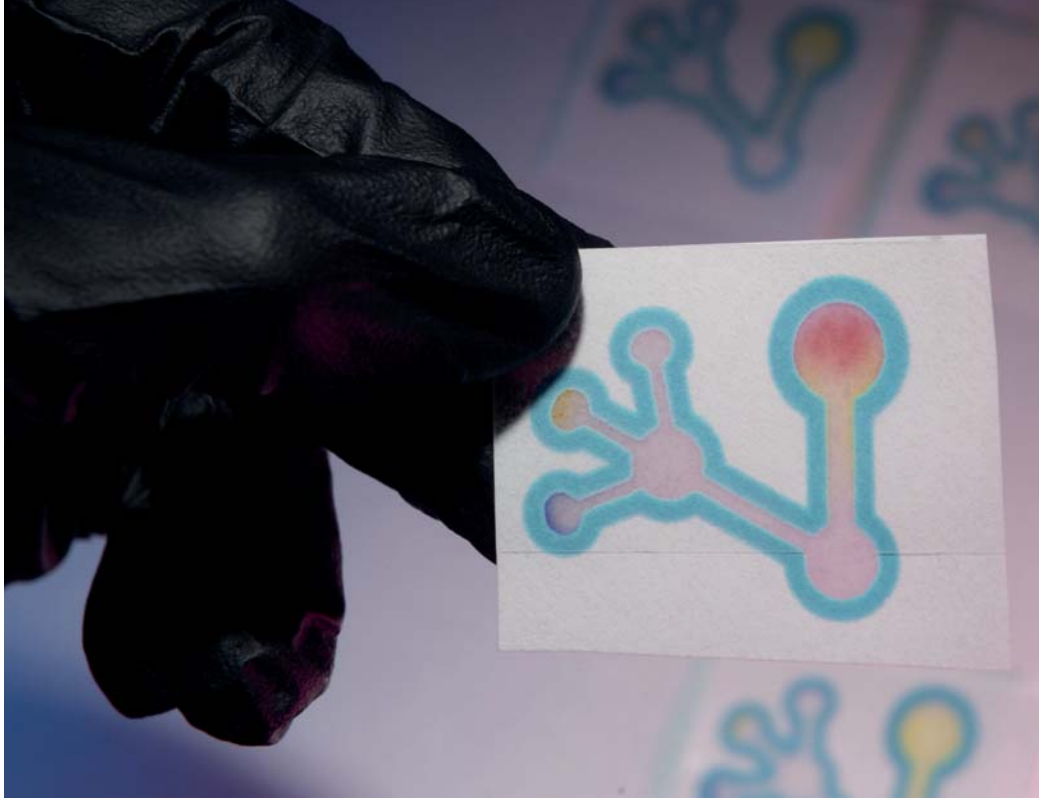
Many of the groups surveyed called for greater involvement from pharma – and pharma's approval among these groups has improved from the previous year, with 35 percent of respondents rating pharma's corporate reputation as "excellent" or "good", up from 20 percent in 2016. To build good relationships with pharma, respondents called for the following conditions:

- Real, not token, ambitions by companies towards being patient-centric: only 28 percent of respondents felt companies were "excellent" or "good" at patient centricity
- Greater transparency
- More sophisticated pricing policies, which consider the impact of prices on patient access to medicine
- More innovation in drug development: patient groups would like to see R&D lead to products in tune with patient's needs.

Wyke adds that there are clear rewards for pharma companies who work to engage mental health patient groups. "The power of the patient movement is only growing, and the reach of these groups today is more profound than ever before. Patient groups are influencing healthcare systems and gaining representation on regulatory bodies. Talking to these groups is the best way to find out what the patients they represent want from you as a company, and pharma an industry."

Reference

1. *PatientView "Corporate reputation of pharma companies, 2017-2018 - the patient perspective of 101 mental health patient groups", (2018). Available at: http://bit.ly/PtntView.*



Don't Have Your Fake, or Eat It

Finding counterfeit antibiotics – using a color-changing paper test

The fight against fake pharma continues: researchers at Colorado State have developed a simple way to detect counterfeit antibiotics using a low-cost paper test. Researcher Charles Henry tells us more.

What was the inspiration behind the test?

For the last decade, I've been working with other scientists in the developing world and I learned much about how healthcare works – or doesn't work – in those countries. This piqued my interest in developing low-cost tests that could improve healthcare for people living in those areas. At the same time, Kat Boehle and I were working on a test for anti-microbial resistance. The test uses an enzyme that bacteria natively produces when it is resistant to some antibiotics to determine if the bacteria is present. In some respects, it was using the bacteria's own machinery against it. Kat and I realized we could use that same enzyme to test for antibiotics using an assay that was both unique and low-cost (1).

How does the test work?

The user simply needs to dissolve the antibiotic in water and add this to the paper-based assay. It then travels down a channel in the paper containing dried nitrocefin, rehydrates the substrate, and is transported to the detection zone where betalactamase is stored. If the antibiotic is not present or diluted, the betalactamase will react with nitrocefin, causing the paper to turn from yellow to red. However, if the antibiotic is genuine, it will outcompete the nitrocefin to bind with betalactamase, resulting in no color change (remaining yellow). The pH indicator section of the paper acts as verification for whether the test is working correctly – alkaline and acidic solutions will not turn the test as red other samples. Basically, if the test does not turn red, it is a legitimate antibiotic, and if the pH indicator shows an alkaline or acidic pH, the user knows that the enzyme reaction is not working and should be cautious.

How do you envision it being used in the field?

We see the test being used primarily by individuals in the developing world. We are hoping that by making the test inexpensive and user-friendly, everyday people can take charge of identifying falsified antibiotics so that they can get the best treatment possible. Also, scientists who study falsified and substandard antibiotics around the world currently have to gather samples in the field and transport them to a central laboratory for expensive and laborious testing – so the test could save time and money. We also hope that by identifying falsified antibiotics before they are taken, less broad spectrum antibiotics will need to be prescribed, which should help slow the emergence of antimicrobial resistance.

What are your plans for the future?

First, our current test needs some additional optimization. When blind-testing different users to confirm the user-friendliness, the most commonly misinterpreted sample was differentiating between legitimate antibiotics and aspirin. This is an area we would like to address for more confident results by users. Additionally, although we have demonstrated that this assay can quantify active ingredients, a desktop scanner and image analysis program is necessary. We would like to develop a cell phone application or portable Raspberry Pi program for users who want to quantify the active ingredient – instead of the simple yes or no answer that is currently in place.

Reference

1. *J KE Boehle et al., "Paper-based enzyme competition assay for detecting falsified ß-lactam antibiotics", ACS Sens, 3, 1299–1307 (2018). DOI: 10.1021/acssensors.8b00163.*

Business-in-Brief

New medicine approvals, a CAR-T rejection in the UK and biosimilar scare tactics… What's new for pharma in business?

Approvals

- In the US, the FDA has approved the first generic competitor to Mylan's EpiPen and EpiPen Jr (epinephrine) for the emergency treatment of allergic reactions. The generic version is made by Teva Pharmaceuticals and will be available in 0.3 mg and 0.15 mg strengths. No pricing details have yet been announced, which will be of high interest given last year's outcry over EpiPen price increases.
- Both the FDA and the European Commission have approved Onpattro (patisiran) – the first in a new class of drugs called siRNAs, which work by silencing a portion of RNA involved in disease. Onpattro is approved to treat hereditary transthyretin-mediated (hATTR) amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Onpattro encases the siRNA into a lipid nanoparticle to deliver the drug directly into the liver, in an infusion treatment.
- Gilead's CAR-T therapy has been approved in the European Union, but only a day later it was rejected by the UK's cost watchdog, the National Institute for Health and Care Excellence, because of the high (undisclosed) price tag. "Although promising, there is still much more we need to know about CAR-T, and unfortunately, in this case, we are not able to recommend axicabtagene ciloleucel for use in the NHS in England at the cost per patient," Meindert Boysen, director of the center for health technology evaluation at NICE, said in a statement.

Regulation

- Pfizer is seeking guidance from the FDA for information dissemination about biosimilars. Specifically, the company wants to know what originator companies can and can't say about biosimilar versions of their products. The company has submitted a citizen's petition to the FDA and also calls out companies for using "scare tactics" to undermine biosimilars.
- The UK's Department of Health and Social Care has released several Technical notices about planning for a potential no-deal Brexit, including information about how medicines, medical devices and clinical trials will be regulated, submitting regulatory information on medical products and batch testing. The notices can be found at https://bit.ly/2o2hDl.

A "Wellcome" Sight

A fresh take on an existing photography competition aims to display the diversity of science

"The man with the golden blood" by Greg White. *Credit: Greg White/Wellcome 2014*

What?

The Wellcome photography prize has a new look for 2019. Previously known as the Wellcome Image Awards, the annual photography competition from the UK's research charity the Wellcome Trust rewards pictures from any country that showcase stories of health, science and medicine. With categories including "hidden worlds", "medicine in focus", "social perspectives" and a special theme for 2019, "outbreaks", the new prize hopes to expand the scope of the competition beyond the traditional clinical and imaging focus. Marianne Dear, Wellcome Photography Prize Manager says, "We wanted to reveal more about health in a broader way, rather than only focusing on researchers in laboratories. The new prize expands this vision to the health challenges we face not only in our own bodies but in families, communities and broader society."

How?

Dear says they were keen not to lose what was so special about the previous awards. "We expect that researchers will feel at home entering microscopy and medical imaging into the new 'Hidden Worlds' category but it could be interpreted in more lateral ways too. Social Perspectives is perhaps the broadest category, where we expect to see images that reflect on how health is impacted by environment, conflict, economics or geography," says Dear. "Medicine in Focus allows image-makers to get excited about technology and specialized equipment, or could cover healthcare delivery and surgery. The Outbreaks category encourages entrants to show the molecular features of infectious and non-infectious disease outbreaks, or the social effects outbreaks have on people and infrastructure."

Why?

The competition aims to put health and research in the public eye. Dear adds, "It's important to see diverse interpretations of health to challenge our own perspectives and start conversations with each other about what good health could be. That's how progress in research is made." By shining a spotlight on the health issues facing society and creating conversation, the Trust also hopes to encourage more funding for medical research.

Who?

Photographers, photojournalists, artists, researchers or clinical photographers worldwide are all encouraged to enter for a chance to win the first prize of £15,000. The judging panel includes Joanne Liu, international president of Médecins Sans Frontières and National Geographic photographer, Pete Muller.

When?

Entry is free, and the submission deadline is December 17, 2018. Winners will be presented with their awards the following summer. In addition, the best entries will be exhibited at St Martin's Lethaby Gallery, London, UK. More details can be found at: bit.ly/WellcomePhotography.

The Marijuana Medicine Makers

Interest in cannabinoid drug development is growing. The potential market – and the opportunity to treat unmet patient needs – is enormous.

By Kevin Hennessy

The umbrella term "cannabinoids" covers a variety of compounds that are derived from the cannabis plant, including tetrahydrocannabinol (THC) – the chemical predominantly responsible for the psychoactive effect that accompanies cannabis use. THC was the first cannabinoid to be studied extensively for its therapeutic potential. Indeed, the first cannabinoid-based product to be approved by the FDA was a synthetic version of THC called Marinol in 1985. By improving appetite and reducing nausea and vomiting in patients undergoing chemotherapy or being treated for HIV, Marinol saw great success and continues to be the standard of care in such patients.

Johnson Matthey got involved in the cannabinoid field over 15 years ago when we developed a generic substitute for Marinol. Working with cannabinoids is very complex and APIs produced based on cannabinoids can be challenging to work with. In Marinol, the API oxidizes quickly and is prone to impurities. To add to the challenge, many countries – particularly the US – have strict rules and requirements around the use of controlled substances However, Johnson Matthey already had a great deal of experience with manufacturing controlled substances, so it was a logical step to enter the cannabinoid space. We already had the expertise to handle the complex chemistry and stability challenges, coupled with the infrastructure and resources to navigate the legal landscape.

Plant potential

Today, interest in cannabinoids in the pharma industry and medical community is increasing rapidly as further research emerges. Cannabinoid receptors are being found all over the body and there is potential for cannabis-derived medicines to help in unexpected therapeutic areas; for example, there is a lot of work taking place in employing cannabinoids for dermatological conditions, such as eczema. There is also interest in using cannabinoids as an adjuvant in chemotherapy patients to help manage pain. There could be huge rewards for companies that develop alternative medicines and approaches.

In addition, research with cannabis – historically hindered by the legal landscape – is becoming easier as a number of US states and countries around the world begin to relax rules and regulations around medicinal (and, in some cases, recreational) cannabis use.

This has led to increased availability of cannabis for research purposes and fewer restrictions about what researchers can do. With ongoing research about how cannabinoids can potentially treat a plethora of conditions, the medical community is pushing for GMP-grade products that have been subject to rigorous safety studies. More patients are becoming aware of cannabis' potential health benefits but many of them want to gain access to a controlled, safe and effective product.

Meeting new and natural needs

We have already established large scale expertise in the cannabinoid space, which means we've been able to adapt scale up operations to meet rapidly increasing market demands. Although we initially started with THC, we have since grown our offerings to include other synthetic cannabinoids, including cannabidiol (CBD) and nabilone.

Clearly, to gain FDA approval, you need to produce a very pure product, which requires the right equipment and a significant amount of technical know how. As well as developing a validated process for cannabidiol synthesis (filed with a US DMF), we have also created reference standards for our cannabinoids, which help our customers understand what they are getting, and gives them the confidence to use our APIs in their formulations. We have also considered ease of formulation – our cannabidiol is a free-flowing crystalline powder and the particle size can be adjusted to suit a variety of formulations.

Beyond THC and CBD, there are well over one hundred different cannabinoids within the cannabis plant, and pharma companies are interested in assessing the therapeutic potential of a number of these. In response, we are planning to expand our portfolio to include other synthetic cannabinoids.

The FDA recently approved the seizure drug, Epidiolex, which contains naturally extracted cannabidiol, and we see increasing interest in the use of natural cannabinoids. As one of the largest API manufacturers in the world, Johnson Matthey has gained significant expertise in the extraction of APIs from natural sources, and so we are also expanding our offerings to help those customers wishing to explore botanical cannabinoids.

Kevin Hennessy is Commercial Director at Johnson Matthey.

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

The Costs of the Counterfeit Battle

Fighting counterfeit medicines is a noble goal, but the financial burden of safety features may affect access to medicines in unintended ways.

By Maarten Van Baelen, Market Access Director at Medicines for Europe, Belgium.

The implementation of Europe's Falsified Medicines Directive (FMD) and its Delegated Regulation (1,2), which provide detailed specifications of safety features, such as serialization, will provide an additional obstacle for counterfeiters. The implementation of the Directive aims to prevent falsified medicines from reaching patients and is in the interest of public health. However, the financial burden for manufacturers to implement these additional safety features – as well as the repository system that will allow the verification of authenticity of individual packs of medicine – could threaten the availability of medicines.

In practice, pharmaceutical manufacturers in Europe need to apply a unique identifier (a serialization number) and a tamper verification feature to the outer package of medicinal products. In addition, by February 2019, a European Medicines Verification System (EMVS) will guarantee the verification of medicines throughout the European supply chain and at the time of delivery to the patient. The Directive also specifies that the cost of the system will be funded by the manufacturers of medicinal products.

The scope of falsification and counterfeiting in other sectors (such as clothing and electronics) is proven to be a problem that is driven by price and demand. The same drivers have been identified in the health sector. For example, a Pfizer-sponsored study demonstrated that the counterfeit medicines market (which is almost exclusively via the Internet) is mainly dominated by so-called "lifestyle" medicines, such as well-known erectile dysfunction and weight loss products, followed by oncology and influenza (3,4).

In the legal supply chain, there are very few problems of medicines being falsified. The prevalence of counterfeit medicines in the legal supply chain is only 0.005 percent (5,6). In my view, using a medicines verification system to tackle this very low prevalence of falsified medicines in the supply chain is like using a sledgehammer to crack a nut.

Upgrading pharmaceutical packaging lines to apply serialization and tamper verification features will have a huge financial impact for the generic medicines industry. There are 10,000 packaging lines in efficient operation to supply European patients with generic medicines (7). Upgrading these lines to apply serialization and tamper verification features costs around 500,000 euros (~$580,000 USD) per packaging line (7). As the life-span of a packaging line is 5 years on average, the application of safety features adds a cost of 1 billion euros (~$1.17 billion) per year for generic medicines manufacturers. Each year in Europe, 10 billion packs of generic medicines are dispensed (6), the application of safety features on packaging adds 0.1 euros ($0.12) to the cost of goods per pack of generic medicines. In their impact

assessment, the European Commission acknowledges that the financial impact of their legislation could be greatest for the generic medicines industry and for small and medium sized enterprises (SMEs).

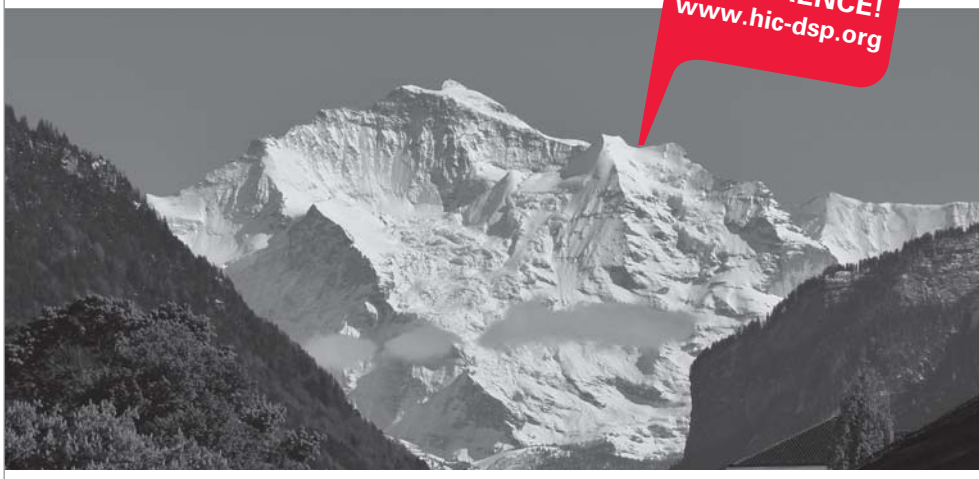
At the same time, the industry is currently investing in the establishment of the EMVS, which will allow supply chain stakeholders to verify the authenticity of medicines. Here too, the FMD dictates that the repositories system shall be paid for by manufacturers of medicinal products. This system will need to be in place and operational by 9 February 2019. It will represent a further cost of around € 100 million (~$117 million) per year for medicine manufacturers.

Medicine manufacturers are concerned about these costs (which add to existing costs of meeting current regulatory requirements) – conversely, payers and health insurers are focused on lowering the prices of medicines. The widening gap will increase the likelihood of medicines being withdrawn from the market as the commercial viability of products is brought into question. Medicine shortages already seem to be occurring more frequently – and the root cause is no longer attributable only to manufacturing disruption, but also to economic issues.

Having said all that, a repositories system that verifies the authenticity of medicines could lead to more transparency in the supply chain, increasing predictability. Manufacturers would then be able manage their supplies more efficiently while addressing the needs of the market more precisely. So, will the system cause or help prevent medicines shortages? Time will tell.

HIC 11th DSP BIOSEPARATION CONFERENCE

BE PART OF THE HIC/DSP CONFERENCE! www.hic-dsp.org



TACKLING FUTURE CHALLENGES - 11TH HIC/DSP BIOSEPARATION CONFERENCE FEBRUARY 18-21, 2019 | INTERLAKEN SWITZERLAND

CONFERENCE TOPICS

- Trends in process chromatography and integrated manufacturing
- Method development and mechanistic understanding of bioprocesses
- Mixed mode / multimodal chromatography - the orthogonality
- DSP applications and case studies:
  - Antibody constructs
  - Blood & plasma proteins
  - Oligonucleotides and peptides
  - Viruses, vaccines and gene therapy vectors
- Hydrophobic separations - a HIC/RPC legacy

Contact us at hic-dsp@tosoh.com

References

1. *Official Journal of the European Union, "Directive 2011/62/Eu Of The European Parliament And Of The Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products" (2011). Available at: https://bit.ly/2k7CZyd. Accessed August 24, 2018.*
2. *Official Journal of the European Union, "Commission Delegated Regulation (Eu) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use" (2015). Available at: https://bit.ly/2kr127a. Accessed August 24, 2018.*
3. *Nunwood survey data November 2009. Online consumer survey, participants 14,000 in 14 countries – available at: https://bit.ly/2O4eexF. Accessed August 30, 2018.*
4. *World Health Organization, "Substandard and falsified medical products" (2018). Available at: https://bit.ly/2jhCnD8. Accessed August 24, 2018.*
5. *MHRA, "Falsified Medical Products Strategy 2012-2015" (2012). Available at: https://bit.ly/2Ljt80U. Accessed August 24, 2018.*
6. *European Commission, EC impact assessment accompanying the proposal for the Falsified Medicines Directive (2008). Available at: https://bit.ly/2NeNkmo. Accessed August 24, 2018.*
7. *European Commission, EC impact assessment accompanying the proposal for the Delegated Regulation Supplementing Directive 2011/62/EU (2015). Available at: https://bit.ly/2MT3Qvy. Accessed August 24, 2018.*

The CHO's Over: An Inflexion Point

Global healthcare costs and demands are changing, and the next wave of complex biologics is entering biopharma pipelines. It is time to look beyond mammalian cell lines.

By Mark Emalfarb, President and Chief Executive Officer, Dyadic International, Jupiter, FL, USA.

Ever since Genentech's plasminogen activator, Activase, became the first human therapeutic product made using CHO cells in 1987, the CHO cell line has become a mainstay of the biopharma industry. Indeed, CHO cells are used to make the bestselling monoclonal antibodies (mAbs), including Rituxan, Humira and Enbrel. However, for the next wave of biologics – bi-specific and tri-specific antibodies, for example – CHO's low expression yields are driving costs beyond commercial viability for many companies. And after more than three decades of CHO cell line improvements, which have seen huge overinvestment, it seems unlikely that any incremental productivity and cost improvements will fundamentally change the game. In my view, we need to look beyond the limitations and costs of CHO – in fact beyond mammalian cell lines altogether.

Microbial cell lines may be what the industry needs in terms of production costs and speed, as well as product quality. Studies have shown that it takes around twice as long to create CHO cell lines and to prepare cells for the fermenter, when compared with microbial cell lines (1). With regard to creating mAbs, CHO entails a higher capital expenditure and operating expenditure than using microbial cell lines, and larger fermentation vessels are needed with CHO to obtain an equal output of mAbs. In addition to lower yield and longer cycle time, CHO cells require expensive enriched growth media and viral purification steps, neither of which are required with certain microbial cells. In other words, manufacturers can grow microbial cells at a lower cost for a given yield, potentially allowing next-generation biologics to be manufactured in smaller (cheaper) facilities, improving commercial viability.

Some biopharma manufacturers are beginning to recognize the limitations of CHO and are seeking alternatives; for example, Biogen's VP of International Manufacturing, Eliana Clark, said last year that they were exploring a "radical departure from the CHO platform" through research into microbial alternatives (2).

I believe one of the most promising alternatives to CHO cells, which has already proven itself in the production of biofuels and enzymes, is a genetically modified form of a fungus called Myceliophthora thermophila, nicknamed C1. C1 was developed by exposing Myceliophthora thermophila cells to ultraviolet light to induce random mutations. Scientists then expanded and reinforced potentially beneficial mutations to drastically change the shape of the cells, from long spaghetti-like strands to short, grain-sized sections. As C1 fungal cells secrete proteins from the ends of their filaments, the selection process resulted in more secreting ends, multiplying the potential total yield. The new shape also meant that C1 could be grown more easily in large tanks. According to our research, C1 offers a much shorter production time for mAbs than CHO, requires significantly smaller production facilities, and does not require viral purification (3).

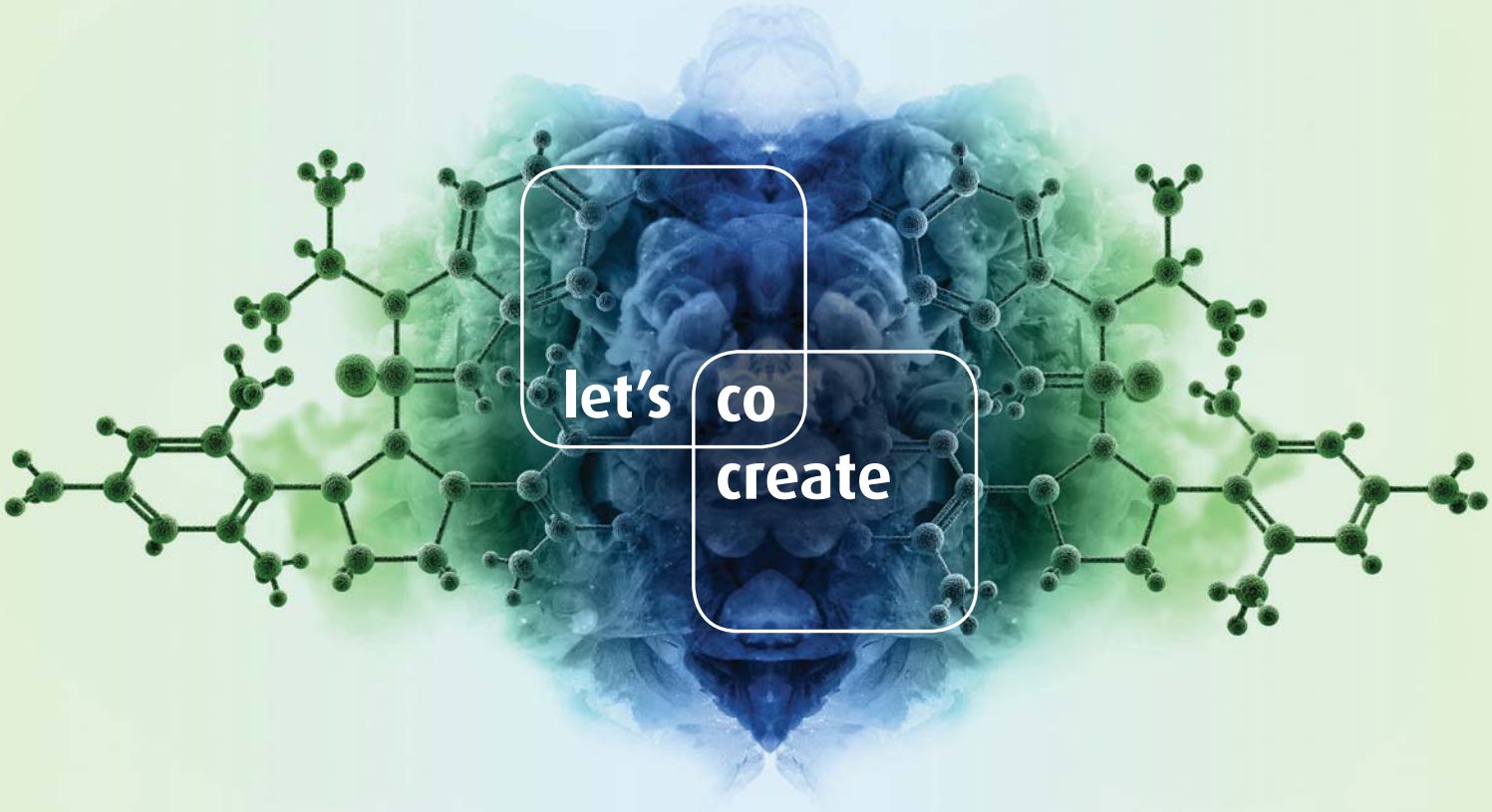
I believe that C1 cells could help speed up the development, lower the production costs and improve the performance of biologic vaccines and drugs at flexible commercial scales. Eventually, C1 could even supplant CHO as the go-to expression system – at least for some companies. We believe it may also enable the development and commercialization of therapeutic products that are difficult to express at reasonable yields in CHO and other cell lines, while also being able to produce larger amounts of protein for drug discovery and development purposes.

Today, any biopharmaceutical company pondering the optimal strategy for producing a new or biosimilar biologic drug should look beyond conventional manufacturing paradigms, such as CHO. It is well worth examining how alternative methods could have beneficial results in terms of speed and cost of production, and product quality.

References

1. *Dyadic, "C1, An Ultra-High Yielding, Game Changing Gene Expression Platform" (2018). Available at https://bit.ly/2N3PGID. Accessed September 10, 2018.*
2. *D Stanton, "CHO stopper? Biogen looks to alternative cell lines for future of bioproduction," BioPharma Reporter (2017). Available at https://bit.ly/2O4bSit. Accessed September 10, 2018.*
3. *Dyadic, "Dyadic – C1 Technology," (2018). Available at https://bit.ly/2Qg8AKh. Accessed September 10, 2018.*

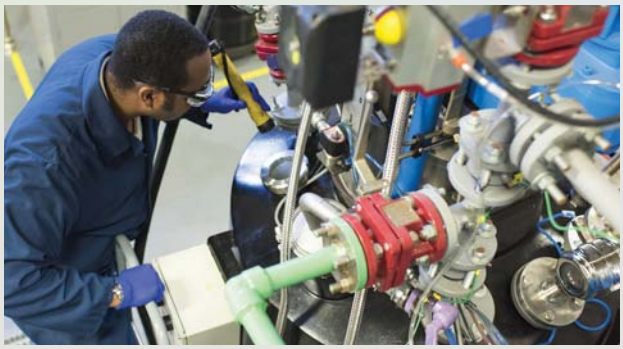
Visit us at CPhI Worldwide
Booth 9H30



Metathesis does it better, Umicore does it best

Our metathesis catalysts deliver highly selective carbon-carbon bonds, with high yields and minimal waste, for more precise and efficient reactions. We support your metathesis needs from research through to commercial scale, offering the very best in R&D, IP security, global manufacturing and security of supply. We will continue to focus on innovation to allow you to develop more efficient, cost-effective and sustainable chemistry.

Let's co-create to make a difference | pmc.umicore.com



materials for a better life

umicore
Precious Metals Chemistry

Right for Patients?

"Right to Try" legislation may have compassion at its heart, but it does not do enough to ensure patient protection.

By Ellen Sigal, Chair, Friends of Cancer Research, Washington DC.

"Right to Try" is a newly passed piece of US legislation that allows terminally ill patients to request access outside of clinical trials to experimental therapies that have completed Phase I testing, but have not been approved by the FDA. In the US, the main advocate for the law was the Goldwater Institute – a libertarian think tank that created the legal template used by many states.

Prior to this bill being passed, hundreds of patient advocacy organizations pushed back against it – and although the bill was signed into law in May 2018, we along with others remain concerned about the impact on patients (1). You may be thinking: but surely, if there is no hope for a patient, is an experimental treatment not worth trying? I think we can all agree that terminally ill patients should have access to promising experimental therapies when they have exhausted all other options. The concerns, however, centered around the need to ensure that patients were not harmed by potentially lethal side effects, as well as the importance of maintaining FDA oversight.

First and foremost – as with any legislation that impacts patients – my organization, Friends of Cancer Research, evaluated how Right to Try may actually affect patients. I admit that personal experience motivated me further: my sister, Gale, died after trying an experimental therapy to treat her breast cancer when she had exhausted all other options. I understand firsthand why people with terminal illness want to try whatever they can to help treat their disease, but prior to Right to Try there were already processes in place that helped achieve this. In my view, this legislation does not protect patients and does not provide any further guarantees for them to gain access.

The new law does not stipulate that drug developers have to provide the experimental therapy to patients. In fact, there is no evidence that Right to Try increases access to new drugs because there is no data on the subject, which is alarming as many states have already passed bills relating to this subject. The former process, which was overseen by the FDA, allowed patients to apply for an experimental therapy (the application process took one hour). The FDA then reviewed the request within 24 hours and the agency approved more than 99 percent of the compassionate use requests they received. However, the drug developers then decided if they would provide the drug. Right to Try does not change that process, but instead aims to remove the FDA's role – in my view, a terrible and dangerous idea. Without FDA input, will we see a scenario where "snake oil salesman" try to take advantage of dying patients by peddling ineffective or even harmful therapies without scientific merit?

We are urging Congress to ensure experimental therapies are developed, made available under appropriate expanded access, and approved rapidly when they are proved to be safe and effective. And that includes increasing research support for the basic, translational, and clinical research conducted by the National Institutes of Health (NIH) and fully funding the FDA.

"The new law does not stipulate that drug developers have to provide the experimental therapy to patients."

In the healthcare and pharma industries, we all share the same goal of helping patients. It is imperative that we keep safeguards in place for patients, which includes FDA maintaining its oversight over the compassionate use process. In any case, the new federal legislation only provides the illusion of helping patients, as it does not stipulate that drug developers have to comply with compassionate use requests and provide experimental therapies to patients. The legislation also does not address the real obstacle to expanded access: very small supplies of experimental therapies, a lack of staff and resources, and safety concerns. All of us in the patient advocacy community will be watching this issue closely, and hope that future changes to the law can be made to ensure patients are protected.

Reference

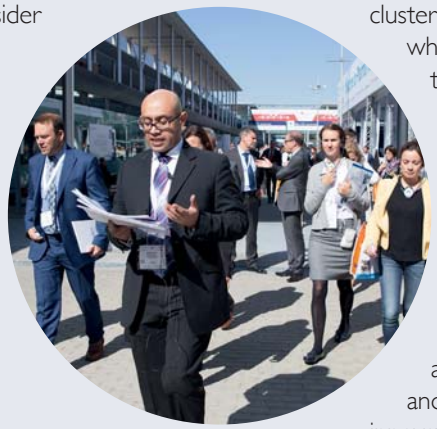
1. *Friends of Cancer Research, Letter to Mitch McConnell and Chuck Schumer (2018). Available at https://bit.ly/2BHZjYb. Last accessed August 24, 2018.*

Returning to Spain

CPhI Worldwide will return on October 9-11, 2018, at the IFEMA, Feria de Madrid, Spain.

CPhI Worldwide 2018 will include 2500 exhibitors and 20 zones covering the entire supply chain, from ingredients, APIs, and excipients, to contract services, packaging, machinery, and more. CPhI Worldwide also includes a number of co-located events:

- ICSE connects the pharmaceutical community with contract service providers – with representatives from clinical trials services, logistics providers, data management, CROs and CDMOs. Jim Miller, former President of PharmSource, will present on the outlook of CDMOs and consider the "what ifs" the industry faces in the next 5 years.
- InnoPack allows buyers to investigate the newest innovations in pharma packaging solutions, including anti-tempering devices, drug-stable barrier solutions and single dose applicator systems. A workshop, run by Victor Bell, President of Environmental Packaging International, will discuss today's common packaging goals and how companies are taking actions to meet them – with a particular focus on overcoming the sustainability crisis.
- P-MEC Europe features international exhibitors and manufacturers from pharmaceutical equipment companies focused on instrumental analysis, measuring and testing technologies, materials testing, laboratory and quality control.
- Finished Dosage Formulation (FDF) brings together every aspect of the finished dosage supply chain, from big pharma and CMOs to in/out licensing and dossier specialists. A panel discussion around "Creating a Sustainable Market" will see industry thought-leaders come together to examine how the world's market is predicted to grow over the next decade. Meanwhile, speeches on the rise of biosimilars and next-in-class biologics by Uwe Gudat from Fresenius Kabi, and Roman Ivanov from BIOCAID will decipher the rules, regulations and barriers surrounding these increasingly valuable products.
- The latest addition to the cluster of events is bioLIVE, which will focus on the intersections between business and biotech. bioLIVE will host special sessions on the potential roles of AI, the emergence of cell and gene therapies, and key bioprocessing and biomanufacturing innovations that are shaping the industry. Representatives from Ireland's National Institute for Bioprocessing Research and Training (NIBRT) will also speak on tackling the global biopharma workforce shortage.



Beyond the exhibition…

Attendees to CPhI Worldwide can also look forward to:

- Pharma Insight Briefings will take place on all three days of the conference and provide a go-to space for pharmaceutical professionals looking to explore emerging therapeutic areas and new business opportunities. Key insights include quality by design, the wider implications of Brexit on the pharma sector, and what the digital future means for pharma.
- A Country Pavillion Roundtable (Tuesday October 9) will provide attendees with the opportunity to network and discuss issues surrounding import and export strategy, regulation, industry growth, new markets and the challenges faced by the pharmaceutical market across the globe.
- The CPhI's Women in Leadership Forum (Wednesday October 10) allows women to share their experiences, expertise and leadership techniques. For the first time, men will also be welcomed to join their female colleagues at this event to facilitate conversation around how men and women can work together to diversify pharma.
- The Big Data & Machine Learning Summit – Europe (Wednesday October 10), in collaboration with The Innovation Enterprise, will bring together forward-thinking researchers and data scientists to discuss their latest findings. Key topics include: the role of big data in the supply chain and analytics in drug development and discovery.
- A snap-shot of the most interesting, innovative products coming to the market can be found in the Innovation Gallery. Attendees can also register for an Innovation Tour, where the CPhI exhibition floor will be explained with inside information on API selection and successful generic formulation development.

Towards Industry 4.0

The fourth industrial revolution – Industry 4.0 – represents a shift in manufacturing mentality and is driven by intelligent automation, big data, applied machine learning, advanced analytics, and even virtual reality. The digital technology is already here, but is biopharma ready? The third – and final – article in our Biopharma Trends series seeks the answers.

By James Strachan

The German government first introduced the concept of a fourth industrial revolution – "Industry 4.0" – in 2011 with its strategy for the future of high-tech manufacturing. The idea was a simple one: new technologies will pave the way for greater automation, flexibility, connectivity and ease of use – improving manufacturing productivity and efficiency, while reducing costs. The term caught on, and the concept is central to China's plans to occupy the highest parts of global production chains by 2050, as we discussed in July (1).

In the seven years since the German government coined Industry 4.0, many of the technologies required to make the concept reality – cloud computing, big data, smart technology, integrated systems – have come on in leaps and bounds, and are already used in several sectors.

But in biopharma, where companies tend to be more risk adverse and face regulatory, time-to-market, and other hurdles to new technology adoption, companies may be reluctant to embrace the changes needed to move towards Industry 4.0. Is it just another buzzword? What does it really mean? What practical applications will it have for my business today and in the next few years?

In this, the third and final in our series of articles based upon the Biopharma Trends report, we seek to answer these questions. Here, we present a roundtable made up of speakers from the upcoming Biopharma Trends 2018: Towards Industry 4.0 conference (www.biopharmatrends.com): Hal Baseman, Chief Operating Officer, ValSource LLC, and Per Liden, Product Strategy Manager, GE Healthcare Life Sciences; along with other experts from the field: Hans Heesakkers, ISPE; and Yvonne Duckworth, Lead Automation Engineer, CRB.

What does Industry 4.0 mean to you?

Hal Baseman: Industry 4.0 is the use of more modern techniques and methods for designing, operating and controlling processes. Examples include manufacturing intelligence systems, big data, applied artificial intelligence, and virtual reality that can help with modeling and planning processes, as well as the evaluation of the performance of processes.

Per Liden: It is a term that I believe very well summarizes the transformative impact of digital technology to industrial productivity. There is no doubt to me that we are on the verge of a quantum leap in productivity that will be of similar magnitude

Looking to the Future with Biopharma Trends

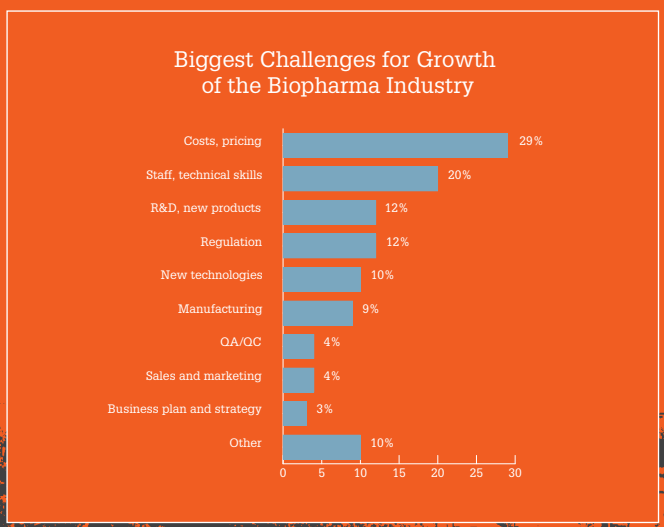
Here, we present the third set of findings from our Biopharma Trends survey (1), conducted in December last year, by The Medicine Maker and NIBRT, about current trends in the biopharma industry. The first article in the series looked at biopharma therapeutics and the most commercially important biotherapeutics now and in the future (2), while the second article focused on how to best equip the biopharma professionals of the future (3). Now, we look at growth opportunities and challenges.

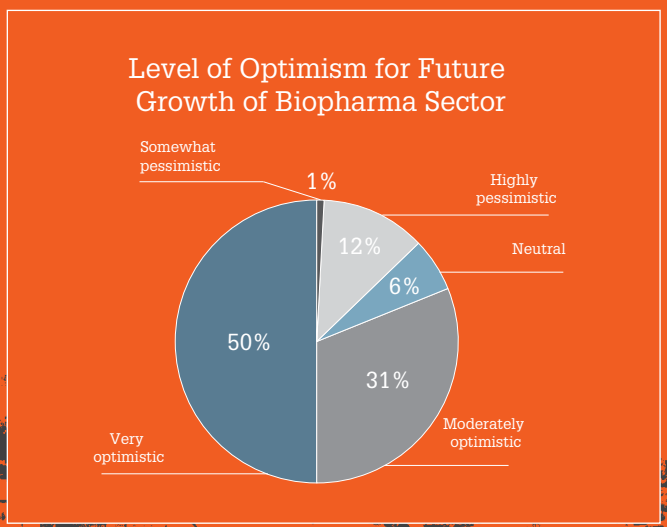
Overall, survey respondents painted a positive picture of the industry, with 50 percent saying they were "very optimistic" and 31 percent saying they were "moderately optimistic" for the future growth of the sector. Regarding opportunities and challenges, costs and pricing were the main concerns, while new products, plus cell and gene therapies, were seen as the biggest opportunities for growth.

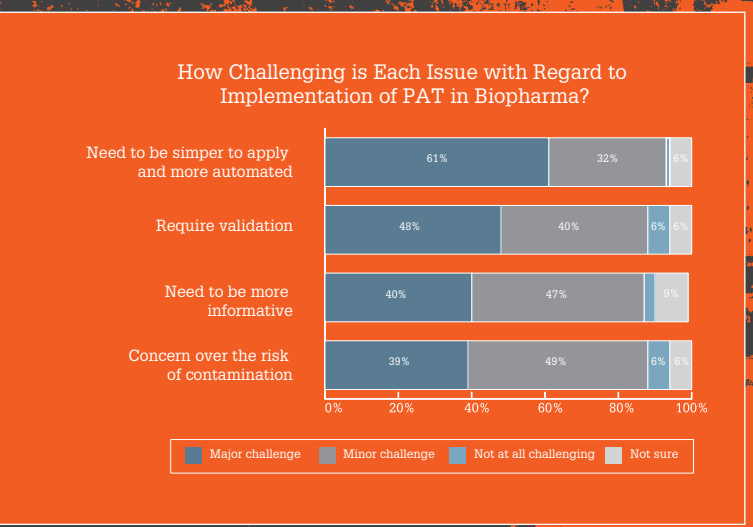
From a technology perspective, our results showed that process development of continuous manufacturing and lack of real-time monitoring technologies were major obstacles to the implementation of continuous bioprocessing – and that PAT needs to be simpler to apply and more automated. Here is a full breakdown on the results.

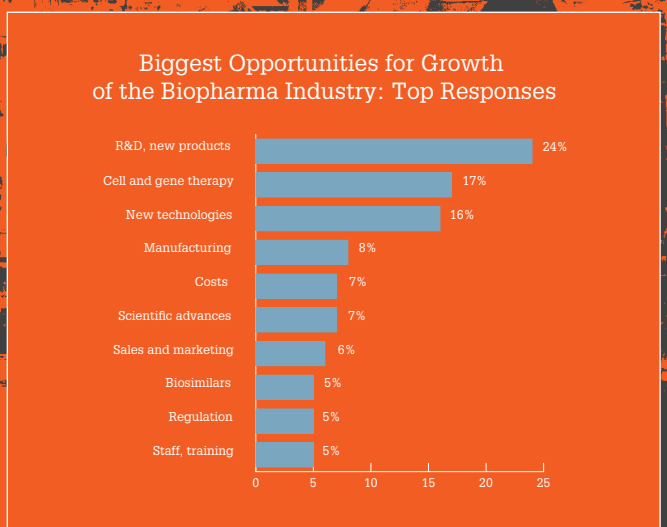
References

1. *NIBRT & The Medicine Maker, "Biopharma Trends: Trends in Biopharma Manufacturing Survey Report" (2017). Available at: bit.ly/2lDuHwl.*
2. *R McGuigan, S Sutton, "All Eyes on Biopharma Trends", The Medicine Maker (2018). Available at: https://bit.ly/2vi5jRZ.*
3. *J Strachan, "Just can't Get the Staff!", The Medicine Maker (2018). Available at: https://bit.ly/2PwEnpe.*









as the three previous revolutions and will have similarly transformative effects on the pharma industry – and society at large.

Hans Heesakkers: Per Liden is correct; we are talking about the fourth major change to industry operating models. It is driven by a leap in technological advancements. Like every revolution, this will only really arrive when it brings major benefits to the majority of mankind. The motor of industry 4.0 is the "ability to connect" many high tech developments that already exist and that are rolling out of development pipelines with increasing speed.

Yvonne Duckworth: I see Industry 4.0 as the trend towards the adoption of automation technology and data collection/exchange in the manufacturing industry, as well as the new technologies such as wearables (smart glasses, for example), new applications for virtual and augmented reality, and software applications using Industrial Internet of Things (IIOT) solutions.

Which Industry 4.0 technologies are you most excited by?

HB: I'm most excited about using manufacturing intelligence and data to predict and model the performance of processes, as opposed to using (as we currently do) lagging indicators – this should help us decipher where we're going and where we should be going. Also, being able to mine larger and larger fields of data – and then link that data from acquisition to process control is really big. That was actually the process analytical technology (PAT) dream of 10 or 12 years ago – and we can do it today.

PL: If I had to choose a single technology, it would be the commoditization and, therefore, democratization of computing power, storage, analytics and communication. The entry-level costs are simply getting lower, which opens up a massive potential for innovation.

HH: What excites me the most about Industry 4.0 is smart and adaptive development and production assets connected with distributed ledger technologies (such as blockchain) to all disciplines, from scientists to patients. In the end, our industry is all about preventing or curing diseases and improving human lives. Connecting all bright minds in our industry and focusing their efforts to improve patient outcomes could be accelerated by a smart, adaptive blockchain. Some tangible examples would be smart packs supporting treatment adherence, electronic batch records enabling quality and adaptivity in production, and blockchain integrating real world patient data with clinical trials.

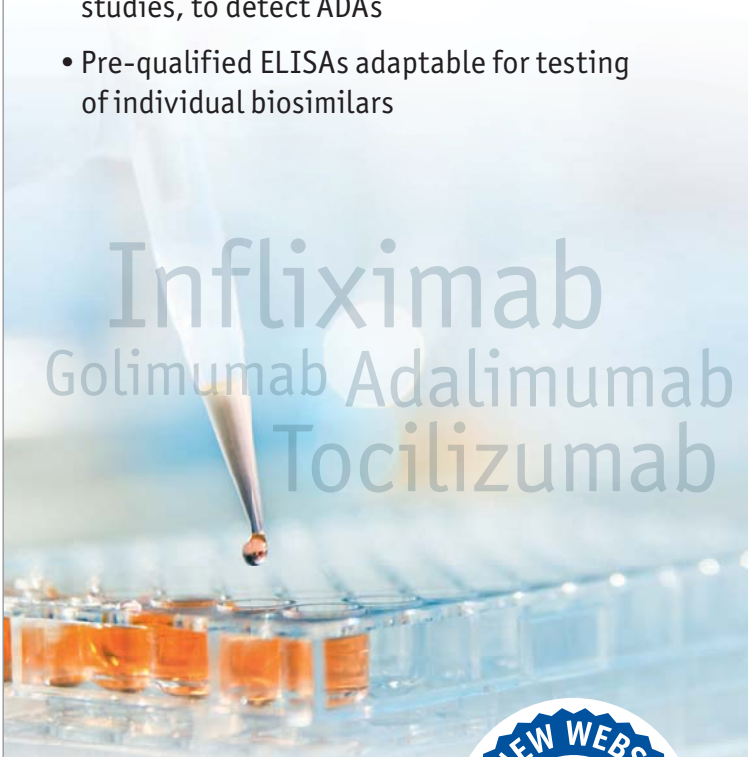
BioGenes

Immunogenicity & PK Assays for the Detection of Biologics and Biosimilars

BioGenes offers **a novel assay approach** based on a special soluble ELISA format, which provides superior detectability even for immune-complexed biologics and ADAs.

Custom ELISA Development of:

- Soluble sandwich ELISAs for pharmacokinetic studies, to detect and quantify biologics and biosimilars
- Soluble bridging ELISAs for immunogenicity studies, to detect ADAs
- Pre-qualified ELISAs adaptable for testing of individual biosimilars



Please contact us:
service@biogenes.de
+49 30 65762396
www.biogenes.de

! NEW WEBSITE !
www.biogenes.de

Industry 4.0 in Action

By Yvonne Duckworth

When discussing Industry 4.0, I hear a lot about new software solutions, including "Ignition". Ignition is an integrated software platform based on a SQL database-centric architecture. We are using it as a SCADA (supervisory control and data acquisition) system, as well as an alarm notification system, in some of our projects. Some of the benefits of this software include unlimited tags, unlimited clients and unlimited displays. The software is built on MQTT, (Message Queuing Telemetry Transport), which is a proven data-transfer protocol that is quickly taking a lead in messaging protocols for the Industrial Internet of Things (IIOT). OPC-UA (Open Platforms Communications Unified Architecture – a machine to machine communication protocol) is built in to both the clients as well as the servers. This provides for a much more flexible and open architecture, and allows for ease of connecting many different types of control systems together on one platform.

For one project, we have multiple skids that have different control systems that must all communicate on the same network. Overall network communication can be tricky in cases like this. The more flexibility that we have with the software helps to make communication easier to configure. Clients can be launched from any computer, or even mobile devices, without having to install anything. The alarm notification configuration is highly flexible and provides many options for notifications. My client requires many different alarm notification configurations, so this software is a great fit for this project. In short, "Ignition" represents just one good example of the kinds of practical advantages that Industry 4.0 can deliver today.

YD: I am really impressed by smart glasses technology. There are a few pharmaceutical companies that have already adopted the use of smart glasses in the warehouse for automated retrieval. I have also seen examples of smart glasses providing "see what I see" technology; where smart glasses allow a person to communicate with someone who is off-site but is more knowledgeable and able to fix the problem remotely; it could help reduce the travel time required for specialists. Another great application for smart glasses is providing work instructions from SOPs, as well as training. All of these applications could potentially save time and money.

In addition, I have noticed a shift, at least with the companies I work with, in that five years ago, they were all using physical servers. Now, many companies either have virtual servers in place already, or are open to switching over and including virtual servers in their control system architecture that we are designing. It's a big step forward in the automation world for pharma – virtual servers are far more cost effective and also scalable and flexible.

What major challenges facing the biopharma industry could be addressed by digital technology?

HB: I like to open some of my talks by pointing out that I started in aseptic processing 40 years ago. And if I had been asked to predict what aseptic processing would look like 40 years in the future, I could never have imagined. This is because it is practically the same. Of course, there are isolators, faster and more reliable equipment, greater automation and so on, but the basic means by which we manufacture – large tanks, expansive clean rooms, limited production shifts, gowned operators, in-process monitoring and final product testing are essentially the same as they were 40 years ago! We have not embraced innovation and change as other technology-based industries have. But now we have the chance to make real changes to our manufacturing processes.

As one example, there is increasing industry interest in moving to a continuous approach for biopharma manufacturing. This is something that we've primarily seen in the small molecule space, but there's a lot of interest in biopharma as well around this technology. This will represent a shift towards smaller manufacturing space footprints and plants – which will rely more heavily on automation and data control, and the linkage of process monitoring, process control, and product attributes as we should see with analytical technology (PAT). The management of knowledge and data envisioned with Industry 4.0 can play a major role in the transition towards continuous manufacturing processes.

PL: Biopharma has many inefficiencies. To take one example, our industry is struggling with realizing continuous improvement in manufacturing performance. In the initial stages, I see the potential for industry 4.0 technology to help address that, simply by unlocking data and providing visibility to quick win types of improvements. In the longer run, and as Hal mentioned, I see the potential for Industry 4.0 technology to help address the shift to continuous manufacturing. A continuous approach to manufacturing should deliver better efficiencies.

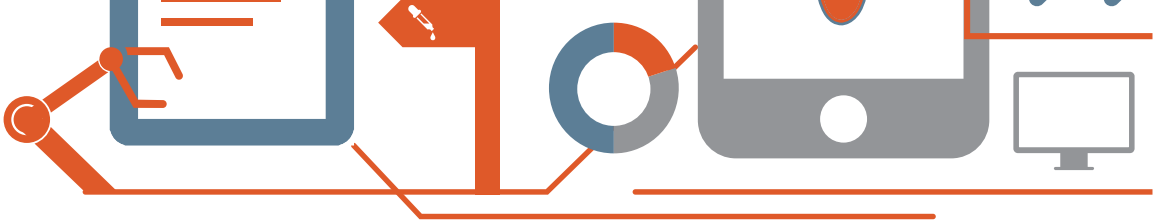
JM

Our complex chemistry helps you create life-changing results

We work globally with our pharmaceutical customers to deliver complex chemistry solutions for a healthier world. We produce sophisticated APIs for life-changing drugs; our expertise in controlled substances helps combat chronic pain and we employ decades of catalysis knowhow to enable faster, cleaner and more efficient reactions. Our custom pharma solutions offering and worldwide manufacturing capabilities help to get your drugs to market faster, making a real difference to the quality of life.

Johnson Matthey
Inspiring science, enhancing life

To find out more visit matthey.com or email pharma@matthey.com



HH: Our industry is laid out for mass production (Industry 2.0) and working with these principles is in our genes. But mass production thinking consists of large organizations, silos, repeatability and products with little variance for a large population. Demographic changes are forcing the industry to consider smaller facilities and increase collaboration to develop a greater variety of medicinal treatments for smaller patient populations. Biopharma is not yet used to this new way of working. It requires a new set of "industry genes" or, as we like to say in ISPE, a new, digitalized operating model: Pharma 4.0.

YD: Facility design – the area I specialize in – is always a challenge for biopharma companies. Even with planning tools it is incredibly difficult to really visualize how a facility will look until it's built – and by then it's too late to change anything you suddenly notice that needs changing! Virtual reality is now starting to be used for build modeling. You can build a model using a software program that includes all of the components of a facility including walls, floors, process equipment (tanks, pumps, transfer panels, etc.), conduit, ductwork and piping. It's really useful (and really cool!) to be able to put a headset on and do a "virtual walk-through" of a facility being designed to see how it will look. And to take this one step further, through the use of laser scanning, we are able to scan an existing construction area and pull this information in and use it as the background for 3D modeling for all of the new process equipment to be added. We can synchronize to an origin point and perform all of the new modeling using the scan as the background. This is a great example of augmented reality (providing spatially registered digital content overlaid onto views of the real world), which is another exciting component of Industry 4.0.

However, Industry 4.0 also poses challenges to facility design, or perhaps we should say that current facilities pose a challenge to implementing Industry 4.0… implementing a wireless infrastructure in a biopharma manufacturing facility is actually a huge challenge because of the amount of stainless steel used. With interest growing in single-use facilities, it is becoming easier to implement wireless infrastructures. I also think that my biopharma clients are realizing the benefits of investing in a more robust infrastructure when they are having new facilities built or renovating existing ones.

What are the hurdles to embracing and implementing Industry 4.0?

HB: I do not believe biopharmaceutical processes are more complicated than what many other industries are doing. This industry should be able to implement much of Industry 4.0 into biopharma manufacturing. However, there is a big question over

Biopharma Trends 2018: Towards Industry 4.0

By Killian O'Driscoll

In essence, Industry 4.0 means improving the efficiency of manufacturing via the implementation of digital technologies. From the perspective of NIBRT – Ireland's National Institute for Bioprocessing Research and Training – we are very interested in the potential of immersive reality (IR) technologies to provide competency development programs. For example, could staff be trained – on an ongoing basis and to an optimum level – using "digital twins" of advanced manufacturing facilities?

As biopharma operations become increasingly globalized, complex and more highly regulated, businesses must become more effective and cost efficient at delivering what patients need and want. Industry 4.0 technologies have the potential to optimize the manufacturing process, reduce cost-of-goods, and ultimately help improve access to high-value biologics by bringing drug costs down. Like all technologies, there is probably a bit of hype and hope associated with Industry 4.0 , but as the industry focuses on the topic we'll soon begin to find out what is possible and what the reality is. I will be interested to hear more opinions and case studies on the topic of Industry 4.0 at the Biopharma Trends conference being held November 13-14, 2018, in Cork, Ireland.

The Biopharma Trends conference was developed in collaboration with The Medicine Maker, with the aim of exploring the future of biopharma manufacturing. Why focus on Industry 4.0 for the inaugural conference? Because interest in this area is high, as highlighted in the recent survey we conducted. A number of survey respondents indicated that continuous manufacturing, process characterization, real-time process control, data dissemination, and IT and data integrity were high-priority areas for innovation in the industry.

Registrations for the conference are now open at www.biopharmatrends.com

CORDENPHARMA

EXPERTS TAKING CARE

FULL-SERVICE CDMO >>
FOR A GLOBAL MARKET

CordenPharma is your full-service CDMO for a global market. Through our network of technology platforms and cGMP facilities for the manufacture of APIs, Drug Products and pharmaceutical Packing, CordenPharma experts translate your complex processes, ideas and projects at any stage of development into high-value products.

www.cordenpharma.com

TECHNOLOGY PLATFORMS

- **PEPTIDES, LIPIDS & CARBOHYDRATES**
- **HIGHLY POTENT & ONCOLOGY**
- **INJECTABLES**
- **SMALL MOLECULES**
- **ANTIBIOTICS**

VISIT US AT

CPhI > Stand 7F30
October 9–11, 2018
Madrid, Spain

whether biopharma is ready to accept or embrace these types of technologies.

There are three significant challenges we must overcome to make Industry 4.0 a reality in biopharma. The first is overcoming a reluctance to try new approaches. We need a system where manufacturers feel comfortable going to regulators with new ideas and where regulators are open to the acceptance of new technologies and approaches. We also need suppliers to listen to users and help create systems that will reduce the time and effort required to implement new technologies. We need to find ways of forming effective partnerships between manufactures, suppliers and regulators.

The second major challenge is the regulatory burden of post approval changes. Once a manufacturer has received approval to manufacture a product a certain way, it can be quite burdensome to then improve the technology. The manufacturer must go through an approval process once again. This is not a matter of just seeking approval from the FDA or the EMA. Any country that the company wishes to distribute product to may require similar approvals. Significant manufacturing technology changes cannot be made until all of these global health authority approvals have been granted, often at multiple sites across the world. Here, the principles of Industry 4.0 can help accumulate and analyze data and generate the evidence needed to show that improved processes remain under control and that the changes are acceptable.

The third challenge is overcoming the risk of compromising speed to market. New technologies can take longer to develop and gain approval than existing approaches. As a response to the perception of additional business risk, companies may decide to use older, and perhaps less effective, manufacturing methods to get their products to market as quickly as possible. To overcome this challenge, we need to recognize the benefit of long term manufacturing efficiency against the risk and make the transition to new technologies as seamless as possible. If we decide to go to market with existing manufacturing approaches, we must plan for the introduction of better technology in the future. Companies should not be forced to live with old technologies forever, because of early product introduction needs.

All three of these challenges boil down to this important question: how can we remove barriers and burden to the implementation of new manufacturing technologies and prove to ourselves and others that these new methods are more effective?

YD: Regulatory hurdles are a big challenge for the adoption of any new technologies in the pharma industry, and that also applies to automation. Data collection is a big issue with pharmaceutical companies and the restrictions put forward by the FDA can make it difficult for pharma companies to use the cloud for data storage, which is an integral part of Industry 4.0 and IIOT. But I am hopeful this will change in the future as more security measures are introduced and put in place. I think that the emerging use of blockchain technology can add some potentially exciting features to data collection in the pharma world.

Industry 4.0: is it hope or hype?

HB: Recently, I attended a conference where a point was made that before we jump completely into some of the possibilities of Industry 4.0, such as artificial intelligence, machine learning and so on, maybe we should take a step back and use some of the things we already have available to us (but we are not using), such as big data acquisition, system integration, and predictive modeling and maintenance. The hype comes in when we say, "Let's just move from where we are today to new, grandiose plans where everything is robotic and only a few human workers are required." A staged approach will deliver practical, and more acceptable benefit to today's biopharma manufacturing operations and prepare our industry for acceptance of improved innovative approaches in the future.

PL: Neither – even though some of the concepts seem like science fiction – especially for an industry that arguably is one of the last to work through the third industrial revolution. Industry 4.0 is real. Even though I expect that full implementation will take longer for biopharma than other industries, I see signs that our industry is already starting to implement some of its concepts, such as augmenting human decision making. We have come a long way, but we still have a lot more to accomplish.

HH: I agree, it's a false dichotomy – Industry 4.0 is fact! I am very optimistic about the future. Pharma 4.0 might come slower or faster, but it is reality. The smaller, connected organizations that give their bright scientists, engineers and other staff the freedom to innovate will unleash a treasure of potential. But we need to ensure that these wonderful new technologies are properly implemented in the biopharma industry so that, ultimately, patients can benefit.

YD: There are some components of Industry 4.0 that are already being used in the biopharma windustry. In addition, there are also some exciting new concepts of Industry 4.0 that have the potential to significantly improve automation technology in the biopharma industry, so I think that gives us hope that it isn't just hype. I would say that this is a pretty exciting time right now for automation technology in the pharmaceutical industry, and I look forward to seeing where these new trends will go in the next few years.

Reference

1. *J Strachan, "Make china great again", The Medicine Maker, 43, 18–25 (2018). Available at: http://bit.ly/2oTDfkj.*

TAKING A PILL IS AS EASY AS PIE? 50% OF YOUR CUSTOMERS WOULD DISAGREE ...

Visit us at CPhI 2018 in Madrid, stand 1G41

A recent study proves that more than half of the population has problems swallowing tablets and capsules. From breaking and dissolving to not taking them at all, people invent their own strategies to cope with tablets – which may reduce efficacy and treatment success.

At HERMES PHARMA, we have over 40 years of experience in making medicines easier to take – from product design through to manufacturing and packaging. If you need support with developing new products that are specifically designed to meet the needs of modern patients, contact us:
www.hermes-pharma.com

Scan QR-code or visit
www.swallowingtablets.com
to get a free copy of the market study.

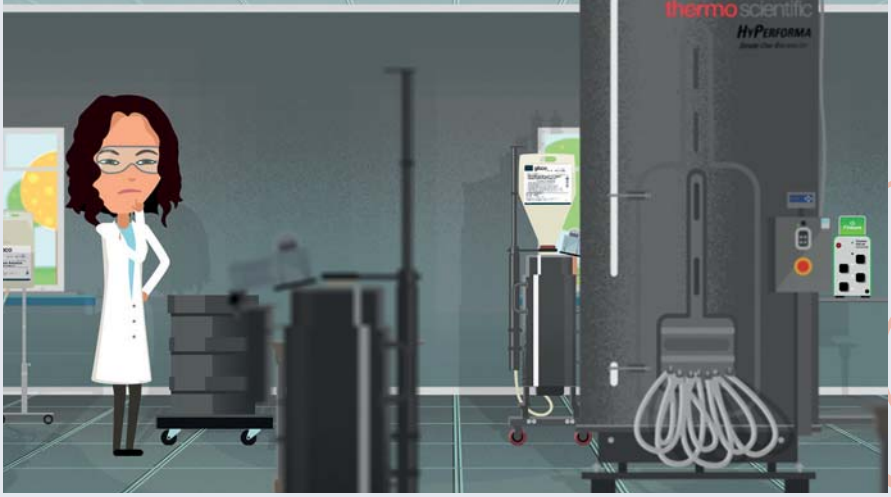
HERMES PHARMA

Get the dose right®

What Makes a "Good" Bioprocess?

The development of an optimized bioprocess requires a holistic approach tailored to the specific needs of the product.

By Serena Fries Smith



Biologic medicines are changing the lives of more and more people around the world, but the increasing complexity of the molecules means that developing the right manufacturing process isn't easy. I've spent over 15 years working in the industry on viral vaccines and therapeutic proteins, focusing on upstream process development, scale-up and cGMP manufacturing. I've developed processes for over a dozen different molecules and I often think about what makes a "good" or "optimized" process – and where the pitfalls lie. To me, an optimized process produces highly purified material in a minimal number of batches to meet your clinical timelines and prepare for commercial launch, all while managing cost, quality and supply. In addition, an optimized process must streamline operations, improve robustness and consistency, and minimize the opportunity for failures. You'll also need to consider engineering controls to prevent contamination events or the introduction of adventitious agents. All of this should result in long-term manufacturing success.

I know this is much easier said than done! With so many critical areas across the bioprocessing workflow, it can be difficult to know where to focus your efforts. I believe that success typically lies in taking a measured approach, balancing trade-offs associated with speed-to-clinic and process optimization – tailored to the specific needs for your molecule. There are a number of different areas that you can focus on to optimize your upstream process performance, but balance is important; it's not always about getting the highest titer. Developing a process that reproducibly achieves a titer of 5 g/L, for example, may be more sensible than identifying the perfect set of conditions required to achieve 7 g/L. If the process needs to run "just right," even a small deviation can lead to much lower titers than the initial 5 g/L, and potentially failure.

Overall, I believe there are three questions that you need to be asking throughout the optimization process:

- *Can I simplify the process?* Something that is easy to run at small-scale in the lab, may result in unnecessary risk and variability in a large-scale GMP environment. You may be able to reduce your risk of failure if you replace a complicated feeding strategy with a simplified approach. You may be able to reduce your risk of contamination if you replace open manipulations with closed systems. And you may be able to reduce your variability by streamlining cell expansion or media preparation.
- *How do I ensure consistent performance?* The closer you get to a commercial manufacturing process, the more batches you will need to run, and consistency and robustness become key – especially if you are aiming for commercial manufacturing of multiple batches per month, or perhaps dozens per year.
- *How is upstream impacting downstream?* You must consider the downstream implications of the upstream process – ensuring the material that is made can be consistently purified downstream.

A holistic approach

Process engineers have to balance speed without compromising on quality… connect upstream and downstream bioprocesses seamlessly…and design a system that is robust and scalable with materials they can count on. Trade-offs are everywhere when it comes to bioprocess development. For example, when thinking about speed-to-clinic, a "brute force" approach may often be best for the initial clinical process. When I used to work in vaccines, one big challenge was working on adherent cell cultures, where scale-up is much more difficult than with suspension cells. Early in the program, you might be thinking about whether you should develop a 2D (cell factory) or 3D (microcarrier) process. A 2D process may be simpler and quicker to develop, but requires more manual manipulations than a 3D process. Here again, there's a trade-off between moving the program forward and facing operational difficulties during material production for a phase I trial. If speed-to-clinic is the focus, then process optimization (transitioning to a 3D process, for example) can be done during the clinical studies to prepare for late-stage or commercial manufacturing.

Whether we are talking about recombinant proteins or viral vaccines, and even if speed is the primary objective, product quality still remains absolutely crucial. It is not just a case of working out whether the quality attributes satisfy the requirements for clinical studies, but also whether they're reproducible in the commercial process. In my view, process and product consistency is something you should be thinking about very early on.

When thinking about quality, there are two factors that you must keep in mind: raw material quality and product quality. An increasingly large body of evidence shows that the quality of the raw material – the presence or absence of impurities – not only impacts process performance but greatly impacts the quality of the drug substance. It is, therefore, imperative to understand the quality of raw materials that are being used during process development and how they compare to what will be available for use during clinical or commercial manufacturing.

Managing quality and supply

The need for quality raw materials also ties into another important consideration: assurance of supply. Stock outs are not something anyone – biopharmaceutical companies nor suppliers – want to deal with. During the development of a biological process, the reliability of the raw material supply chain must be considered. Supply continuity is vital; companies must have strategies for mitigating supply disruptions. There are many approaches to accomplishing this—from closely managing multiple suppliers to partnering with a trusted supplier that can consolidate your direct material supply. In all approaches, transparency in raw material supply requirements and the necessity for safety stocks, redundant site qualification or other means of preventing supply interruption is key.

Managing raw material supplies can be daunting, and collaboration can help drive success. Instead of focusing only on the functional aspects of the upstream or downstream process, a holistic approach leads towards a successful outcome. The FDA is expecting more and more effort from drug companies when it comes to supply chain transparency – another great reason to collaborate with suppliers so that all parties gain a good understanding of where raw materials come from, how they're used, and how the whole process is being managed.

The importance of a good relationship with suppliers cannot be overstated as it affects everything from performance, to product quality and assurance of supply. You need to trust that your suppliers will deliver exactly what you are expecting so that you can troubleshoot effectively any process deviations that occur. Often it's difficult to find the root cause of a problem, but having a close and trusted relationship with your supplier can help assess raw materials as the potential cause.

Bioprocessing by design

Overall, there is no one-size-fits-all solution to bioprocessing. In addition to quality and supply chain requirements, you must understand the performance of your process in terms of titer, purity, biological activity and other important attributes. Knowing this enables a greater opportunity to balance development costs with the probability of molecule success. And if your product is a biosimilar, getting the product quality attributes to match the innovator is important. This may make it necessary to sacrifice some titer (upstream) or yield loss (downstream) to ensure the quality of the purified product, but remember that the market is competitive, which means heightened attention to speed and costs.

Balancing process optimization with timeline constraints is often the biggest challenge a process development engineer will face. Upstream scientists will work to get the highest possible titers. Downstream scientists will work to get the most purified product. And the program lead will want the material in the clinic yesterday! My advice: understand what is absolutely critical for the program, prioritize those activities and utilize insights and technical engagement with trusted partners to design the right bioprocessing solution for your molecule.

Serena Smith is Director of Strategic Customer Engagements at Thermo Fisher Scientific, and a bioprocessing leader with over 17 years of industry experience.

PHARMA INTEGRATES

12-13 November 2018

Grange Tower Bridge Hotel, London

Pharma Integrates
Shaping Pharma's Future

CONTINUED GROWTH FOR SEVENTH EDITION OF PHARMA INTEGRATES

The top leaders in Pharma are coming to an event that will shape the future of the industry. And you're invited.

With more than 350 senior industry executives, 90 prestigious speakers, and 7 years of successful events behind it, Pharma Integrates 2018 is where the leaders of Pharma share the conversations that help to shape its future.

Life Science Integrates, the producers of the debate-led events shaping Pharma and BioPharma, invite you to attend this year's conference at the Grange Tower Bridge Hotel, London from the 12 - 13th of November 2018.

Register now to secure your early bird discount and to network with high-profile speakers from NICE, Pfizer, GlaxoSmithKline, NIHR, Takeda, MHRA and more.

Attend both days to hear our panels' insights into the forces and trends affecting the industry. Will Blockchain reduce counterfeit medicines? What can serialisation offer beyond data collection? Should Pharma be doing more for the patient experience? These are just a few of the thought-provoking discussions taking place across the event.

With dedicated networking sessions throughout the day providing an opportunity to engage with these experts, we together, as an industry can collaborate, innovate, and shape the future of Pharma.

Our mission is to bring together the top leaders in their fields, so they can share insights into the current and future states of the industry.

SIR ANDREW DILLON
Chief Executive
NICE

ERIK NORDKAMP
UK Managing Director
Pfizer

NATHALIE MOLL
Director General
EFPIA

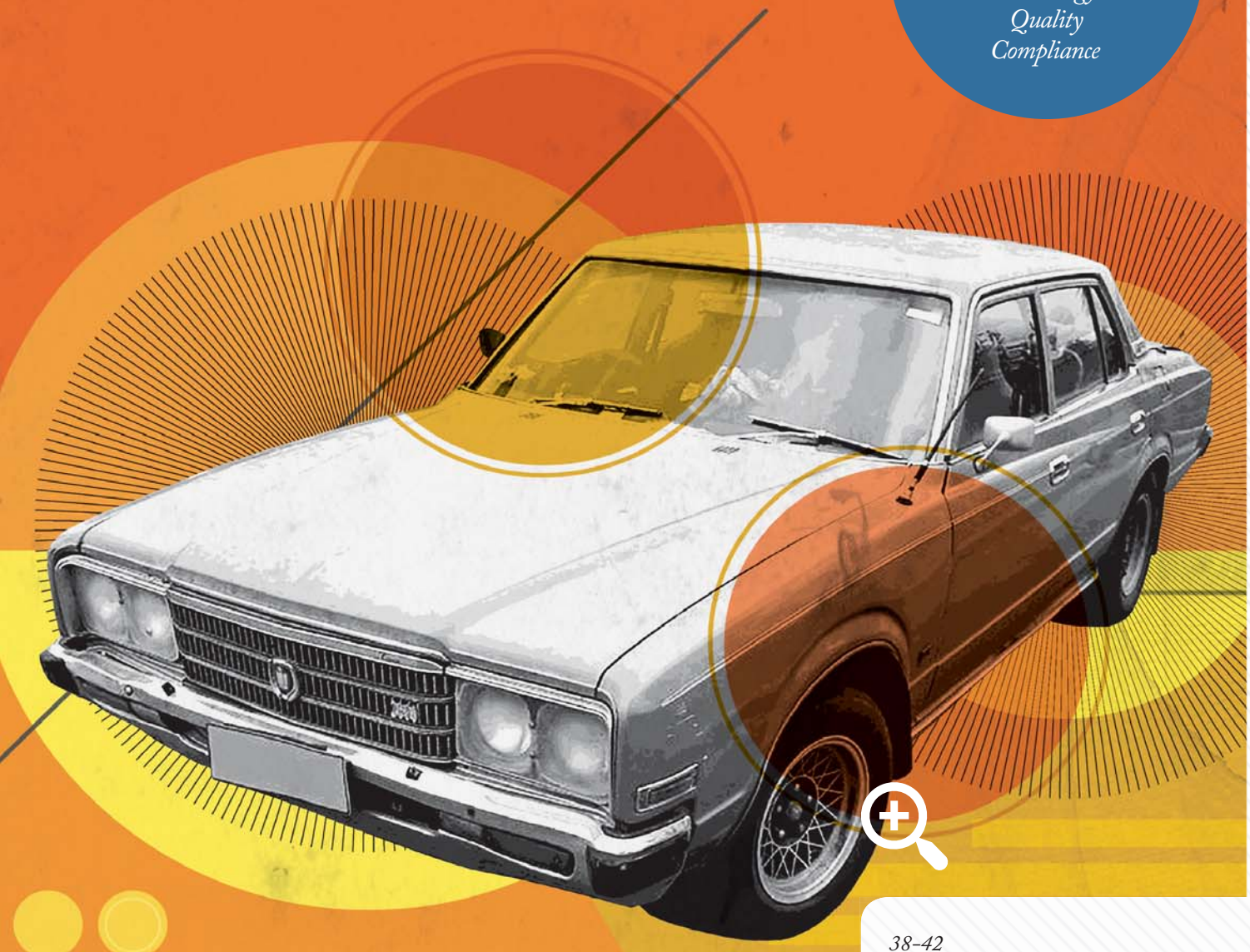
REGISTER NOW TO MEET, LEARN FROM, AND NETWORK WITH THEM.

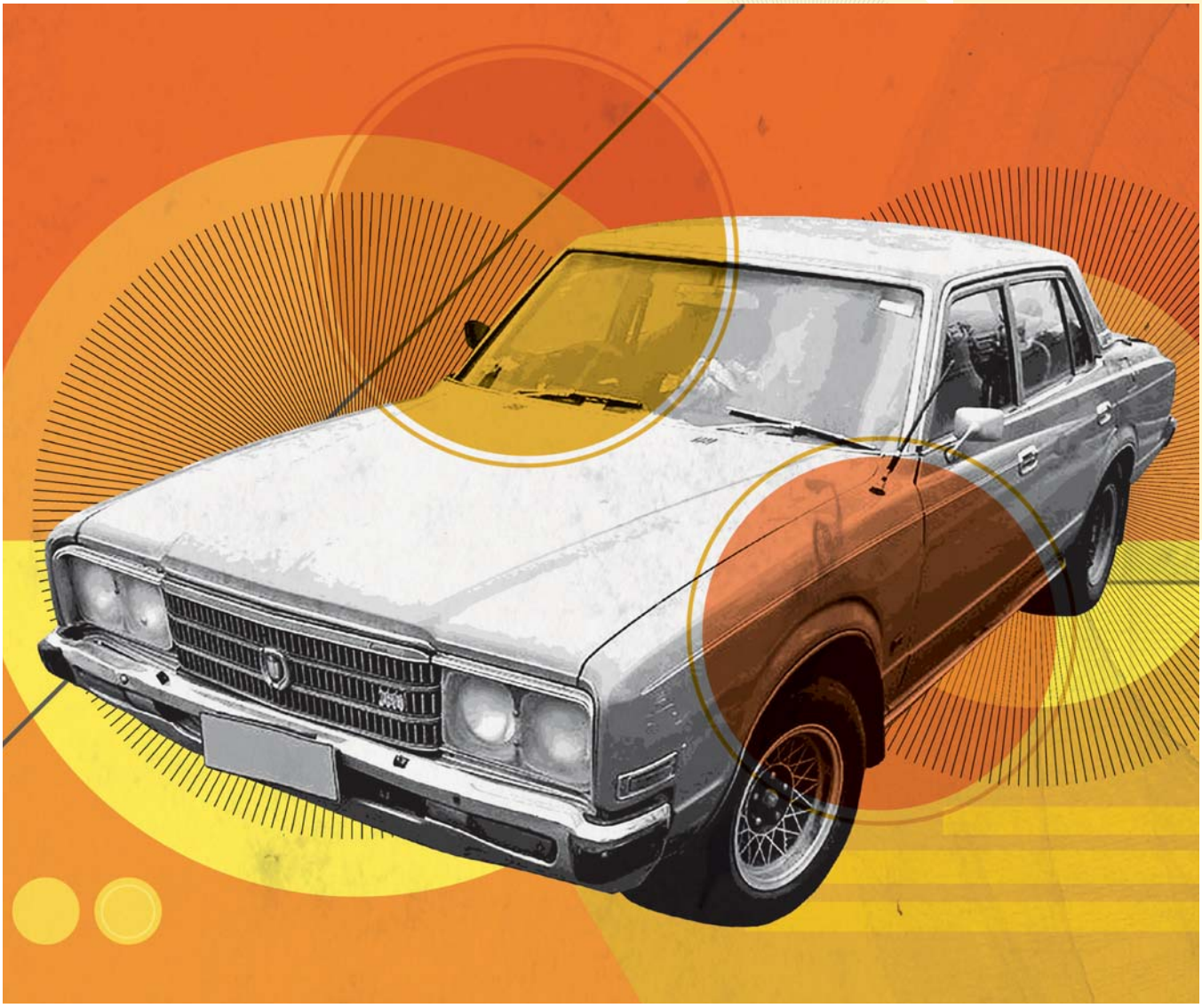
www.pharma-integrates.com

Early bird discount available

Best Practice

Technology
Quality
Compliance





Kaizen Chiefs

Pharma companies have ample room to improve productivity. Lean manufacturing and continuous improvement could be the key to success, and the automotive sector – Toyota, in particular – is a rich source of inspiration.

By Chris Owen

All pharma manufacturers face pressure to reduce prices, yet companies differ greatly in their efficiency. The most productive companies are twice as productive as the average, which means many businesses have plenty of room for improvement. And even the best must move forward to avoid being left behind. The keys to success can be found in lean manufacturing and continuous improvement. One company that takes these principles to heart, with impressive results, recently invited pharma businesses to see how they do it.

Medicine makers attended a "lean manufacturing" workshop and factory tour at Toyota's Deeside Engine Plant in North Wales, UK. Toyota is widely regarded as the world's most effective practitioner of continuous improvement and lean manufacturing; and although they make cars and engines, the automotive industry has already tackled many of the cost

and efficiency challenges now facing pharma manufacturers, so there's much we can learn from the sector. Here, I'll share a brief overview of what was seen and discussed.

The SMMT (Society of Motor Manufacturers & Traders) Industry Forum, a specialist training and consultancy provider for manufacturers, co-hosted the workshop with Toyota. In addition to assisting automotive firms, the Industry Forum also helps transform manufacturing competitiveness in many diverse industries, including pharma. As Industry Forum's Chief Executive, I was one of the workshop speakers in Deeside and was able to see first-hand how Toyota's approach to manufacturing truly inspired our guests.

The 115-acre site at Deeside employs almost 700 people and produced more than 337,000 engines last year for the Toyota Auris and Auris Hybrid models. Deeside's engines and component sets are shipped to Toyota car-building plants in Derbyshire (UK), South Africa, Turkey, Brazil, and Japan. Deeside is also home to the Toyota Lean Management Centre, which shares knowledge, understanding and experience with non-competitive organizations with a desire to develop people and processes. The Centre works with small, medium and large multinational companies in a wide range of sectors including food, chemicals, aerospace, and pharma. Toyota Deeside also provides unique opportunities for study and benchmarking.

Benchmarking can help pharma look at itself in the mirror objectively. According to McKinsey & Company's research (1), pharma's strengths are research and development, as well as sales and marketing, but the industry needs to build on these by improving productivity and reining-in costs. Inventory lead times need to be shortened and inventory levels must be slashed; manufacturing equipment and labor must be employed more efficiently; and waste caused by unplanned speed losses or stoppages on production lines must be reduced.

These are all challenges that Toyota has faced – and tackled successfully through lean manufacturing and the Japanese concept of "kaizen." So let's

The most compact, hygienic and user-friendly valve on the market.

Mucon Oyster Hygienic Stainless Steel Butterfly valves offer outstanding operator end user benefits.

- Perfect solution for the handling of powders, granules and liquids in the pharmaceutical, fine chemical and food sectors
- Fast and easy to strip, clean and reassemble. Ideal for hygienic applications
- Used within a wide range of process applications
- Lightweight and easy to maintain
- Manual or Powered actuation

mucon.com
sales@mucon.com | +44 (0)1625 412000

take a brief look at kaizen and four other cornerstones adopted by Toyota in the pursuit of manufacturing efficiency. At the Deeside plant, we saw some good examples of how these have helped make production-line working practices more standardized, reduced lead times, enabled better allocation of resources, reduced headcount in some areas so that it can be re-deployed to others, and improved overall plant productivity.

Five cornerstones

Toyota's leadership style is founded on the principles of Plan, Do, Check, Action (PDCA). The company recognizes that leadership capability is essential to ensure that the tools of lean and human resources are deployed in harmony with one another. The aim is persistent leadership and the adoption of best practices by everyone.

The first cornerstone is "challenge." It's vital to have a medium- and long-term vision, which necessitates managing change. To ensure that the forward-looking vision is sharp, there has to be detailed study of manufacturing processes and capacity.

The second is "kaizen," perhaps the most-used word in the Japanese business vocabulary. Kaizen denotes continuous improvement and has long been one of the major tools of the Toyota Production System. Kaizen is the process of making small improvements continuously by targeting the elimination of waste and none-value-added activities. Kaizen isn't about efficiencies resulting in headcount reduction; quite the opposite, it's about

"Toyota uses hoshin as its starting point to align business strategy with shop floor activity."

engaging, empowering and motivating employees (who Toyota refers to as "members") at all levels to strive for perfection. In fact, every member is asked to come up with two improvement ideas per month and there's a reward scheme for the best ideas. On the assembly line, members are rotated between four (of the six) different line tasks every day so that they stay engaged with the job and keep looking for ways to eliminate waste with fresh eyes. Because kaizen is practiced daily, the Toyota Production System constantly evolves. To encourage this, information about targets and performance is displayed prominently at many locations throughout Toyota's plant.

The third is "hoshin kanri." In corporate-speak, this means "policy deployment," but to everyone in the workplace it means teamwork. And it's how the company's strategic goals drive progress and action at every level. Toyota uses hoshin as its starting point to align business strategy with shop floor activity, then deploys high-level strategy at all levels through daily management. What's more, all levels in the company create their own hoshin, with assigned responsibilities.

"Genchi genbutsu" – "go and see" – is the fourth cornerstone. It spells out that it is imperative for managers to go to the production line and see whether individuals are all working to exactly

the same, standardized methods. Standardized work is a tool that can be applied to any process where human interaction is present by organizing and defining process-steps and human movements. It ensures that safety, quality and efficiency are built into human processes. One Toyota manager told us, "We standardize everything, but we don't stifle creativity, because the challenge for our members is to create the standard and then constantly improve it."

It is the job of assembly line team leaders to observe that standardized procedures are adhered to. This manual monitoring is supplemented by the installation, and frequent re-location, of video cameras around the plant. Far from being the first step in a blame game, it is designed to better-direct mentoring and support. One manager told us, "Trust is essential. We're not using the cameras to catch anyone out, but to bring improvements. We never blame the individual, we analyze and improve the process."

Team leaders are also responsible for dealing with any line issues. If members experience abnormalities on the line, they are asked not to take countermeasures because these can cause more problems. Instead, it's down to the team leader to make the fix, then bring members together to see how it was done.

The final cornerstone is "respect." Toyota's team-working mindset starts with the belief that everyone wants to do a good job. Each level of management ensures that high levels of operational performance are achieved on a daily basis through true teamwork, and the company regards itself as responsible for creating an environment in which people can develop and grow. A development map is created for every individual, with a clear path for training and advancement.

Continuous rewards

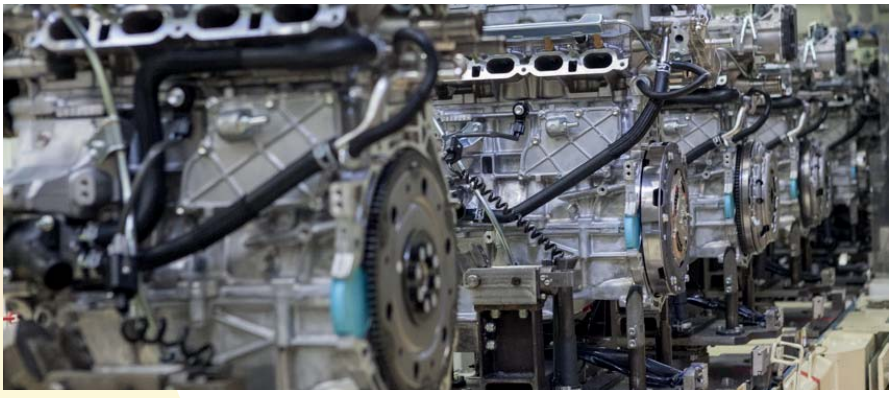
You might have heard some businesses say they "tried lean" and were disappointed with the results. But I suspect many such companies only half-heartedly adopted lean practices, limiting any potential impact to the bottom line. And if lean practices are not properly sustained, their efficiency gains will fizzle out. A common mistake made by under-performing businesses is to regard lean tools as an objective in themselves, rather than as a way to

Recipharm
good for business

Discover how we bring your brilliant ideas to life.

For nearly a quarter of a century, bringing pharmaceuticals to market has earned us a solid reputation in the CDMO industry. At Recipharm, we've grown our business by making sure we always produce for the benefit of our customers. From development through to delivery, we'll earn your trust. Discover what we can do for your business.

Book a meeting with us at CPhI Madrid at recipharm.com/cphi



introduce a fundamentally new way of working – and, indeed, thinking.

Some of the many gains from implementing this way of thinking, as revealed on the factory tour, were mind-boggling. For example, a plant that produces 1,300 engines per day cut the number of engines stocked from 2,700 to 450 – and is now targeting 350! This is quite a contrast with the average pharma company, which holds 180 days' of finished inventory, or even with top-performing pharma businesses, which typically hold about 100 days' worth.

Another example was a plant designed to produce an engine (with 25 variants) every 54 seconds that initially achieved a production rate of 57 seconds; now, it's down to 42 seconds. It wasn't necessary to make big investments to achieve this productivity gain; it happened, step-by-step, entirely through kaizen and eliminating waste.

It is true that some of the easiest and biggest gains will probably be made first, but after the low-hanging fruit, smaller rewards will be found by looking harder and further. But when every member of the company is looking and reaching, as they are at Toyota, small improvements keep coming in such large numbers that they add up to something significant. Why not implement similar best practices to reap the benefits of lean manufacturing and continuous improvement?

Chris Owen is Chief Executive of the SMMT Industry Forum.

If you are interested in learning more about kaizen and how Toyota can offer support in applying lean management techniques, contact: tmuk.tlmc@toyotauk.com (Toyota Lean Management Centre at Deeside). charitabletrust@toyotauk.com (Lean approach seminars at Toyota Manufacturing UK Burnaston, Derby).

Reference

1. *McKinsey & Company, "Building New Strengths in the Healthcare Supply Chain," (2013). Available at: https://bit.ly/2MgOLPH. Accessed September 10, 2018.*

45+
HOURS OF CONTENT

3
DAYS OF NETWORKING OPPORTUNITIES

bio LIVE

IFEMA MADRID • SPAIN • 9-11 OCTOBER 2018

At the heart of Business and Innovation in Biopharma

Join us for the brand-new bioLIVE event, the place to build business and find out about exciting developments in the rapidly-growing biopharmaceutical industry - with a focus on biomanufacturing & processing!

REGISTER NOW
bit.ly/visitbioLIVE

Take advantage of 45+ hours of on-site content as well as unparalleled networking opportunities, via the daily 5PM cocktail receptions and Partnering at bioLIVE - powered by Inova

www.bio.live

ADJACENT TO
CPhI worldwide

Antibody About Turn

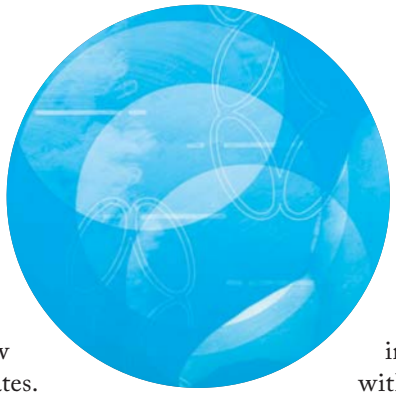
A promising candidate is on the verge of entering clinical development… What happens when you see an opportunity to make it even better? Do you delay – or stick with it in the hope that it's "good enough"?

By Sam Cobb

The introduction of antibody therapeutics has been one of the greatest, recent advances in drug development. These are often thought of as the large molecular weight monoclonal antibodies, but there are many other interesting antibody formats too with significant potential for human medicine. I am the founding CEO of AdAlta, a company that was launched with a focus on both shark antibodies and a human equivalent called the i-body. Both the shark antibody and the i-body have unique characteristics that support their inclusion in this next generation of antibody therapeutics.

A traditional mAb possesses both a heavy and light chain, but shark antibodies have only a heavy chain (similar to camel antibodies, which are attracting a great deal of attention in the research community). Both shark and camel antibodies have a very long CDR3 binding loop. The traditional binding loop in a human antibody is 8-10 amino acids, but in the shark it can consist of up to 30 residues, increasing binding affinity. Shark proteins are also very stable, you can boil them or put them in acid! We have even put the i-body and shark antibodies in proteases and found that they did not degrade.

Some companies are looking to use the actual shark antibody as the basis for a biotherapeutic, but we have instead used them as a blueprint to engineer two loops into a human protein; one of the loops is extremely long like that of the shark antibody, enabling tight binding to the drug target. This new engineered human protein is our i-body. It is a proprietary



technology of AdAlta and we've developed a library containing billions of i-body compounds that are unique, which can easily be screened against any disease target to identify new innovative drug candidates.

i-bodies, as well as shark antibodies, are certainly interesting, but rather than dive into the details of our platform I wanted to share an important lesson we learnt through the development of our lead candidate...

Prior to commencing my current role at AdAlta, I worked as a research scientist developing diagnostic tests. I also studied law part time and did a Master's in intellectual property law, which gave me a great introduction to the business side of science. This led me to work in technology transfer with several Australian universities, including one that set up a cooperative research center focused on diagnostics – bringing together 12 partners from industry and academia. When government funding for this program ended, it was my job to help wrap it up – and as an outcome of this, AdAlta was spun out and I joined the company as the founding CEO.

When we first started out, we had the two technologies – the human i-body and the shark antibody. Eventually, we reached a crossroad: did we focus on the shark, or did our human i-body

"The positive data for this molecule just kept on coming, and in January 2017 we received orphan drug status from the FDA."

Series K2P
powered iris valve technology

- Extensively used in the pharmaceutical and food sectors
- FDA approved diaphragm materials
- Full product flow control
- Non-jamming
- No mechanical parts in contact with product
- Slim design
- Electric or Pneumatic actuation
- ATEX approved Cat. 1D/2D

mucon.com
sales@mucon.com | +44 (0)1625 412000

Mucon is a registered trademark of Process Components Ltd

"Many promising drugs enter clinical trials but then fail because of a lack of efficacy in humans."

hold more promise? When we received private venture capital investment in 2011, we pivoted towards the human i-body platform.

The i-body library generated a number of potentially therapeutic molecules, with the most promising being AD-114 – an i-body that demonstrated efficacy against the chronic lung disease, idiopathic pulmonary fibrosis (IPF). Importantly, the drug only has an effect on diseased lung tissue because our target (CXCR4) is highly expressed in IPF lung tissue and not present in normal lung tissue. This means the drug is less likely to have unwanted side effects. The positive data for this molecule just kept on coming, and in January 2017 we received orphan drug status from the FDA. There was also excitement in the patient community about AD-114 and we were invited to conferences to talk about our work.

To pivot or not to pivot

Throughout the development of AD-114, we have had consistent dialogue with potential pharmaceutical partners as well as our exceptional scientific advisory board, which includes executives from Pfizer and Novartis. They have developed over 10 well-known products currently on the market, including Viagra, Zithromax, Xolar, Seebri, and several other still in clinical development. Our director, Robert Peach (the founding scientist of Receptos, which was acquired by Celgene in 2015), was also involved in the development of Orencia, a multi-billion dollar Fc-fusion drug product for the treatment of rheumatoid arthritis.

AdAlta's scientific advisory board raised the idea of an Fc-fusion version for the i-body platform. Pharmaceutical companies had also provided AdAlta with initial feedback regarding the half-life of AD-114; while patient demand for novel IPF treatments is high, a longer half-life would be more desirable.

The generation of the AD-114 Fc-fusion and the preliminary evaluations generated data to show that by combining two of the AD-114 molecules with an Fc fusion protein, the new molecule (AD-214) resulted in the same pharmacology, but improved potency and drug half-life.

We were so close to entering the clinic with an already promising protein, but suddenly we had this new data which demonstrated improved activity and half-life. What should we do? Do we continue with the old design or delay clinical development to pursue this new version of the protein?

Further Reading

K Griffiths et al., "Anti-fibrotic Effects of CXCR4-Targeting i-body AD-114 in Preclinical Models of Pulmonary Fibrosis," Scientific Reports 8 (2018).

K Griffiths et al., "i-body AD-114 targeting CXCR4 has Anti-fibrotic Activity". Presented at the IPF Summit 21-23 August, 2017, Boston, USA.

K Griffiths et al., "i-bodies, Human Single Domain antibodies That Antagonize Chemokine Receptor CXCR4," JBC 10 (2016).

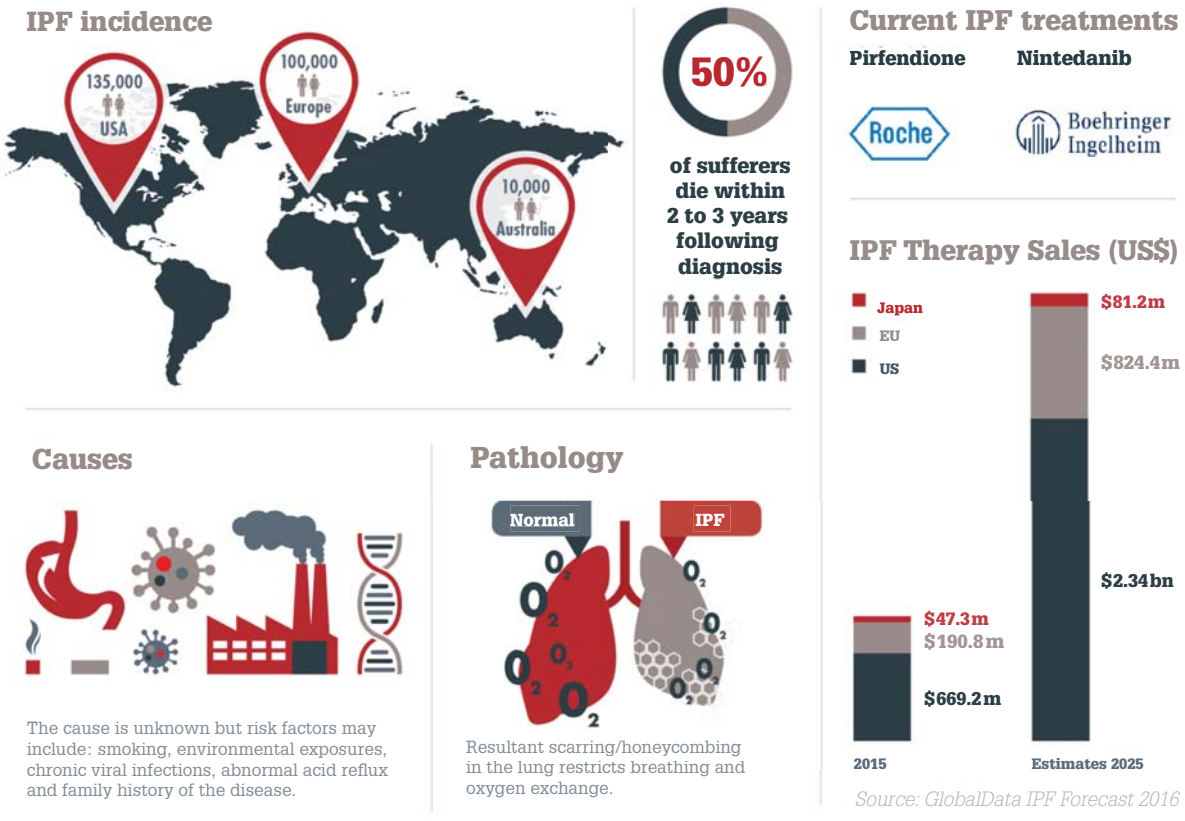
galenIQ™ –
the bulk filler-binder.
Great choice.
Great taste.

- galenIQ™ is pharma-grade Isomalt (Ph. Eur., USP-NF, BP, JP) that makes medicine taste pleasant.
- The filler-binder with sweet sugar-like taste.
- Due to its multifunctionality your best choice excipient to be used for a broad variety of dosage forms.

Our team of experts is available for your product development with galenIQ™.
Please contact us: **info@galenIQ.com · www.galenIQ.com**

Come and visit us at
CPhI worldwide
9-11 October 2018
IFEMA, Feria de Madrid, Spain
BOOTH #8F90

galenIQ™
a brand of beneo



Follow the science

Many promising drugs enter clinical trials but then fail because of a lack of efficacy in humans. We wanted our molecule to have the best chances of making it through clinical trials. And so, when we saw the improved potency and half-life, it was (almost) a no brainer. Redesigning the molecule would give it higher efficacy and enable less frequent dosing, which would be an advantage for patients – right?

But once you are at the tantalizing step of entering the clinic, it can be difficult to turn back. Many companies at this point may already have developed their cell lines, designed the manufacturing process and performed toxicology studies. If you want to change something you need to start over, which is not cheap. Many small companies are also always in a race to reach the clinic while they still have money, or to reach investor milestones.

However, you cannot ignore the data that's right in front of you and the advice of potential partners. We opted to redesign the molecule and delay our entry to the clinic. Our board of directors also understood and, therefore, agreed that pursuing this new approach was the right decision. The redesigned molecule is called AD-214 and contains two AD-114 i-body molecules that bind with high affinity to the human target CXCR4 to elicit anti-fibrotic activity and the Fc-Fragment to improve the half-life.

It was not an easy decision for us. We were fortunate not to have commenced toxicology studies, but we will have to repeat our manufacturing work. Manufacturing an Fc fusion protein requires a completely different process to what we had set out for AD-114 – and we've had to look for experts in the area to assist. To reach our final goal posts, we've partnered with specialist companies to help us – Selexis SA for

IPF Outlook

Idiopathic Pulmonary Fibrosis (IPF) is considered the most common Interstitial Lung Disease (ILD) and results in scarring of the lungs, which gradually worsens until patients find it difficult to breath. Prognosis is poor and there are only two existing treatments. Both slow the disease but there is no cure and patients generally only survive 3–5 years. The scarring process is thought to be driven by collagen-expressing immune and structural cells. CXCR4 is seen as a candidate therapeutic target for IPF because of its role in the recruitment of CXCR4+ fibrocytes from the bone marrow to fibrotic lung tissue, and its increased expression levels by structural cells in fibrotic lung tissue.

cell line development, and KBI Biopharma for process development, analytical development, formulation development and clinical manufacturing services. We should be ready for toxicology studies in the second half of 2019, and be in the clinic early in 2020.

My key advice for all companies? Surround yourselves with good scientific advisors – and then heed their advice! The feedback of our scientific board has been invaluable in this early stage of development and it's really exciting to see what an impact it has made to the protein. I would also say it's also never too early to speak with potential pharmaceutical partners about what they are looking for in terms of a partnered drug candidate. Getting their feedback helped us to make the decision to improve the potential therapeutic application of our i-body. The delays are frustrating given that we were so excited about the original protein, but the new data has given us even more confidence that we will be able to bring a new effective treatment to market for patients.

If we had gone through with the trial, and the results had come back negative because of the half-life or efficacy, it would have been far more frustrating and painful! It is much more difficult – and expensive – to make changes later on; it's far better to uncover potential problems in the early stages and to address them before entering the clinic.

Sam Cobb is CEO of AdAlta, Australia.

Nemera

Patient-focused
drug delivery devices

Drug Delivery Devices
Innovative developments
Customized solutions
GMP contract manufacturing

we put patients first

www.nemera.net
information@nemera.net • Phone: +33 (0)4 74 94 06 54

CPhI Pharma Awards 2018

9 October 2018
Eurostars Madrid Tower
Madrid, Spain

Brought to you by:

CPhI worldwide | P-mec | InnoPack | ICSE | FDF

Recognising Excellence in Pharma

The CPhI Pharma Awards celebrate thinkers and creators breaking new ground in the industry.

Enjoy an amazing night at the **CPhI Pharma Awards Gala,** held at the luxurious Eurostars Madrid Tower Hotel! **Connect with over 500 industry leaders** in a celebratory setting, network, receive recognition and boost your company's profile!

All pharma and biotechnology companies are welcome!

BOOK YOUR SEAT FOR THE PRESTIGIOUS CPHI PHARMA AWARDS GALA

awards.cphi.com/gala

UBM

NextGen

R&D pipeline
New technology
Future trends

The Medicinal Chemistry Puzzle: Lessons Learned with James Hitchin

From big pharma, to cancer research, to joining a fast-growing CRO, James Hitchin has gained multiple perspectives on a subject that has become his passion – medicinal chemistry. Here, he reflects on the changing landscape within the UK, its impact on his career path, and the pitfalls and perks of the field.

By James Hitchin

Always try to gain exposure to talent…

After completing a PhD in synthetic chemistry at the University of Liverpool in the UK, the first industry position I had was with Pfizer. I was promoted after a few months to lead six people in the synthetic services team, as well as running some synthesis myself. This position exposed me to a wide range of chemistries, different therapeutic areas, and a lot of talented people. After that, I experienced different roles and working practices in several companies. I initially moved up to Scotland to work for a Finnish company called Kemira Kemfine, where I was employed as team leader, running GMP manufacturing processes for a range of big pharmaceutical partners. I subsequently headed south to Dorset, where I worked as a chemistry leader for SAFC Pharma for three years, again working on the development and implementation of GMP manufacturing processes of APIs. It was a fascinating role because I was involved in everything from really small-scale medicinal chemistry work, all the way up to large-scale manufacturing processes that were conducted in their pilot plant facility. Some of these materials were also taken into human clinical trials at various stages. However, SAFC began consolidating their interests in the UK in 2009, which prompted me to move into a different kind of role – a senior scientist with Cancer Research UK (CRUK).

But don't forget clinicians and patients!

At CRUK, I had the opportunity to work on a wide range of projects, from hit finding all the way through to lead optimization. One of the projects I worked on is currently going into preclinical development for the treatment of breast cancer, so this was a really interesting time in my career and very different to the commercial work that I had been involved with before. I was also able to contribute to a large number of publications.

The way in which the organization was set up meant that we were embedded within the Christie NHS Foundation Trust in Manchester, UK, which functions exclusively as a cancer hospital. At the time, CRUK had a strategy of creating drug discovery units (DDUs) which they embedded in specialist locations, giving us direct interaction with clinical researchers at the cutting edge of cancer research. They were generating novel discoveries, and we were getting pre-publication access to the information that they were finding – some of which was related to novel therapeutic targets. Part of my role involved being a key liaison for the cancer research community in Manchester, which meant that I got to do a lot of work with clinical researchers and interact directly with patients.

I have so many memorable moments from my work at CRUK. I remember one woman presenting with leukaemia. At that time, we were working on a program with a specific target: lysine-specific demethylase 1 (LSD1), which is linked to acute myeloid leukaemia (AML). We'd synthesized some small molecules within the unit, which we prepared as compounds against LSD1 for one of the clinical fellows in the hospital. He took a blood sample from this young lady, and confirmed that she had AML. He brought the sample back to his lab, took a solution of our compound, treated the

sample with it, and cultured the cells. He was able to show that the compound was having an effect on the disease state, leading to differentiation of these leukaemia cells. This was the power of our position within that unit – you could make discoveries and potentially follow up on them immediately. Ultimately, the work led to a clinical trial.

Keep your eyes on the end result

One of the big philosophies of CRUK was the importance of target validation – being able to demonstrate categorically that if you modulate the activity of a particular protein, for example, that it is going to deliver a desirable therapeutic benefit. No matter what therapeutic area you are working in, it is important to remember the "line of sight to the clinic" – and that means being able to ask clinical researchers and doctors about the relevance of your work.

Having such expertise and insight to draw on helped massively with our task of identifying new targets and validating their role in cancer. We were then able to set up robust screening platforms to identify relevant small molecules, allowing us to thoroughly interrogate their pharmacology, and show in vitro and, ultimately, in an in vivo setting, that modulating the activity of a given target was going to deliver the desired benefit in a patient. Coupled with the expertise of our biochemistry and cellular pharmacology colleagues in the DDU, this work provided a solid platform for full target validation.

Know when to move on

"Moving on" has been a theme throughout my career. I stayed at CRUK for a long time until eventually, I felt that I'd gone as far as I could. My goal was to learn about the drug discovery process in an oncology setting, and to play a small role in delivering molecules that would have an impact on oncology patients – and I feel that I had achieved that. So, what was next? I needed an opportunity for change, and for personal growth.

That opportunity came at Charnwood Molecular, a UK-based contract research organization (CRO) with research sites in Loughborough and BioCity, Nottingham. Joining the company as Head of Medicinal Chemistry and Site Director at their BioCity labs gave me the opportunity to drive the expansion of their medicinal chemistry services, which sit alongside their synthetic and process research chemistry offerings (predominantly carried out in Loughborough). Speaking with the senior management team and owners at interview, I could see that they were heavily invested in the idea of building a world-class offering, and would be supportive of continuing to build a highly skilled team. Although I'd only ever looked after relatively small teams before, we are now close to employing 50 scientists across the company, up from just around 30 when I joined Charnwood at the end of 2016. The number of scientists at BioCity has almost tripled! In fact, our company has more than doubled its turnover in the last three years, and we have recently won a regional award for Export Achievement. In short, we delivered on our shared vision of an aggressive expansion – and it continues apace!

We now have many projects in medicinal chemistry, and we're continuing with our traditional strengths in synthetic chemistry projects too. So, although I loved my time with CRUK, it couldn't give me the opportunity I have now.

Outsourcing is growing, but people want to be close to home

Being at Charnwood as it grows so quickly is exciting, but you do have to consider how to grow sustainably when the industry is

changing so much. I did an industrial year for Roche in 1999 in Welwyn Garden City; however, that site is no longer occupied by Roche – a similar and unfortunate development to that occurring at several other big organizations and sites that I used to work for. Some of these organizations have closed down their main research and development facilities in the UK, opting instead to outsource large amounts of their chemistry to CROs, like ours, allowing greater flexibility and cost savings. This has changed drug discovery considerably; however, as the cost differential between different countries narrows and therapeutic companies focus more on the added value propositions of their outsourcing partnerships, we're seeing a lot of work that was traditionally done in the Far East coming back to the UK.

Many people were initially worried when larger companies began contracting out work and pulling out of the UK as a research location – there was a real fear that it would result in a skills gap, but contract research organizations, biotechs and academic groups are keeping skilled people in the UK, and supporting the skills required for drug discovery for the next generation of scientists coming through.

Stay on target

To succeed as a medicinal chemist, you have to be interested in solving complex, multi-parameter puzzles. Medicinal chemistry is the practice of designing small molecules – in principle to ask specific pharmacological questions about specific biological targets. If you can create a measurable effect, you gain a better understanding of your target and how it impacts the body. Next, you can work to design and optimize your compounds further. It's almost like Lego on a molecular scale, but you have a strict set of parameters that you need to work within to eventually deliver compounds that will have the intended effect in a clinical setting (line of sight to the clinic!), whilst also avoiding unwanted side effects.

One obvious prerequisite for a successful molecule is potency against the target. In our projects, clients often come in with high-throughput screening data and have a few initial hit series that they'd like us to develop further. It's all about prioritizing these hit series and understanding their potential limitations. This initial investigation can be used to prioritize hits that don't contain any concerning structural features. At this stage, it's also important to have a good understanding of the exact property profile that you're looking for – generally referred to as a target product profile. You need to understand what you want in a hit or a lead compound, and understand the potential complexities and pitfalls you could face – it's crucial to make good choices at the beginning of the process and pick a candidate that has the potential to go all the way.

Obviously, this is a multiparameter optimization process – your molecule has to have the right properties, but also unique structural characteristics that provide strong intellectual property position for eventual patenting purposes. Potential liabilities include poor solubility or poor permeability. Lipophilicity is also important to consider – if your compound is too lipophilic it can lead to high levels of metabolism, poor solubility and off-target effects. You have to really understand your compound and be able to juggle all of these parameters in a way that allows you to produce something that is well tolerated by the body, is rapidly absorbed, and goes directly to where you want it to be – and then stays there long enough to elicit the desired effect. Certainly, it's a complex and challenging task, but it's important to remember that there is a wealth of information to be found in the literature. You can learn a lot from compounds that have been made previously; why not benefit from the hard work and hard-fought victories of yesteryear?

Scaling up isn't simple

Many projects that I've worked on in the past have come from big pharma companies, and it is often the case that you are handed a medicinal chemistry-scale route that is not suitable for large-scale manufacture – usually because of time constraints and market pressures. I have fond memories of one client who said, "We've only ever made several 300 mg batches of this material, but we now need 20 kg – here is the eight-stage linear route that we used. We need the material in three months." Unfortunately, because of the different requirements and

CPhI worldwide

Co-located with:

P-mec | InnoPack | iCSE | FDF

9 - 11 October 2018
IFEMA, Feria de Madrid • Spain

Adjacent to: bio LIVE

CPhI Worldwide - the world's leading pharmaceutical exhibition

REGISTER NOW
gotocphi.com/register

WHY ATTEND CPhI?

- **Cost Effective: 45,000** pharma professionals from **150+** countries in one location
- **Entire pharma supply chain: 2,500+** exhibitors covering **ingredients, APIs, excipients, finished dosage, contract services, packaging, machinery** and more
- **Industry developments:** stay up-to-date on market news and trends during the **CPhI Pharma Innovation Awards and Pharma Insight Briefings**
- **Free access: 1 ticket, 6 shows,** 150 free seminars, innovation tours, innovation gallery and matchmaking

"...you can actually come and see what everything under one roof means!"

Taru Jain
Senior Manager, Akums drugs and Pharmaceuticals

"CPhI is a big event with participation of almost all pharma companies across the globe"

Shailesh Shinde
Head of Business Development
Callidus Research Laboratories

Join the conversation
@cphiww

Organised by
UBM

pressure of the two disciplines, you often receive a route and immediately realize that it is based on processes or materials that you simply can't use on a larger scale. Scale up is a completely different mentality to the early stages of drug discovery! A former colleague of mine once said, "There are two yields in medicinal chemistry: no yield, or some yield." But in process chemistry, you should be getting as close to 100 percent yield as possible with the cleanest possible profile. For every single impurity that appears in that reaction, you need to know why it's there, how it's formed, and develop a really intimate understanding of the process so you can control it, and understand entirely how different parameters will impact on the outcome of the reaction.

However, synthesis is usually a means to an end for a medicinal chemist – they just want the molecules needed to interrogate their targets. Asking a medicinal chemist to focus on scaling up can take away from their core activities. Another mistake I often see is too much focus on the synthetic tractability of a compound series – if you have five similar hits from a screen, people may choose the one that looks easy to make. In my view, that is always a bad decision – if you're basing your choice entirely on synthetic tractability, you are missing a trick! Some of the best compounds can be the most difficult to synthesize. Perhaps counterintuitively, if you spend a bit more time figuring out the challenges in synthesis, you could ultimately end up with something more interesting not only in terms of its medicinal chemistry properties, but also more amenable to process-scale chemistry because you took the time to understand it in the first place.

Failure should be shared

In my experience, one of the most common pitfalls in medicinal chemistry is poor target validation. You have to be absolutely sure that modulation of the target will deliver the desired therapeutic benefit (preferably before you've invested millions of pounds!). It still surprises me how often you see weak target validation in terms of the link between their target and a disease, and how far they've gone to convince themselves that their target is important. I've seen a few projects come unstuck this way. Often, it isn't reported as it's seen as a source of embarrassment, but it's probably costing the industry a great deal of money, especially as other companies will repeat the same mistakes.

"Investments are being poured into new technologies, such as CRISPR gene editing and artificial intelligence."

Investments are being poured into new technologies, such as CRISPR gene editing and artificial intelligence. Many groups are now using these techniques in conjunction with existing target validation platforms to identify new targets, and improve our understanding of disease-related pharmacological processes. It is well documented that the reproducibility of novel landmark studies in leading peer-reviewed papers (the results of which are used across the industry as a source of new targets) can be as low as 20 to 25 percent.. During my time at CRUK, it was always stressed that although you may see something in the literature suggesting a particular target is interesting, you must always repeat the experiment, and then expand upon it, using different cell lines, tissue types, and so on. This is also why small molecules are so important: if you use gene editing to remove a protein from the system, you may see an effect that is different to what might happen if you modulate the activity of the target with a small molecule instead, indicating, for example, that the protein may be involved in an important protein-protein interaction.

Knowledge is out there – computers can help us find it

Looking forward, many new tools are being developed to help with molecule design. We are beginning to see machine learning and artificial intelligence applied to reaction optimization and route selection, and it appears to be effective, in some cases, for delivering efficient processes and designing molecules based on X-ray crystallographic information, for example. I predict an increasing role for computational approaches in the future as they should be able to reduce the amount of time we spend working out certain problems. In some respects, this will help to eliminate human error and allow us to look at large data sets much more objectively and effectively, and use them to direct design. There's a whole wealth of information to be found in the literature, and any systems or platforms that will allow us to consolidate and interrogate that in a way that improves drug discovery can only be a good thing. However, there's still a lot to be said for human experience! I think the real benefit of computational approaches is helping people access the information they need to ask the right questions of their target in a structured and rapid way.

The ultimate objective is to find a compound that makes it all the way to market to have a positive effect for patients. I can only hope that by the end of my career, I have been able to be part of delivering several drugs that impact patients, allowing people to live richer and fuller lives – that would be a wonderful thing to achieve.

James Hitchin is Head of Medicinal Chemistry at Charnwood Molecular, UK.

BIOPHARMA TRENDS

NOV 13 – 14, 2018
CORK, IRELAND

INDUSTRY 4.0: REVOLUTION, EVOLUTION, OR SPECULATION?

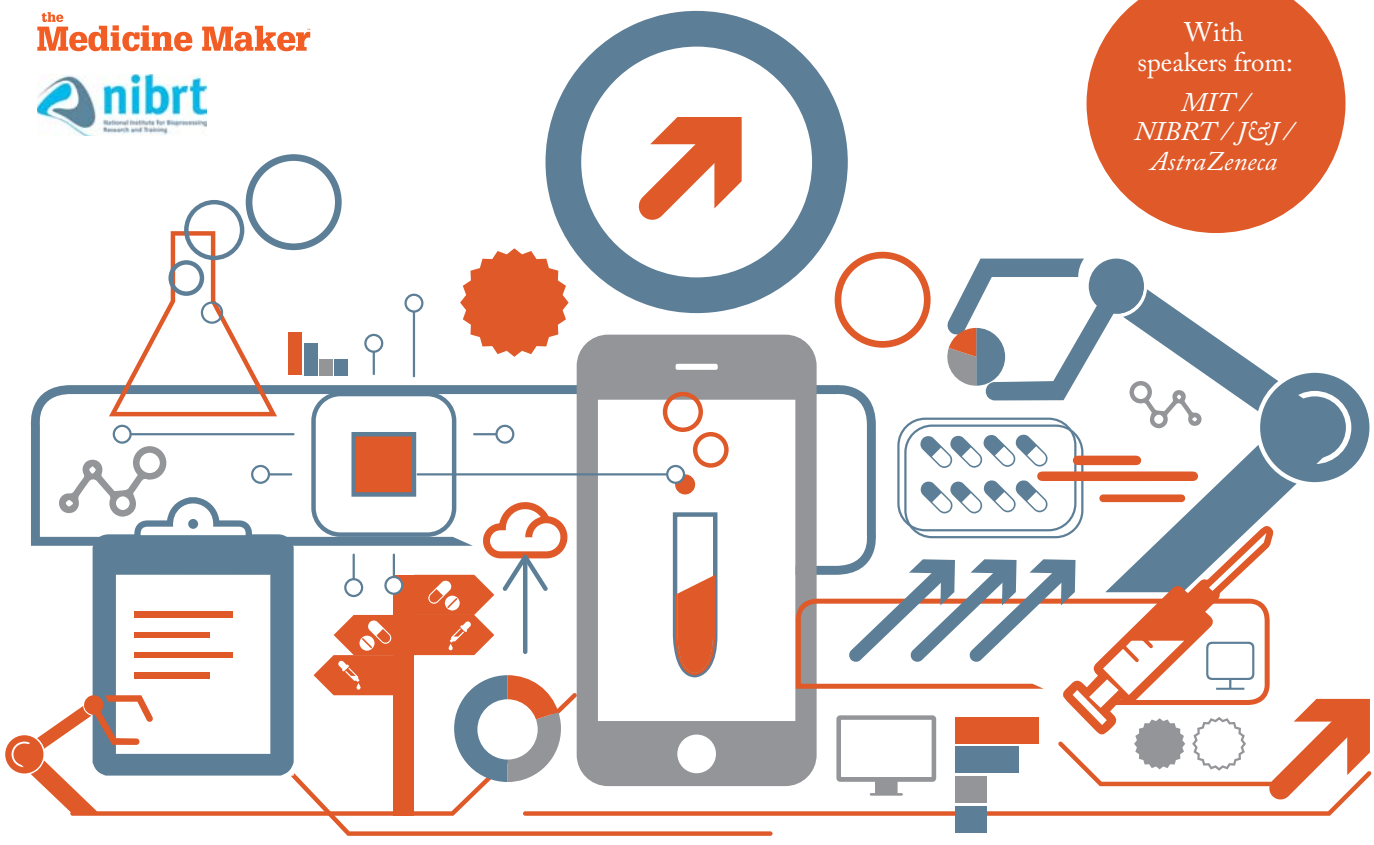
Join us at Biopharma Trends 2018 as we explore the impact of Industry 4.0 on biopharmaceutical manufacturing

Supported by

the Medicine Maker

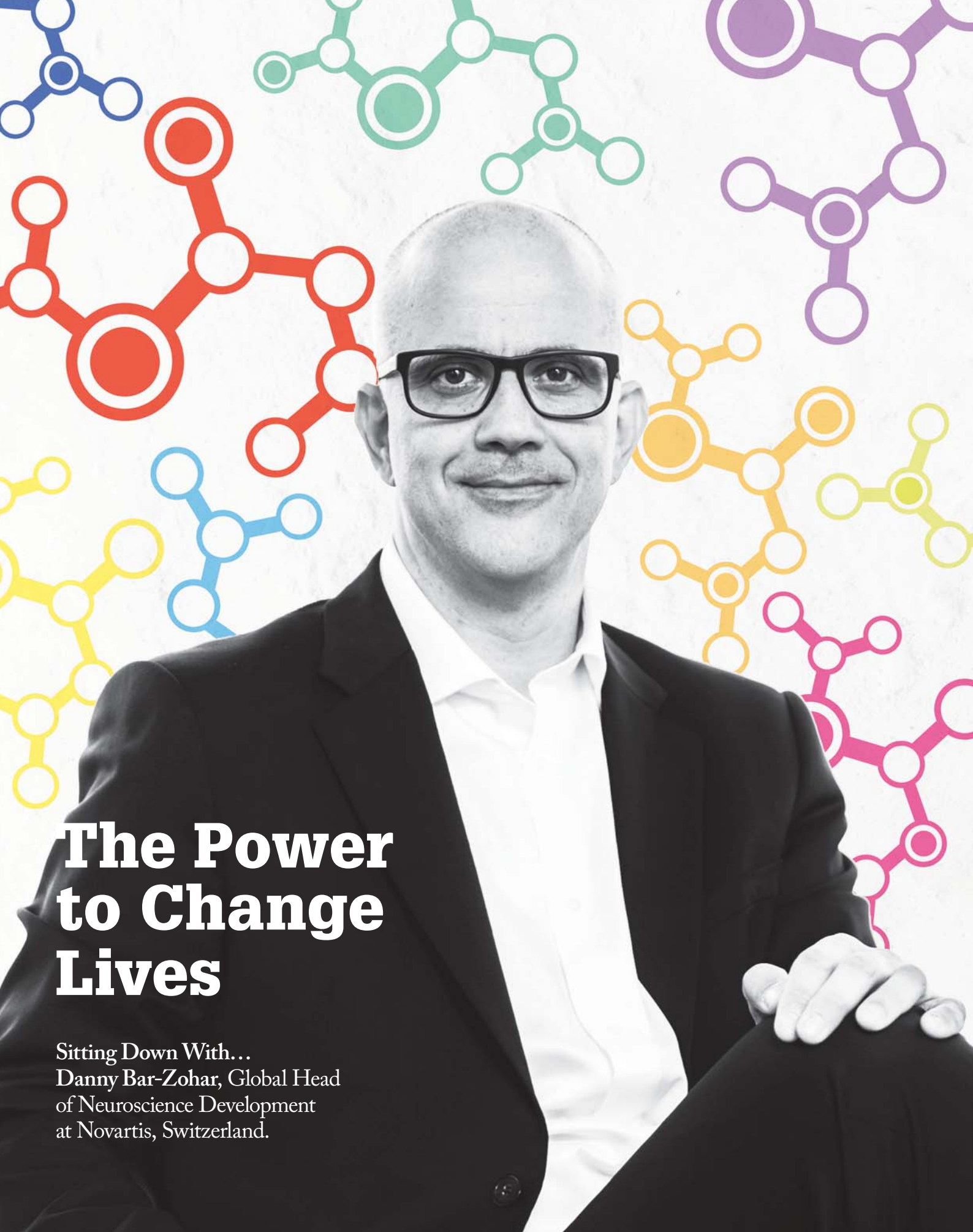
nibrt

With speakers from:
MIT / NIBRT / J&J / AstraZeneca



VISIT WWW.BIOPHARMATRENDS.COM TO FIND OUT MORE AND REGISTER

#BIOPHARMATRENDS



The Power to Change Lives

Sitting Down With…
Danny Bar-Zohar, Global Head of Neuroscience Development at Novartis, Switzerland.

Why neuroscience?

I've always been driven by questions. Why? What if? How? And I've always been practical and willing to take action. Looking back, I must have been a very annoying child! Despite my current role, I am not a neuroscientist by background. I initially chose to become a surgeon. My main focus was on trauma and transplantation, but I was fascinated by the science behind what I was doing and, in particular, the connection between the brain and the gut. Surgery, of course, is not a place to ask too many questions! Working in neuroscience today fulfils my need for acting and science – asking questions about the brain and taking those questions to a practical end point – a new drug, or a new solution for humanity.

Can you remember the first time you made a real difference to a patient's life?

At the hospital, there were many significant moments. In trauma and transplantation, there can be a lot of drama. I have worked with patients facing a total loss situation – physically and mentally – but then twelve weeks later I've seen them in café or elsewhere with their life back on track. When you see that, you know you've done something remarkable.

In surgery, you see the impact of your actions first hand, but there is also a conglomerate of more invisible players that go into making a patient's life better. In the pharma industry, I'm no longer in direct contact with patients, but a few years ago at a Novartis event I met an associate with multiple sclerosis. Over a five-year period, she experienced 14 attacks of blindness and loss of motor control when she was on an injectable therapy. She then started taking Novartis' Gilenya (fingolimod) and had no further attacks over a three-year period. She got a job and was identified as a significant talent in the organization. Put simply, she got her life back – thanks to that drug. Even in less dramatic cases, if someone takes a medicine and feels better, instead of staying at home and feeling ill they may go on to have the most important day of their lives. Medicine creates opportunities and changes lives.

How did you adjust when moving to pharma?

In surgery, you tend to feel alone; it's just you, the patient and God (or whoever you believe in). The success or failure of that surgery is on your shoulders. Drug development is about working as part of a team. You are not expected to know the answers to everything but you need to ask the right questions at the right time and accumulate knowledge. It was challenging to adjust to a new mindset.

I remember seeing a presentation about the clinical trial results of Gilenya. It had a super complex mechanism of action and I was fascinated. Years later, I had the opportunity to apply for a position at Novartis, as well as a similar position at a different company in the US. Both offered similar challenges but Novartis' company culture seemed more balanced and collaborative. My journey as a Novartis employee began in 2013.

What achievements are you most proud of?

I am incredibly proud of our pediatric MS work; Novartis was the first company to start and complete a controlled, randomized trial specifically for pediatric MS. The findings showed unprecedented efficacy in children and so the drug is now on the market (FDA approved) making a big difference to young patients.

A significant personal achievement has been recognizing that I cannot be an expert in everything! Whether it's clinical trial statistics, basic science, or regulation, you need the right people with you, and you need to create the right atmosphere between them. I enjoy seeing the spark in the eyes of my people – my role is to encourage them to innovate outside out of the box – or at least be able to think in a different box.

Why has neuroscience proven so challenging?

The brutal truth is that everything in neuroscience drug development works against you: we do not have a full understanding of the central nervous system; it is difficult to deliver medicines to the brain without off-target effects; there are no good biomarkers; many of the degenerative diseases require long follow ups and thousands of patients who may have other co-morbidities. The costs of trials are also enormous…

To succeed, you need to balance your portfolio carefully and not put all of your eggs in one basket. But as well as de-risking your portfolio wherever possible, you also need to ensure that you do not miss the boat. Incremental improvement is easy, but will hardly take us anywhere. Developing, for example, an anti-depressant with 10 percent fewer adverse events is OK, but – as it will require full development cost – will this move the needle in meeting huge unmet need? And that's time and money that could instead be invested into something more pioneering and life changing, such as cell or gene therapy. Drug developers should strive to make the standard of care nothing short of obsolete.

Importantly, although the instinct is to fight the fear of failure, I would recommend embracing it. Embracing failure means first learning from it, acknowledging the fear and not letting it deter you from pursuing the next science-based innovation to change people's lives.

Catalent®

COME VISIT US AT CPHI 2018
STAND 3D10

DEVELOPMENT

your molecule has so much potential. our passion for development will help unlock it.

As the #1 global leader in drug development, Catalent's comprehensive capabilities, robust scientific approach, and broadest selection of enabling technologies can help you overcome the toughest development challenges. With the acquisition of Juniper Pharma Services in Nottingham, UK, Catalent's multi-site network provides innovators with a more complete and integrated solution to accelerate development from clinical to commercial supply.

COMPREHENSIVE DEVELOPMENT OFFERINGS:

CANDIDATE SELECTION & DMPK MODELING
SOLID STATE & PREFORMULATION
PRECLINICAL & CLINICAL FORMULATION
BIOAVAILABILITY ENHANCEMENT
CLINICAL cGMP MANUFACTURING
COMPREHENSIVE ANALYTICAL SOLUTIONS
CLINICAL SUPPLY SERVICES

EXPANDED OPTIFORM® SOLUTION SUITE

One accelerated, flexible, and data-driven solution combines all analytics, services and materials your molecule needs from candidate selection into Phase 1.

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™
us + 1 888 SOLUTION (765-8846) **eu** 00800 8855 6178 catalent.com/optiform

© 2018 Catalent Pharma Solutions. All rights reserved.