SEPTEMBER 2016 # 22

the Medicine Maker

Clinton or Trump

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Online this Month

Obama's Legacy

Our cover feature on page 32 examines the potential pharmaceutical pricing changes that may be introduced after the US elections in November, given that both candidates view the rising costs of medicines as something that must be combatted. But when looking at US politics, we should not forget the current President, Barack Obama, and the Affordable Care Act. Read more about the history of Obamacare and how the pharma industry has been affected on our website.

http://tmm.txp.to/0816/Obama

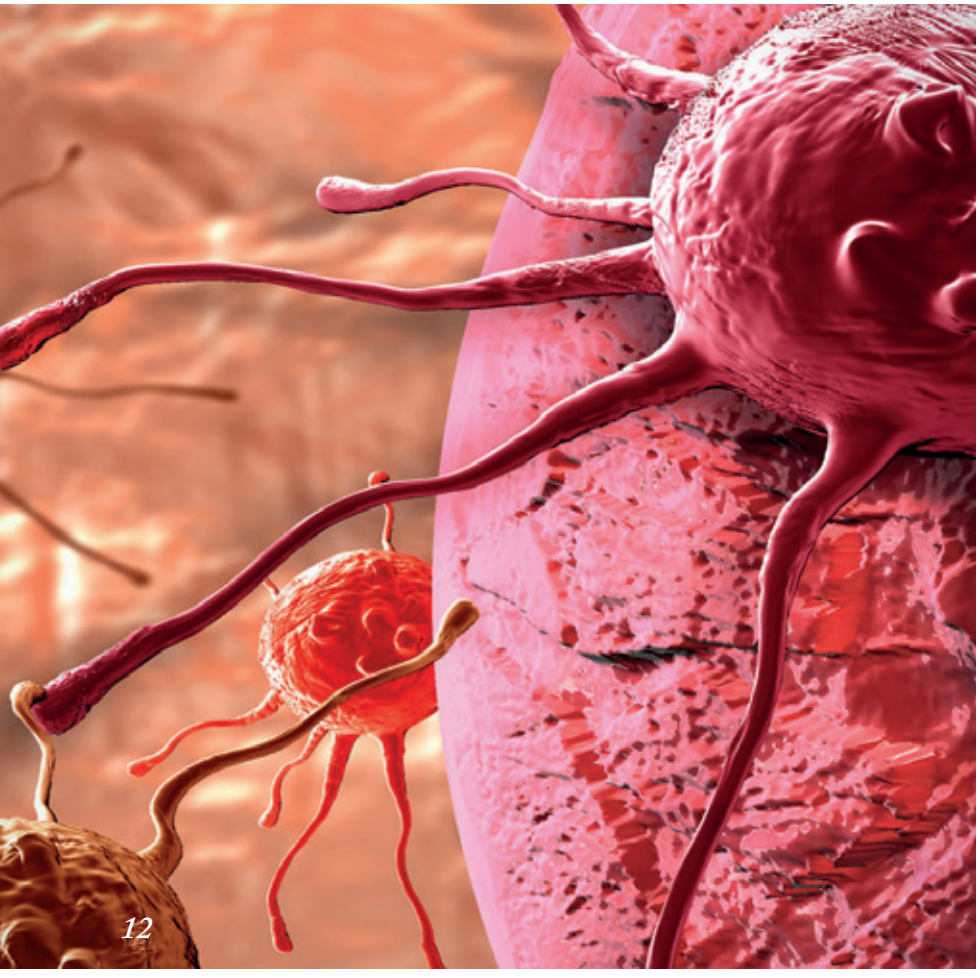
You've Got the Power

Nominations for The Medicine Maker Power List 2017 are open. Who are the most influential and inspirational individuals in drug development and manufacturing? It's up to you to decide. You can submit a nomination via our website http://tmm.txp.to/2017/powerlist or email: james.strachan@texerepublishing.com. The top 100 individuals, as nominated by readers and chosen by an independent judging panel, will be celebrated in the April 2017 issue of The Medicine Maker.

The Innovation Awards

Innovation is the bread and butter of the pharma industry, which is why every December, The Medicine Maker celebrates the most exciting and innovative new drug development and manufacturing technologies released onto the market during the past 12 months. Nominations for The Medicine Maker Innovation Awards 2016 are open now, but will close in mid-November. Nominate now via our website http://tmm.txp.to/2016/innovationawards or email Stephanie.sutton@texerepublishing.com.

Contents



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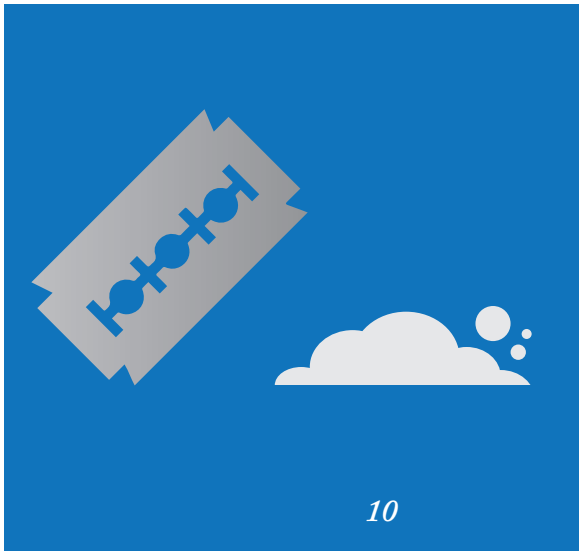

10

On The Cover

It's Donald Trump versus Hilary Clinton for the coveted place in the White House.

Upfront

In My View

Feature

Reports

Best Practice

NextGen

Business

Sitting Down With

the Medicine Maker

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Public Enemy

How can an industry that saves lives be so despised?

Consider all the industries in the world; surely, pharma must be ranked highly in terms of doing good and saving lives? Unfortunately, big pharma doesn't always do a very good job of telling its story. As someone recently pointed out to me, we can easily assess how the general public feels about pharma by looking at fictional villains – pharma companies make frequent appearances. Classic movie The Fugitive, for example, revolves around a covered up drug trial. And in Resident Evil (the popular video game and film series) the 'evil' stems from Umbrella, a giant conglomerate with strong ties to pharma.

Everyone I speak with in the industry is passionate about doing good, so pharma can't be inherently evil, although there are certainly some individuals who portray the industry in a bad light – Martin Shkreli being a notorious example. More recently, the well-publicized price hikes of Mylan's EpiPen seem to have convinced the public that pharma is still everyone's worst enemy. Whereas Shkreli was open that the price increases of Daraprin were to line his own pocket, Mylan has blamed US healthcare insurance for rising medicine costs, and has since doubled eligibility for its patient assistance programs and announced plans to develop a generic EpiPen. However, the company hasn't been forthcoming on exactly why it chose to increase the price so much (more about this on page 22).

The growing costs of medicines is of global concern. Recently, the United Nations released a report on access to medicines (1), with Winnie Byanyima, executive director of Oxfam International, claiming, "This report gets to the heart of the problem with access to medicines – that the intellectual property rules promoted by the pharmaceutical industry are at odds with the human right to health."

Strangely, this statement reminds me of a conversation I had in 2014 with video game designer Tim Wicksteed. With little direct knowledge of the pharma industry, Wicksteed hit the nail on the head when he developed Big Pharma – a video game where players take on the role of running a pharma company. "There are difficulties when you have to make money out of health and medicines," he told me (2). "It's not about choosing to be a 'good guy' or a 'bad guy'... you need money to grow your business. Players may go about this in different ways."

Pharma needs enormous profits to conduct R&D and ultimately survive, but these profits are at the heart of public distrust. Let me conclude with this question: out of all the industries that exist, is it really such a bad thing if the one responsible for saving so many lives is also the richest?

Stephanie Sutton
Editor

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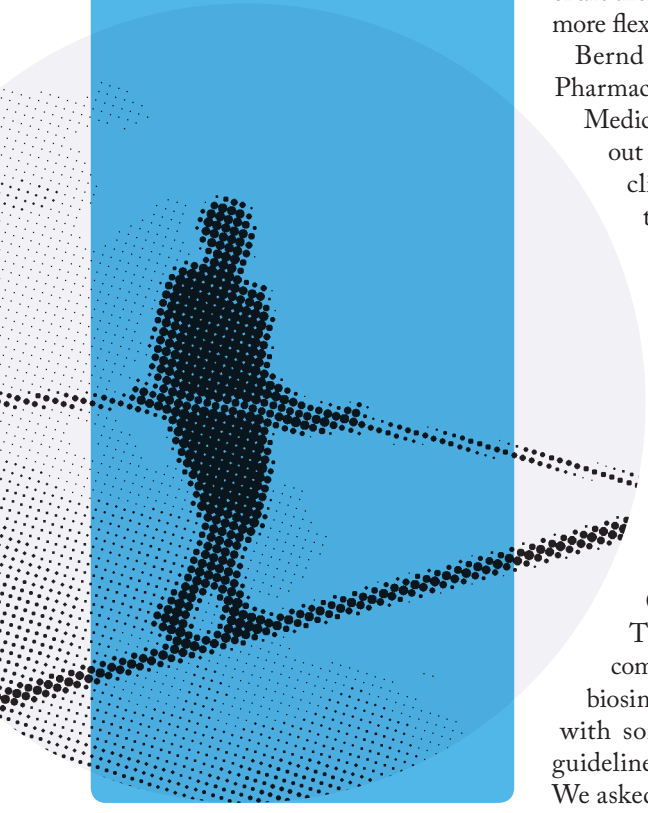
2. *The Medicine Maker, "Game on", (2014). Available at: http://bit.ly/2cM3AL9. Accessed September 15, 2016.*

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



Walking the Biosimilar Guideline

Not all successful biosimilar applications in Europe follow regulatory guidelines to the letter

Biosimilars have been available in Europe for more than a decade and during this time the European Medicines Agency's (EMA's) original 2005 biosimilars guidelines have been regularly updated. Although many papers have been published describing how the regulations have changed over time, few have focused on how these regulations are applied in practice. For example, do all successful applications follow the guidelines exactly or are there instances where regulators are more flexible?

Bernd Jilma, Professor of Clinical Pharmacology, and his colleagues at the Medical University of Vienna, carried out a systematic comparison of all clinical development programs that were approved by the EMA (1). The research was part of an IDEAS project – a European training network for early-stage researchers working on statistical methods for early drug development – and funded by the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement. The researchers found that companies go about demonstrating biosimilarity in many different ways, with some even deviating from the guidelines but still receiving approval. We asked Jilma to tell us more.

What were the main findings of your study?

We found that there is a large variability between the clinical development programs submitted to the EMA for getting biosimilar approval. Clearly, there will always be variability in applications because of the differences in the characteristics of the reference product. However, even for biosimilars with the same reference product, the development strategies could not always be considered comparable; for example, some companies conducted more studies that focused on whether the pharmacokinetics were comparable to the reference product, whereas others put a greater emphasis on clinical trials in patients with the target disease. Our study shows that the details of the development programs are negotiable with the EMA and there are many ways in which companies can show biosimilarity.

Do some applications deviate from the guidelines?

There seem to be some negotiations between companies and health authorities on this matter; for example, by seeking Scientific Advice from EMA when planning a biosimilar drug development program. Our study relied on publicly available information, we have no insights into these. Sometimes, the relevant product-specific guidelines may not have been available at the time the study was planned. In addition, the overarching guideline only gives general advice for biosimilars to all biologics, which might not be applicable to all active substances due to the great diversity between biologics. For example, guidelines ask applicants to add pharmacodynamic markers to the pharmacokinetic studies, but this was not done in three applications we studied. Perhaps the reason for this is that there was no established pharmacodynamic marker.

Where there was no pharmacodynamic assessment, the companies conducted large Phase III trials – and this seemed to compensate for the lack of pharmacodynamic comparison. A very interesting aspect is that some products were approved even though not all primary pharmacokinetic/ pharmacodynamic endpoints met the equivalence margins. In these cases, the sponsor provided additional studies, explanations or modeling results that were convincing enough to make the development program successful. It is important to keep in mind that biosimilars are still fairly new drugs and the process might become more standardized and regulated within the next few years as the industry gains more experience.

Although deviations from the guidelines seem to be possible if justified, not all applications for biosimilars were successful, which shows that companies have to provide convincing evidence to receive approval. We definitely don't recommend companies to embark on developmental programs that contradict guidelines without seeking scientific advice from the regulators.

Do you have any recommendations for the regulators, based on your findings?

The European public assessment reports (EPAR) for human medicines published by the EMA are a great source for gaining insight into the most important factors in the scientific assessment of a new drug. However, to better inform the public, a more standardized format for the scientific discussion section of the EPAR would be desirable. Due to the recent data transparency initiative of the EMA we assume that in the (near) future, even more information will become publically available.

In order to link the results reported in the EPARs to other sources more easily, it would be valuable to also report the registration number in relevant clinical trial registries (such as the EudraCT number) by default for all trials referred to in an EPAR. Furthermore, to understand the rationale of the design, it would be valuable if the underlying assumptions for the sample size calculations would be made publically available in the future – an important example is the choice of equivalence margins in Phase III trials for biosimilars. These margins are crucial for trial success so it would be beneficial to understand the reasons for them.

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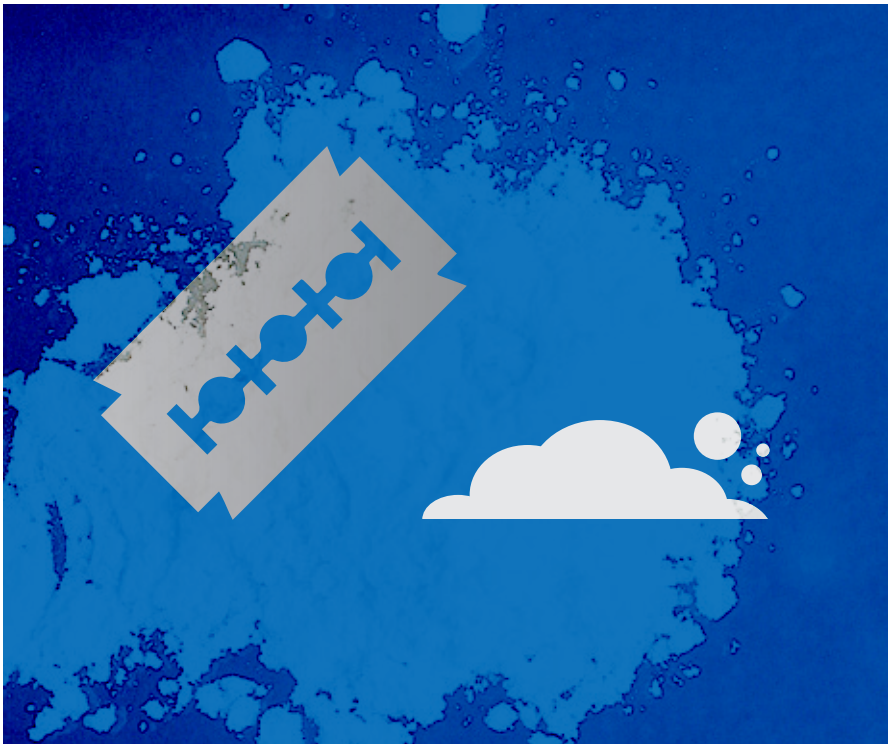
Breaking the Habit

Can a cancer drug be repurposed to cure cocaine addiction?



Illegal drug use is on the rise and there is a need for new treatments that can break addiction, particularly cocaine use, for which there is no approved medication in the US. But perhaps drugs already in development could provide a helping hand.

The key to the transition from recreational to compulsive drug user lies in the creation of long lasting memories and cues that become associated with the intense pleasure felt when taking the drug. This is especially true of cocaine, which produces its addictive effects partially by acting on the brain's limbic system. For a number of years, researchers at Cardiff University in the UK have been studying the Ras-ERK signaling pathway – a neuronal cascade involved in learning and memory, and behavior plasticity – and its role in addiction. Previous animal studies from the researchers have shown that manipulating this signaling cascade can correspondingly change behavioral responses to both cocaine and morphine (1–3).

From there, the research team began to examine whether drugs already in clinical trials could potentially inhibit Ras-ERK signaling (4). "We tested a number of MEK and RAF inhibitors already in clinical trials for cancer therapy, but only one – the MEK inhibitor PD325901 from Pfizer – effectively and completely blocked Ras-ERK signaling in the nanomolar range," says Riccardo Brambilla, lead author of the study and Professor of Neuroscience at Cardiff University.

Brambilla and his collaborators are not just relying on drugs being developed by others; they have also devised cell-penetrating peptides that hold "interesting promises" for CNS drug development. Two of the molecules – RB1 and RB3 – could also block Ras-ERK signaling.

"A single administration of both RB1/RB3 and PD325901 completely blocked expression of cocaine mediated conditioned place preference (CPP) in mice," explains Brambilla. CPP occurs when a subject prefers a location that has previously been paired with something rewarding – in this instance, cocaine. Brambilla adds, "The memory associated with cocaine is likely to be entirely erased, since it cannot be recovered after three weeks from testing."

Next, the researchers are hoping to reach a deal with Pfizer to take PD325901 to clinical testing for cocaine addiction. "We also plan to evaluate the effectiveness of PD325901 and RB1/RB3 in blocking other drugs of abuse, especially legal drugs like nicotine and alcohol," says Brambilla. *JS*

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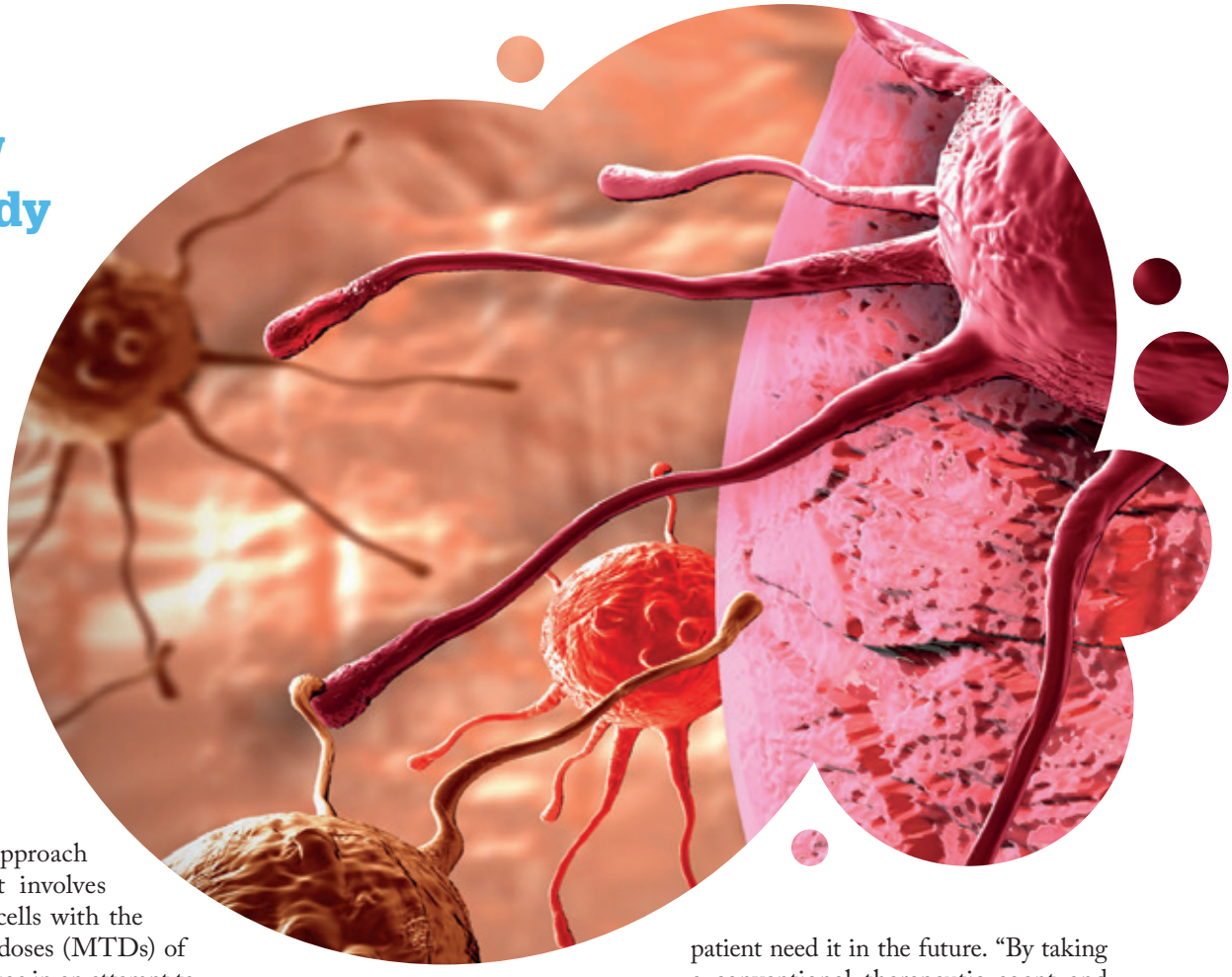
Can Slow and Steady Win the Cancer Race?

Researchers argue it's time to consider cancer as a chronic disease. And that means more frequent treatment at lower doses



The conventional approach to cancer treatment involves bombarding cancer cells with the maximum tolerated doses (MTDs) of chemotherapeutic drugs in an attempt to eradicate the disease from the body. But for more complex cancers, like ovarian cancer, drugs have to be administered in three-week intervals to allow patients to recover from the adverse effects caused by treatment. During this drug-free interval, however, the tumor may reinitiate growth – and resistance to treatment is always a possibility. But what if, rather than treating cancer as an acute disorder, doctors approached cancer as they do chronic conditions, like diabetes?

In a collaboration between US (Pacific University and Oregon State University) and UK researchers (Kingston University), a new study used an approach known as "metronomic therapy" to treat ovarian cancer in mice (1). Metronomic therapy involves administering chemotherapeutic agents at doses significantly below the MTD, but given frequent intervals (several times a week or weekly) with no extended interruptions or breaks. The approach also utilized polymeric nanocarriers to deliver the drugs (paclitaxel and rapamycin).

"We found that the metronomic approach could significantly reduce tumor volume with no acute toxicity over 21 days," says Adam Alani, lead author of the study and Assistant Professor at Oregon State University. "The combination of these agents work synergistically against the tumor microenvironment by inhibiting proliferation and inducing apoptosis of cancer cells, as well as by inhibiting tumor angiogenesis."

Eventually, the researchers hope that such an approach could simplify the treatment regimen, reduce drug related side effects and extend the life of the drugs by preventing resistance should the patient need it in the future. "By taking a conventional therapeutic agent and administering it more frequently in lower doses, using a nanocarrier formulation, the direct effects on cancer cell proliferation can be extended to target the entire tumor microenvironment," says Alani. "The nanocarrier formulation also allowed us to deliver the drugs at doses much higher than the commercially available formulations – making possible their potential use in traditional MTD based treatment regimens."

Next, the research team will assess the effect of the developed nanocarriers on the immune response in ovarian cancer orthotropic models. *JS*

Reference

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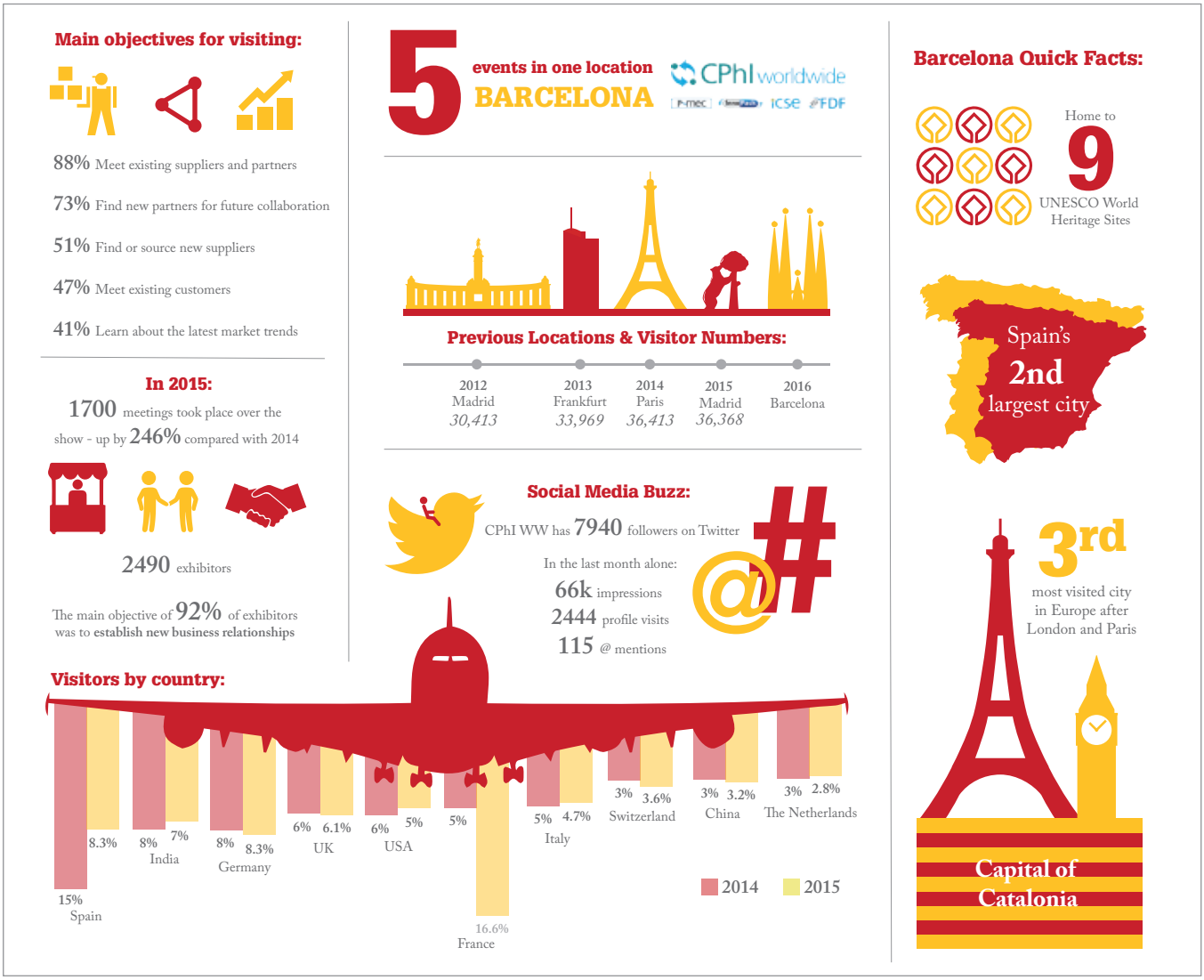

CPhI in Numbers

CPhI returns to Spain for the second year in a row, but it is the show's first appearance in the City of Counts - Barcelona

No doubt many of you reading this have already booked flights to Barcelona at the start of October. CPhI Worldwide and its co-located events are due to make their Barcelona debut at Conference Centre 1, Fira de Barcelona Gran Via, on 4 to 6 October, 2016.

CPhI's main focus is on pharmaceutical ingredients, but over the years the event has also expanded to include ICSE (outsourcing and contract services), P-MEC (pharma machinery, technology and equipment), InnoPack (packaging and drug delivery) and FDF (finished dosage formulation – new for 2016). The location of CPhI Worldwide usually varies between Germany, Spain and France, but separate CPhI events have also been set up by the organizers in other countries including China, India, Turkey, Japan, Korea, North America, Russia and South East Asia. In 2015, CPhI Worldwide took place in Madrid, drawing over 36,000 attendees.

As well as the main exhibition and trade show, a Pre-Connect Congress will take place on October 3, covering topics such as contract services, drug design and delivery, pharma ingredients, biologics and biosimilars, finished dosages and generics and pharma packaging.

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A Question of Access

A report from the United Nations offers recommendations to increase access to medicines, but not everyone is on board

The United Nations (UN) has released a long-awaited report on "Access to Medicines", which provides a number of recommendations that the UN believes will help boost medicines access in both rich and poor countries feeling the strain of the increased costs of new medicines and health technologies (1).

But does the report take into account the real-world complexity of the pharma and biopharma industries? Critics of the report believe not.

"The UN High Level Panel (HLP) on Access to Medicines was a missed opportunity to address the wide array of barriers to access that far too many people face every day," said Stephen J. Ubl, president and CEO of Pharmaceutical Research and Manufacturers of America (PhRMA), in a statement (2). "Neither this report nor its recommendations can be a sound basis for further consideration or action by the UN system."

The origins of the report date back to September 2015, when member states of the UN adopted the 2030 Agenda for Sustainable Development. The agenda includes a number of goals, one of which is to support research, development and access to essential medicines and vaccines. A high level panel was established in November 2015, with a mandate from UN Secretary-General Ban Ki-moon to "review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies."

The panel was co-chaired by former President of Botswana, Festus Mogae, and Swiss politician Ruth Dreifuss, and included diplomats, legal experts, economists, and academics, as well as representatives from the pharma industry.

The report makes a number of recommendations, including making public grants to pharmaceutical companies, provided there is transparency in trial results and R&D spending. However, the primary focus of the report is on intellectual property. The panel recommended a strict interpretation of patent law to prevent companies "evergreening" patents, and allowing patenting only of technologies that represent "genuine innovation". Perhaps most controversially, they call for governments to issue "compulsory licenses" for drugs with a public health impact – allowing cheaper generic versions to be produced without the consent of the patent holder, provided "adequate remuneration" is paid. Though allowed under the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights Agreement, most governments have been reluctant to pursue compulsory licensing.

Joseph Damond, Senior Vice President of International Affairs at the Biotechnology Innovation Organization, argues that the recommendations will hinder, rather than help, innovation. "While we are still reviewing the full report released today by the UN High Level Panel on Access to Medicines, it is clear from an initial review that this report ignores the real issues that impact or delay delivery of innovative treatments and cures throughout the developing world, while focusing on policy recommendations in the one area – intellectual property – that would actually undermine ongoing research and development by hundreds of companies, universities and researchers," he said in a statement (3).

The report has been broadly welcomed by patient advocacy groups and charities, with Doctors Without Borders calling it a "landmark". However, the US Department of State agreed with pharma industry bodies that the panel's recommendations could stifle medical innovation. *CB*

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End of an Era at EFPIA

Richard Bergström has resigned – who will replace him?

Stepping down from his five-year role as Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA), Richard Bergström says that he is ready to take on a "fresh challenge." The resignation signals an end to 15 "fantastic" years of leading industry associations in Sweden and Brussels for Bergström.

In a statement, Joe Jimenez, President of EFPIA, said, "As the voice of the pharmaceutical industry in Europe for the past five years, Richard has been instrumental in building collaborative relationships with many stakeholders. We have a strong foundation on which to build our vision of a sustainable future for patients, society, and industry."

Bergström's early career began in Sweden. He obtained his MScPharm degree from the University of Uppsala in 1988 and until 1992 he worked for the Medical Products Agency – the Swedish national authority for regulating medicines – as Assistant Head of Registration. He then moved to Switzerland, spending a number of years in regulatory affairs roles at Roche and Novartis. He was also Director-General of LIF, the Swedish Pharmaceutical Industry Association, before joining the EFPIA in April 2011.

During his time at EFPIA, Bergström has pushed for greater collaboration across the healthcare sector as a whole, and has been vocal in his support of clinical trials data transparency, transparency in relationships between healthcare professionals and the pharma industry, greater use of big data, and the need for more action to address anti-microbial resistance. More recently, he has been involved in discussions around European medicine prices and the need to reorient towards an outcomes-focused approach to healthcare.

He was included on The Medicine Maker Power List in 2015 and 2016.

The search for a new Director General is now on, with Bergström leading the quest for a successor who "stays the course of engagement and dialogue". Bergström will remain in the role until a suitable successor can be found. *SS*

And a New Era at GSK

Emma Walmsley is selected to succeed Andrew Witty as GlaxoSmithKline's new CEO

Back in March of this year, Andrew Witty announced that he would retire from the role of GlaxoSmithKline's CEO as of March 2017. Since then, the company has been looking for a replacement – and has now found one. Emma Walmsley, currently CEO of GSK's Consumer Healthcare division, has been selected as Witty's successor. She will join the company's Board of Directors from January 2017 and formally take over as CEO on March 31, 2017 (1).

Prior to GSK, Walmsley spent 17 years working for L'Oreal, working in both Europe, the US and China. She is reported to have first met Andrew Witty in 2010 at a networking lunch where an "inspiring conversation ended up spiralling into a job offer alarmingly fast" (2). Her first role at GSK was President of Consumer Healthcare in Europe in 2011. In 2015, she was appointed CEO of GSK's Consumer Healthcare division.

In a statement, GSK's Chairman, Philip Hampton, described Walmsley as "an outstanding leader with highly valuable experience of building and running major global businesses and a strong track record of delivering growth and driving performance in healthcare."

Some investors and analysts have previously questioned GSK's continuing focus on consumer health, but the new appointment would suggest that the company intends to retain this business as an important part of its operations. *SS*

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When Single Use Meets Continuous Bioprocessing

Single-use technology has made its mark on traditional biopharma manufacturing – now, it promises to help pave the way for continuous bioprocessing.

The biopharma industry can be cautious when it comes to change and new manufacturing technologies, which is understandable given the temperamental nature of cells and the inherent difficulties of biopharma manufacturing. Single-use systems offer a range of benefits including reduced cleaning, increased flexibility and decreased footprint, but many in the industry were wary when the concept was first introduced many years ago. As use has increased, the technologies have become well accepted by users and regulators alike.

Perhaps the main challenge is the limits of scale; single-use systems are generally more suited to small-scale production, but this also makes them highly appropriate for continuous bioprocessing operations. Continuous bioprocessing is a relatively new concept that allows more economical production – but flexible technologies are key to its implementation.

Pall recently announced its intent to focus on continuous bioprocessing and has been exploring options and technologies. We speak to Mario Philips, Vice President and General Manager of Single-Use Technologies at Pall, to find out why single-use systems are key to making continuous bioprocessing a reality.

How have single-use technologies evolved?

Single-use bags have been used in a number of industries for storage, but the biopharma industry has taken this one step further by performing operations, such as mixing, directly inside the bag. At the end of the day, single-use bags are just plastic, but this plastic is highly complex and must also be delivered at a high degree of quality for biopharma applications.. Over the last 60 years, Pall has built up a huge credibility in filtration and has gradually moved into single-use technologies. Initially, the company started out with sterile connectors before moving into storage and downstream single-use processing. In 2013, Pall also acquired ATMI's life sciences business, which gave the company access to a portfolio of upstream single-use technologies. More recently, we've gotten involved with continuous bioprocessing and have launched systems for continuous purification (BioSMB), continuous clarification (Cadence Acoustic Separator) and tangential flow filtration (Cadence Inline Concentrator).

The biopharma industry can be quite conservative when it comes to adopting new technologies, but there is no question that single use is getting more mature and is here to stay. Single-use systems are usually combined with stainless steel in a hybrid approach, but some new factories are being built to use single use almost exclusively. In the early days, the biggest challenge for the single-use market was uptake – it's difficult to change the way that the industry does things; the fact that the ultimate end user of biopharma products is the patient means that changes in biopharma are never taken lightly. Today, however, the value proposition of single use is well understood and companies are very comfortable with the technology. In particular, Pall has focused on ensuring that single-use technologies are fit for purpose, as well as being reliable and easy to use; after all, if an operator cannot use and install the system correctly then it's meaningless. When talking about single use, we shouldn't forget about connectors, which also need to be reliable and easy to use.

What are the next steps for single use?

Single-use bioreactors have gained a lot of momentum over the past few years. To some extent, single-use tangential flow filtration is seeing more interest too. We're also at the point where some people in the industry are talking about single-use facilities. The market is filled with different customers with different visions and single use is a great way to create more flexibility in a facility. Although some small customers may buy a complete single-use factory, I don't think that large companies will give "the keys of the factory" to just one vendor.

When using single-use technologies, you become reliant on vendors for ongoing supply of bags and other components. Most companies don't like to rely on just one vendor, so they typically divide the process up and use different vendors for various upstream and downstream processes, as well as retaining some independence with stainless steel. That said, as single-use technologies have matured and gained greater acceptance, many customers have realized that relying on a large vendor is nothing to be nervous about. A big company like Pall isn't just suddenly going to disappear and is also experienced enough to help ensure a consistent supply of consumables.

However, there is still a lot of work to be done in terms of modular design. As a vendor, we supply the equipment and we can recommend that the company places a bioreactor here, a mixer there, tangential flow filtration here, and so on, but the customer still has to figure out how to connect everything. The next step will be for vendors to help with modular design via pre-fabricated manifolds that allow customers to easily connect everything to get the process up and running quickly. In turn, this will also lead to standardization.

How is single-use affecting continuous bioprocessing?

Continuous bioprocessing has been discussed on and off in the industry for over a decade and there have even been dedicated conferences where everyone came together to discuss the problem – but then nothing happened. Neither manufacturers nor vendors were committing – but this is starting to change. As my colleague, Michael Egholm, discussed in a previous article (https://themedicinemaker.com/issues/0616/breaking-the-bioprocessing-mold/), Pall has taken the decision to try out continuous bioprocessing because we believe in its potential. As a first mover in this field, we are learning a lot and solving many problems, which will help us to be even more innovative in the future. Single-use technologies are a real enabler in moving forward with continuous processing because they can help to make processes more flexible and modular, and are essential for connecting different operations. At the moment, I don't think most companies are ready to go continuous. We are introducing our continuous bioprocessing systems gradually to allow customers to get used to them. At first, I think our customers will use the systems as unit operations but as they become more confident they will start to consider full bioprocessing. The "sweet spot" for single use is around 2000 liters because larger bags are tricky to handle. Some companies need large volumes, but producing a product continuously means that smaller equipment can do the job. The industry won't need 10,000-liter bioreactors anymore, which saves a lot of factory floor space and capital investment.

What are your thoughts on the future of biopharma?

Continuous bioprocessing will only be used for new products. I don't believe there will be a market for retrofitting an old batch process to a continuous process for a marketed product. For single use, it's a different story because it's relatively easy for companies to replace certain stainless steel unit operations with single use.

I'm sure we all agree that biopharma is a fantastic industry. At the moment, it's very exciting because we are seeing a shift not only in manufacturing technologies, but also in how we look at treatment versus cure. For example, there is a lot of hype around next-generation gene and cell therapies, which can cure patients. There is now a huge need for us, as suppliers, to help scientists realize their dreams. We can never impact the life of a patient in the way that a biopharma manufacturer can, but we can help those manufacturers scale up their operations. I genuinely believe that the future of biopharma manufacturing lies in flexibility – and that means single-use technologies and continuous processing. Pall is no longer a filtration company; we have become a bioprocessing company and our role is to help our customers from a process perspective, so they can concentrate on the science and clinical trials for their treatments.

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

Imprudent Pricing

The Mylan "episode" is a prime example of what happens when a company makes a pricing decision without full consideration of the bigger picture.

By George P. Sillup, Chair and Associate Professor of Pharmaceutical & Healthcare Marketing, Saint Joseph's University, USA.

Mylan had a lot of good fortune after obtaining the EpiPen in 2007. They settled a lawsuit that forbade generic competition until 2015; their main non-generic competitor (Sanofi's Auvi-Q) ran into problems in 2014; and Teva's generic was rejected by the FDA in 2015. With each blessing, Mylan upped the US price. Today, an Epipen costs around 500 percent more than it did when Mylan first acquired it.

But their good luck ran out when news of the soaring prices began to reach Congress people and went viral in the national media. The story snowballed until Mylan released their reactionary response, which included plans to develop a generic at half the cost. Unfortunately, the damage has been done.

Mylan's pricing decisions fundamentally failed to take into consideration brand loyalty and profitability over the long term. The patients who use the EpiPen are unlikely to outgrow their life-threatening allergies and, in my view, Mylan should have been asking, "How do we retain our customers?" rather than, "How can we maximize our profits whilst we still have a monopoly in the market?"

The truth is that a large number of customers are going to dump the EpiPen as soon as there is a viable alternative on the market. Epinephrine (the drug that the EpiPen injects) is labile and can go out of date relatively quickly – as well as be perturbed by bad weather conditions. Mylan currently offer a refill alert, but why not a free refill program? Or perhaps a replacement program for the injector? These kind of promises can engender loyalty and create lifelong customers.

Mylan says that changes to the US healthcare insurance landscape are to blame for the price increase, but neglects the fact that the manufacturer has been the prime mover. At Saint Joseph's University, we teach a course on pharmaceutical pricing and one of the primary considerations is how the drug will fit, and be integrated, into the US healthcare system. There are some special plans; for instance, if you want to sell your drug into a federal supply area then you have to offer a 24 percent discount. Since you know that from the beginning though you just need to adjust the price accordingly.

I spent 28 years in pharmaceutical sales before moving into academia, and when we carried out our market research we always had to clearly define our effective population and work out the insurance status of that effective population. In the US, companies have reimbursement assistance programs and a hotline that customers can ring to talk about reimbursement or product replacement. You've got to answer the question: how can our product comprehensively fit into the healthcare system in a way that we can induce loyalty from the patients who are going to be using our products routinely – hopefully over a number of years?

The price of the EpiPen, in many cases, is being passed on to individual patients – and the sad story is that some

won't be able to afford it. Mylan should have foreseen that increasing the price of a potentially lifesaving device by such a substantial amount – particularly after the Turing Pharmaceuticals debacle, and in an election year – would cause controversy. Mylan have perhaps been their own worst enemy by creating this scenario. And though their response has elements of what they should have been thinking about from the outset, the time to plan is not when you're under duress.

For companies deciding how to price their products, I can't stress enough the importance of a fully considered strategy that positions you product for long-term integration into the healthcare system, including plans for working specifically with patients to engender brand loyalty. I believe that Mylan failed to do this – and they are now paying the price.

Who Are You?

You may know what your company does, but does the wider world know? Costs of failing to communicate can range from collaborations to investment.

By Neil Hunter, Director, Image Box PR, UK.

The efforts of scientists working directly in drug development laboratories is well appreciated, as is the role of those outside of the lab, such as people in manufacturing, commercial operations, marketing, regulatory affairs, investors, and, of course, the people who contribute through collaborations and partnerships.

But not all supporting disciplines are valued, recognized or understood. One critical field in particular is public relations (PR) and communications. The lack of communications professionals at board level in life science companies is one well-documented example of how under utilized the field and skillset are. Even those that do recognize the value of communications enough to hire a PR firm seem to have little understanding about what goes on behind the scenes. That's fair enough; a CEO is mostly concerned with the current status of a company's product pipeline and does not need to intimately understand each step of, for example, automated CAR-T cell adoptive immunotherapy bioprocessing – or what happens in a PR operation. That said, the CEO does need to know the critical advantages of the company's profile and its visibility across stakeholders.

For small and medium life sciences companies, one of the big challenges is finding investment – and lots of it. Bringing a new drug to market costs billions of dollars; add to that the years of development time, a high rate of attrition, and the challenges of investors even understanding what they are investing in, and you can see why investors place the life sciences industry in the "high-risk" element of their portfolio. In addition, there is an inexhaustible choice of life science companies for investors to choose from. So how does one company stand out?

Communication and strategy are key. A company needs to be known by – and be able to interact with – all of its stakeholders, such as investors and public funding bodies. These stakeholders need to know about the company, including what efforts the company is making to reach its goals, why it stands the best chance of achieving them, why it's worth investing in, and why the current senior management are the best people positioned to help the company succeed. It is also important to communicate science in a way that investors will understand – not everyone can make sense of technical jargon! You need to highlight the real benefits of your technology and scientific discoveries. I also recommend putting out press statements and announcements about ongoing activities at a company; a well-developed newsflow demonstrates a high level of proactivity. The benefits don't stop at potential investors. What about invitations for collaborations or partnerships? Or keeping potential buyers aware for a future acquisition? When you start that conversation at a conference, or set up that meeting, you're in a far stronger position if the other party knows about you and what you have achieved.

PR can also turn threats into opportunities. It is well known that there is a high rate of failure in drug development. When drugs do not meet their trial endpoints, those that communicate the advantages of their wider portfolio, platforms or technology are better set to ride out the rapids. A well-planned crisis communication strategy is also essential right across the sector; a pioneering industry such as the life science sector involves risk. I've managed communications around major toxic leaks, explosions and serious fundamental problems in scientific foundations. Good communication can help companies to thrive post-crisis.

As technology continues to evolve, through mediums such as video and social media, fresh opportunities have opened up for two-way and more instant communication. Your website is no longer a static shop window – customers, partners, regulators, funders, investors, potential employees and acquisition targets or buyers should all be able to interact with you. But this is only possible if you have a communication and PR strategy. After all, if no one knows about you, they can't invest in or work with you. Moreover, they are unlikely to work with you if no one else knows about you either.

The Placebo Effect

A warning about using lyophilization placebos that are inappropriate or incongruous with your actual product.

By David Banks, R&D and Laboratory Manager at Biopharma Group, Winchester, UK.

We have all heard about the use of placebos in clinical trials and healthcare, but a placebo can also be useful when developing or scaling up manufacturing processes, such as lyophilization. Freeze drying is primarily used as a means of preservation, yielding a stable product that has a prolonged shelf life and can cope with ambient storage conditions (eliminating the need for an expensive and onerous cold chain). In my view, placebos are a vital tool in freeze-drying research and development projects – after all, why waste valuable amounts of active pharmaceutical ingredient (API) if you don't need to? Often, developers find themselves faced with low availability of the API or restrictions due to high toxicity.

In development projects, the role of the placebo is not to act as a decoy, as with clinical trials, but to actually replicate, as closely as possible, the physiochemical properties of the API in terms of its freezing and freeze-drying behavior. Inappropriate use of placebo formulations is not uncommon in the industry; for example, the API may simply be removed from the formulation even though it exerts an influence on its freeze-drying behavior. I've also seen active protein being substituted with a common sugar, even though the sugar has very different thermal characteristics!

If the API is present in very low concentrations, it can sometimes be removed completely for freeze-drying studies with no ill effect. It is also possible to replace the API with a molecule that will simulate its presence in the formulation. Care must be taken, however, in choice of the simulant to ensure that it does not alter any significant behavior shown by the product. The simulant should be a match in terms of any critical frozen state or drying events inherent to the product such as collapse, glass transitions or eutectic melts.

"Inappropriate use of placebo formulations is not uncommon in the industry."

If there is a higher quantity of API, this can make simulant selection even more difficult, as the API is more likely to exert a strong impact on the critical properties of the formulation and how it behaves during freeze drying. Here, careful consideration must be given to the selection of an appropriate placebo formulation and, indeed, whether the use of a placebo is a viable option at all. From my own experience, designing a placebo in this instance, although difficult, is not usually impossible. The trick is to create a placebo that acts as a suitable thermal simulant. For example, if the API is a protein, it may be possible to replace it with a routine protein, such as human serum albumin or bovine serum albumin, but it is essential to characterize both the placebo and the API to ensure equivalency.

It is also very important to match the overall weight/volume concentration of the placebo to the API to replicate product resistance during drying; a higher concentration formulation will give a denser structure of dried solute solution as drying progresses down from the top of the sample, giving a greater resistance to vapor flow. A placebo formulation that is less concentrated may dry quicker and give misleading results. It goes without saying that it is also important to ensure that the same materials (vials, trays, and so on) and fill depth are used for the placebo as for the actual product. You may be surprised at how many developmental scientists do not consider these parameters...

Placebos really are an essential part of developing and validating the freeze-drying process and we'll no doubt be seeing more activity in terms of formulation and reformulation with placebos in the future. The big challenge, however, will be overcoming the industry's common misconceptions. I would like to stress that simply removing the API, or substituting it with an unsuitable alternative will definitely not give you equivalent results of how the formulation will behave when using the API. And such mistakes are very expensive. It's important to spend time ensuring that the properties of placebo you are using are equal to the API; it will ultimately streamline the performance and productivity of your development project.

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mAbs: Hybrid Style

Batch or continuous processing? That is the question. With monoclonal antibodies, there are benefits in combining the best of both worlds.

By Laura Holtmann, Stephan Klutz, and Martin Lobedann, all from Invite GmbH, and Gerhard Schembecker, from TU Dortmund University, Germany.

The community of monoclonal antibody (mAb) producers and researchers continues to work hard to realize fully continuous production of mAbs. The main focus is on implementing continuous production using disposable equipment. Nearly all the necessary unit operations are available in continuous process mode today and, although there are still obstacles, such as the validated viral clearance step, major progress has been made, with successes at the miniplant scale (1).

Most publications focus on fully continuous or semi-continuous processing using continuously operated equipment for the upstream part of the process, with the remaining processes being operated in batch mode. Economical comparisons of fed-batch and continuous processing have been published for the upstream part of the process only (2, 3). Hammerschmidt and colleagues focused on the comparison of a complete fed-batch process with a continuous process based on precipitation (4). But what about the cost of goods (CoG) between a typical fed-batch platform process and a fully continuous platform process for mAb production? Information in this important area is lacking, which is why we decided to perform a study to address the question: does the fully continuous production of mAb offer CoG benefits?

Our CoG analysis (5) considered the main process related costs, such as labor, capital, consumable, medium, waste treatment, maintenance, and buffer and media preparation costs (but not building costs). The initial base case scenario was set to an annual production of 200 kg_{API}. The results? A fed-batch upstream process (USP) is more favorable than a continuous USP, but the continuous downstream process (DSP) is more favorable than a batch DSP.

Specifically, within the upstream part of the fed-batch, as well as the continuous process, the fermentation medium costs dominate the CoG. Although the cell-specific perfusion rate was set to the lowest level published so far – 0.05 nL $cell^{-1}$ d^{-1} (6) – the perfusion medium costs of the continuous process were much higher than the fed-batch fermentation medium costs. Overall, the analysis showed a CoG difference between continuous and fed-batch USP of 33 €/g_{mAb}. Further analysis revealed that the continuous USP CoG stayed higher than the fed-batch USP CoG over a large range of cell specific productivities (20-90 pg $cell^{-1}$ d^{-1}) and perfusion medium prices (10–30 €/L). The picture only changed in the unlikely event of perfusion medium prices as low as 5 €/L. Therefore, fed-batch mode is more cost-effective for the upstream part of the process.

Regarding the DSP, the continuous process mode was more cost effective than the batch mode by 8 €/g_{mAb}. Within the continuous DSP, resins and filters were used much more effectively than batch DSP, leading to lower consumable costs and lower overall costs.

To conclude, the fed-batch USP and the continuous DSP were the preferred variants, which led us to investigate a hybrid process. The hybrid process consists of a fed-batch USP and a continuous DSP, which were connected through a harvest vessel. The hybrid process combined the advantages of both process modes; the hybrid process led to total CoG of 50 €/g_{mAb}, whereas the fed-batch process CoG was 59 €/gmAb and continuous process CoG was 84 €/g_{mAb}.

The hybrid process stayed the preferred process mode within a wide range of capacities between 100 and 1000 kg/a. The fully continuous process could only be more cost effective if the cell-specific perfusion rate of the culture could be decreased below 0.017 nL $cell^{-1}$ d^{-1} – a goal that can only be reached through the development of new types of media.

In the future, fully continuous processes may provide a good alternative regarding CoG. For now, we believe the hybrid process shows great potential, and should be considered as a process mode for mAb production based on disposables. Our current research focuses on the successful demonstration of the hybrid process at miniplant scale.

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The Great Debate: Stainless Steel Versus Single Use

Initially viewed with caution by the bioprocessing industry, single-use systems have become mainstream technology. Will single-use eventually win out over traditional stainless steel, or will hybrid systems offer the best of both worlds?

Which technology is the best for bioprocessing? Stainless steel is the old favourite and boasts a long history in biopharma manufacturing, but single-use systems offer reduced cleaning and validation – and are gaining ground fast. In many cases, companies are reaping the unique benefits of both by implementing hybrid approaches, but in some corners the great debate rages on.

Ken Clapp entered the industry before the advent of single-use systems. When first introduced to the technology, he was an immediate convert and eventually joined single-use pioneer Xcellerex™, which was acquired by GE in 2012. Today he is Senior Manager, Applications, Technology & Integration at GE Healthcare Life Sciences. However, he still fondly recalls his days with stainless steel and believes that such systems still have a place in industry. We caught up with Ken to get his take on the stainless steel vs single use debate.

How have single-use systems advanced over time?

Today, single-use systems are increasingly popular in bioprocessing and I'm hearing many exciting conversations in the industry. Initially, single use was viewed with caution but conversations are now moving on from concerns around extractables and leachables, to how to deploy the technologies most effectively in a given plant.

Over the years, there have been countless improvements in single-use technology. Single-use tubing and filter technology have been available for a long time – and advances there have certainly aided the speed and quality of biological manufacture – but the biggest innovation in the field was the creation of the single-use bioreactor. If we look back to the early 1990s, no one was thinking about single-use bioreactors at all because stainless steel was getting the job done. The first single-use bioreactor was the rocking WAVE Bioreactor™, developed in the late 1990s. That really got the industry talking and thinking about the potential of single use – and paved the way for the development of larger, more sophisticated single-use, stirred-tank bioreactors. At first there was scepticism about whether a single-use bioreactor could perform the same as a stainless steel bioreactor, but vendors have done a lot of work in this area to demonstrate equivalence.

Changes in biopharma manufacturing, as a whole, have also had a role to play in making single-use a viable technology. In the 1990s, biopharma manufacturers were generally used to sub-gram/L titers, and there was a very formulaic approach to biologics production; the benchmark set-up for manufacturing was six packs of 20,000 litre tanks. This was great for engineering companies – allowing them to repeat the same model for anyone who wanted biomanufacturing capacity! These huge tanks still make sense for products that have low titer and a large patient population, but as biopharma manufacturing has advanced, processes have intensified and yields improved, which reduces production volumes and makes smaller, single-use bioreactors more feasible. Today, we live in the age of flexible manufacturing and smaller systems are increasingly practical/appropriate. Many new facilities – particularly those being built in emerging markets, such as China –

are being built to primarily house single-use systems because of the tremendous advantages that single-use offers in terms of reduced cleaning, lowered utility costs, a more flexible facility design and improved capital efficiency. With stainless steel, once built, you have a fixed infrastructure and layout.

Are there benefits of sticking with stainless steel?

For some companies, yes. Stainless steel is the foundation of the industry and there's a lot of experience in stainless steel operations, facility design and project execution. In a conservative industry, many companies prefer to stick with what they know. A common sentiment that I hear is, "Yes, single-use systems make sense but I'm very comfortable with stainless steel. Single-use is a big unknown and I don't want to take that risk."

As well as fear of the unknown, there is also the issue of scale. Companies that manufacture very large volumes of a drug may have to use stainless steel because there are limits to the capacities offered by single use. For instance, for a single-use bioreactor, 2000 L is the most practical size. For many companies this is enough, but some manufacturers need to have larger systems. Larger single-use bioreactors do exist, but handling a large bag is more challenging and the consequences, should a leak occur, have been considered too great. – though, in my experience, bag leakage or breakage is very rare.

Stainless steel tanks definitely don't pose a leak risk like single-use, but they do have their own set of problems – contamination happens more often than you might think. Problems with steam-in-place and temperatures not being high enough are common, as are issues relating to incorrectly positioned o- rings, gaskets or seals. I mentioned the danger of mishandling single-use bags, but it's also common for people to mishandle their stainless steel equipment. For example, I've seen people standing on piping to use it as a ladder! Eventually, this can lead to problems with the pipes due to compression – and these issues can be difficult to track down in a large maze of stainless steel piping infrastructure. To isolate such problems you will need to systematically take the system apart, reassemble and resterilize, until you find the problem source – which creates a lot of downtime.

How challenging is it to switch from stainless steel to single use?

First and foremost, you must consider the volumes that you are working with, since these will dictate the best technology for you. You also need to look at what your organization is capable of operating with. Changing to or implementing single-use bioreactors will need to begin prior to manufacturing – this may alter time to market as well as the financial picture.

Generally speaking, single-use equipment is relatively simple to set up – and most of the operators I've met prefer single-use once they get used to the equipment because there is no concern for soil carry-over and no batch-to-batch product contamination. However, using a single-use bioreactor is different than using a stainless steel bioreactor, which can make operators uncomfortable when they first start to use single use. The operator will need to learn to handle and install the single-use bag correctly – all relatively easy, but very different than working with stainless steel systems.

What are the benefits of a hybrid approach?

Many facilitates today make use of both stainless steel and single-use in a hybrid approach. I am seeing a lot of companies still opting to build a stainless steel plant, but then implementing some single-use systems for certain processes to make them more efficient or cost effective. A hybrid plant is good way of building familiarity and confidence in single-use systems while maintaining production capacity.

"At the moment, you can't use single-use technology for every part of the bioprocess, so even if this is your technology of choice you will still have a hybrid environment that uses some stainless steel."

At the moment, you can't use single-use technology for every part of the bioprocess at some scales, so even if this is your technology of choice you will still have a hybrid environment that uses some stainless steel. As an example, take single-use microbial fermentation, which is currently at the level where single-use cell culture was around 10 years ago. Single-use fermentation can add value to a microbial process, but it should be approached with a good deal of caution because it is very demanding in terms of materials and process performance. The metabolism of the microorganisms establishes specific limitations around heat generation and heat transfer. In that regard, there is a lower practical limit

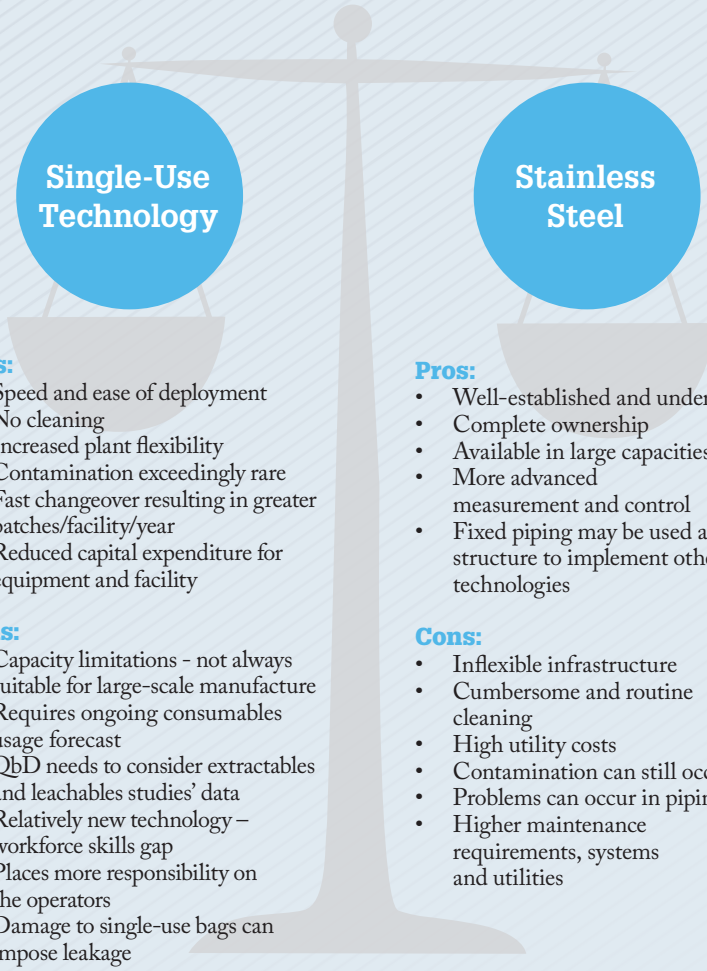
in volume for single-use fermentation than for cell culture. Right now, we have single-use fermentors that go up to 500 L, and we have found equivalent performance between these and stainless steel technology. In some instances, small volume systems can be enough; for example, you can use a single-use fermentor to seed a larger scale stainless steel fermentor (this is analogous to what we are seeing in large facilities for cell culture). Or, where it makes sense, you could scale-out multiple single-use fermentors to achieve the required manufacturing volume.

Where is biopharma manufacturing heading?

My opinion is that we need a better business model for biomanufacturing in today's challenging world – and single-use provides a tool to create a better and more flexible manufacturing facility as a basis. In some cases, manufacturers will have to use stainless steel to produce large (product) volumes, but there will still be opportunities for them to exploit single-use technologies to improve processes. Personally, I think that one of the biggest drawbacks to using stainless steel is when production ceases permanently; perhaps a drug goes off patent and is no longer commercially viable. The manufacturer may be left with a stainless steel monument to a bygone product. Reclamation or re-use of that space, for other products, is likely to be economically impractical. With a single-use technology infrastructure, a company can quickly scale down their operation or transfer the portable equipment within their manufacturing network to support new production demand.

The biopharma industry is conservative, and not everyone is keen to embrace new technologies, but there is also danger in ignoring them. I think it is good practice to always evaluate new technologies and assess which ones will be viable for your own business model – new technologies that allow for more effective manufacturing are key to remaining competitive. The early adopters of single-use were the newer companies that wanted to make their mark on the industry, to gain an advantage. They saw single-use as an opportunity to establish a facility or develop a process in a short timeframe – to get their product to market quickly, or at least advanced enough to sell or license it to somebody else. The large biopharma companies, on the other hand, were more cautious, watching carefully and performing evaluations to assess the potential impact single-use might have on their operations. Recently, I've seen an avalanche of big companies making the transition to single-use in manufacturing – the evaluations are complete and the benefits single-use can offer alongside stainless steel are beginning to shine through.

Weighing Up the Great Debate



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The Great American Debate

It's Trump versus Clinton in the US elections race. Who will become the 45th President of the United States of America? And how will the pharma industry be affected?

By James Strachan

In the May issue of The Medicine Maker, we dipped our toes into the choppy waters of European politics with our coverage of the United Kingdom's referendum on EU membership. Now, we direct our attention across the Atlantic to the election that will take place on November 8, 2016.

Many have drawn parallels between the UK's referendum and US elections. Much like the "Remain" campaign in the EU referendum, Hillary Clinton, the Democratic Party nominee, is seen as the safe choice – an establishment figure representing a continuation of the status-quo. Republican Donald Trump, on the other hand, is the renegade, anti-establishment outsider – whose slogan "Make America Great Again" taps into a feeling held by some Americans that their country has lost its way. Clinton has swathes of endorsements from business leaders, newspapers and academics, to musicians, actors and comedians (1), as well as strong support among female, African American and Latino voters, whereas Trump appeals to the so-called "white working-class", who, like a large chunk of "Leave" voters in the UK, are concerned about the effects of mass immigration and skeptical of the supposed benefits of globalization.

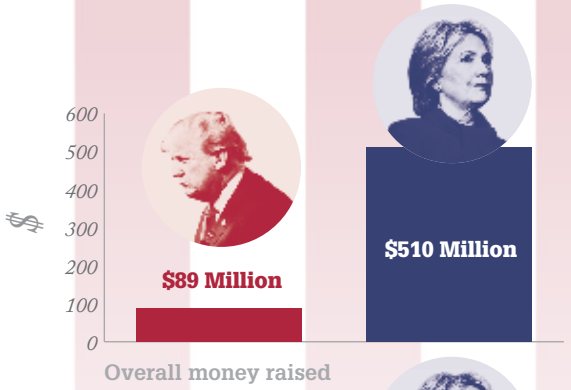
Trump is only slightly behind in The New York Times' polls (41 percent national polling average vs 43 percent for Clinton) but other statisticians claim the odds are in Clinton's favor. At the time of writing, for example, the pollster and statistician Nate Silver gave Hillary a 67 percent chance of winning (2). But the UK's shock "Brexit" vote has taught us that polling stats can't always be relied on. Just six hours before the final result in the UK's EU referendum, the bookmakers were giving "Leave" a mere 10 percent chance of winning. We all know how that panned out in the end. Trump himself seems confident of a win – recently tweeting that people will soon be calling him "Mr. Brexit".

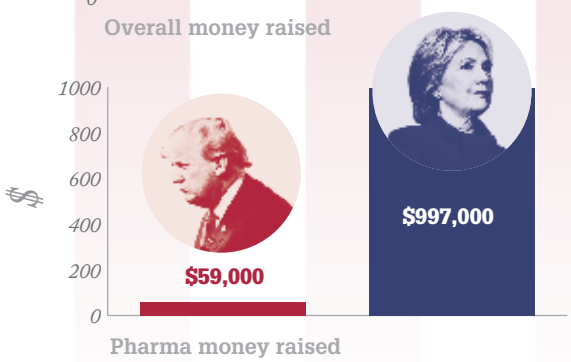
Which side is pharma backing?

How have the Top 9 pharma companies spent their money?

Novaris: $1450 (Trump) $28,290 (Clinton)
Pfizer: $2100 (Trump) $115,091 (Clinton)
Roche: $4572 (Trump) $73,005 (Clinton)
Sanofi: $1,086 (Trump) $24,889 (Clinton)
Merck & Co.: $950 (Trump) $28,620 (Clinton)
Johnson & Johnson: $2,329 (Trump) $72,236 (Clinton)
GSK: $145 (Trump) $12,010 (Clinton)
AstraZeneca: $627 (Trump) $13,144 (Clinton)
Gilead Sciences: $1,350 (Trump) $34,344 (Clinton)

Data obtained from www.opensecrets.org





With over a month still to go and the presidential debates yet to take place, anything can happen, and our crystal ball is once again shrouded in mist. But whatever the result of the election, there are likely to be some big changes to the pharma industry, particularly when it comes to drug pricing.

Pharma feels the winds of change

Unlike the presidential election, in the British referendum only one side of the debate guaranteed change; trade, regulation and investment in the pharma industry could all be affected by Britain's vote to leave the EU,, but a Remain vote would have most likely meant business as usual for companies. In the US election, there is a strong possibility that regardless of who becomes the next President, changes with stark implications for companies in the pharmaceutical sector are almost guaranteed.

Drug pricing controversies, fueled by the Turing Pharmaceuticals situation last year and Mylan's recent decision to raise the price of the EpiPen, have brought to the fore concerns that many Americans have with the cost of medicines. One poll found that 72 percent of Americans think that the cost of prescription drugs is unreasonable, with 74 percent thinking that drug companies put profits before people (3). "Companies often complain, saying 'it's just the media picking on us'," says George Sillup, Chair and Associate Professor of Pharmaceutical and Healthcare Marketing at

"Regardless of who becomes the next President, changes with stark implications for companies in the pharmaceutical sector are almost guaranteed."

Saint Joseph's University, US. "But more often than not, it's an imprudent price that attracts media attention."

Both candidates view the rising cost of medicines and the recent price-gouging activities of certain companies as something that must be combated, which led Novartis CEO, Joe Jimenez, to tell the Financial Times, "We believe that, no matter which candidate wins, we will see a more difficult pricing environment in the US." (4)

In the aftermath of the Turing controversy, Trump, though light on policy proposals, was quick to denounce the company's infamous CEO Martin Shkreli, calling him a "brat" and describing the price hike as "a disgrace". Clinton, meanwhile, has released three specific policies in direct response to the EpiPen price hike, which include: making alternatives available and increasing competition; penalties for unjustified price increases; and emergency importation of alternative treatments. These policies are in addition to Clinton's broad plan for reducing the cost of drugs, which includes changes to the healthcare landscape that she has been advocating for the best part of two decades.

Medicare negotiations – a hard sell

Clinton has a long history of opposition to rising prices in the pharma industry. In 1993, shortly after Bill Clinton became President, Hillary was made Chair of the President's Task Force on Health Care Reform. In the fall of that year, The Health Security Act of 1993 was introduced in Congress. Under Title 1, Section 1572 of the bill, Hillary Clinton's team wanted the FDA to make "cost" a central consideration when evaluating whether or not a drug would be fit for market – a proposal that raised eyebrows in pharma circles at the time (5). The bill collapsed, but Clinton remained steadfast in her opposition to rising drug prices.

During her unsuccessful bid to become the Democrat Nominee for the presidency in 2008, Clinton again argued for reforms to curb the cost of prescription drug prices, this time advocating Medicare price negotiations. Medicare is a national social insurance program, mainly for the over 65s, and Part D of that program subsidizes the costs of prescription drugs and prescription drug insurance premiums for Medicare beneficiaries. Clinton proposed repealing the "non-interference" clause, which prohibits the Secretary of Health and Human Services from interfering in the private price negotiations between Medicare Part D plans and drug manufacturers. Again, the plan failed to come to fruition when the Obama administration opted to keep the non-inference clause. In her team's own words, "She's been committed to this fight throughout her career, and is continuing it today" (6).

Since Clinton won the Democratic nomination, she has again argued for Medicare price negotiations in her plan to reduce drug prices. Moreover, Trump has broken party line by publically stating that Medicare could "save $300 billion" a year if it negotiated discounts (unlikely, considering Medicare's total spend on drugs is around $78 billion). "We don't do it. Why? Because of the drug companies," he told a crowd in New Hampshire earlier this year (7). However, whether Trump would push to repeal the non-interference clause is unclear, as he (unlike Clinton) did not include the policy in his list of healthcare reforms (8).

Curbing the Cost of Medicines

We asked four experts how they would keep the cost of prescription drugs under control.

Patricia Danzon, University of Pennsylvania

I am mainly concerned about the way drugs are reimbursed. The current system means that there is no limit on prices at launch or on price increases, resulting in continuously higher launch and post-launch prices, which of course leads to higher costs for payers and consumers.

I would like to see a more structured value-based approach that sets limits on reimbursement, and to see payers given the ability to negotiate prices based on some notion of value creation in terms of the health outcomes delivered. This could be similar to NICE in the UK, which looks at the quality-adjusted life year (QALY) and cost savings delivered by a new drug.

Fiona Scott-Morton, Yale University

The way that we get price concessions in the US today is the process of creating a formulary and omitting drugs from that formulary, or giving them preferential placements. So a tier 1 drug has a co-payment of $20 and a tier 2 drug has a co-payment of $50, which encourages the consumer to buy the one on tier 1. In Medicare Part D, the government says the formulary must include all the drugs in the six protected classes – this means insurance companies must buy all of them, limiting their ability to bargain for low prices. I think we should loosen these restrictions so that pharmacy benefit managers can create substitutes and thus bring down prices.

Robert Zirkelbach, PhRMA

Patients in the US are being asked by insurers to pay more towards the cost of their medicines than ever before with ever-higher deductibles. When we talk about the costs of treatments, we also need to discuss the cost of healthcare coverage and ensure that patients have adequate insurance.

There are things that can be done to address the cost concerns that people have raised. One is to continue to spur competition in the marketplace, but another is to modernize the FDA so that regulators have the tools to evaluate 21st century medicines. Science is evolving to a point where it can now accomplish what was previously believed to be impossible and we need to ensure that regulators have access to the right tools to understand and evaluate new medicines and technologies.

We also need to look at how we pay for medicines. There is a move towards paying for value through a value-based healthcare arrangement. Many of our companies have arrangements with health insurance companies around the world, but there are barriers in the US regulatory system that make it harder to do this. Moves towards loosening these restrictions and allowing the marketplace to experiment with different ways to pay for new medicines will go a long way to addressing the rising cost of medicines for patients.

Dean Baker, Center for Economic and Policy Research

The basic problem is the huge disconnect between drug prices and the cost of production as a result of patent monopolies and other forms of protection. Granting patent monopolies may be a good way to finance research in other areas, but it leads to enormous distortions in the pharma sector that both lead to serious access problems and distort the direction of research.

In terms of access, if we start from the standpoint that drugs could be produced and sold as generics, we see that the problem of access is almost entirely due to the protections granted by the government. Almost all drugs would be relatively cheap in a free market: we create the problem of drugs costing tens or hundreds of thousands of dollars per treatment through patent protection.

I would really like to see the next president experiment with ways to expand the role of public open research. This could mean paying for some clinical trials and the government could even pay for parts of trials with the condition that the patent or data exclusivity doesn't last long, and that the test results are posted. Alternatively, the government could pay for pediatric trials as an alternative to extending a patent for six months. It would give us a basis for comparing relative costs.

"Medicare is a huge proportion of business for a number of the large pharma companies," says Sillup, who spent 30 years in the healthcare industry. "This was up for negotiation when Obamacare was being developed." When Part D was being drafted, pharma actually helped fund the program so that Medicare price negotiations would be ruled out. "From the perspective of a big pharma company, this alone could have a decisive impact on the profitability of your corporation," says Sillup.

There is also a question of whether the policy would actually work to bring down the cost of medicines at all. Patricia Danzon, Professor of Health Care Management and an expert on drug pricing, argues that it could, but only under one condition. "The policy would have to be combined with some loosening of requirements that Medicare should cover every drug in certain classes," she says. "When a payer negotiates with drug companies for discounts, what gives them leverage in the negotiations is the ability to either refuse to put the drug on formulary, or to put the drug in the non-preferred position on the formulary – so they essentially have to be willing to walk away if they don't get a reasonable discount." For the policy to achieve its aim of negotiating down drug prices, Danzon adds that Medicare must be able to choose selectively between drugs in classes where there are multiple drugs available.

Danzon also argues that Medicare should use the value created by a new drug to assess what they are willing to pay. "I think it would make a lot of sense if Medicare was willing to pay higher prices for drugs that deliver innovative benefits for patients or cost savings for the system, while being able to be more hard-nosed in the negotiation for drugs that don't deliver much incremental benefit."

But whether Medicare would be willing to leave drugs off formularies is difficult to gauge. Fiona Scott-Morton, Theodore Nierenberg Professor of Economics at Yale University, argues that Medicare price negotiations suffer from the difficulty in creating a credible threat to leave drugs off formularies. "Let's say there are three statins and I only need one or two, so companies bid to have their drugs on the formulary and Medicare negotiates a lower price – is Medicare really willing to exclude two statins from the whole of Medicare?" she says. "I don't think patients would be happy with such an arrangement. If Medicare has to buy all three, it isn't really a negotiation. But if this isn't what people mean by 'negotiation', then what they are really talking about is

Trumponomics Explained

Trump's main economic policy is based on redefining the US's trading relationship with China. Trump has proposed slapping a 45 percent tariff on Chinese imports if China doesn't stop undercutting US manufacturers through export subsidies, currency manipulation, intellectual property theft and lax worker safety and environmental regulations. He also seeks to punish US companies who have moved jobs offshore with 35 percent tariffs on their goods. His aim is to reduce the enormous $365-billion trade deficit with China and retain US jobs – but would it work?

Most economists warn against perturbing free trade and the free market. But Steve Keen, Professor of Economics at Kingston University, UK, is critical of the prevailing "neoclassical" school of economics. We asked for his thoughts on Trumponomics…

What would Trump's tariffs mean for US businesses?

For anybody who has production located off-shore, particularly if they're in China, their costs of exports will increase by 45 percent – which is pretty heavy. At that level of change, companies will have to ask whether it's worth their while investing in countries that now face a 35 percent tariff for exports back to America. That is the device that Trump wants to use to push American firms back on-shore.

How will Trump's tariffs impact the US economy as a whole?

I don't think these tariffs will have the damaging impact that most people are expecting, but the 45 percent tariff on Chinese imports would throw the whole international World Trade Organization system into chaos – making it difficult to implement. One thing that Trump might be able to do is to force American multinationals to relocate production back home – thereby treating it is as a domestic impulse rather than one allying to international production in general.

You expressed support for Bernie Sanders in the primaries – what are your thoughts on Hillary Clinton?

Clinton stands for business as usual – a continuation of what you've already seen from the Bush, Bill Clinton and even the Reagan administration before that. Clinton is basically pro globalization. Trump and Sanders are both appealing to working class and middle class Americans, who have seen the guts ripped out of their cities and their industries over the last 30 or 40 years because of globalization. My analogy for globalization is castor oil. Advocates of castor oil used to say "you're not going to like the taste, but it's good for you". The US working class is now saying "we've been drinking this globalization castor oil stuff for 40 years. It tastes vile, and it's been vile for us."

the government setting price controls."

Dean Baker, co-founder of the Center for Economic Policy and Research, produced a report a decade ago pointing out that foreign governments and the Veterans Administration are able to secure prices that are much lower than what consumers pay in the US (9). "We should at least try to reduce drug prices to the levels paid in Canada and Europe," he says. "This should still leave the industry with plenty of money to fund research."

Robert Zirkelbach, Senior Vice President of Communications at Pharmaceutical Research and Manufacturers of America (PhRMA), disagrees. "The current policy is working," he says. "Having the government set prices, and having the government determine what medicines patients can get access to, is not something that people want – and has been rejected in the past. Insurance companies and pharmacy benefit managers (the people who negotiate on their behalf) already negotiate medicine prices with pharmaceutical manufacturers. In fact, that negotiation is so aggressive that the congressional budget office – the 'scorekeepers' in Washington – said that allowing Medicare to negotiate prices wouldn't save any money unless they were willing to limit the medicines patients can get access to."

If the scheme did go ahead and Medicare was able and willing to leave certain drugs off the formulary, drug manufacturers may be going head-to-head in bidding for the coveted spot on the Medicare formulary – not an appealing prospect for pharma companies. But with the scheme dependent on limiting patient access to drugs, it remains to be seen whether it would be politically viable.

Is R&D priceless?

In Clinton's comprehensive "Plan for Lowering Prescription Drug Costs", she lists a number of policies aimed at getting pharmaceutical companies to spend less on marketing – especially direct-to-consumer advertising – and more on research and development. The document states: "Clinton's proposal would require pharmaceutical companies that benefit from federal support to invest a sufficient amount of their revenue in R&D, and if they do not meet targets, boost their investment or pay rebates to support basic research." The document goes on to say that the idea is based on a provision of the Affordable Care Act that required insurance companies to pay rebates to consumers if their profits and administrative costs were an excessive share of benefits actually paid out to consumers. Research suggests that the policy has brought down premiums (10), despite critics claiming that the scheme would reward inefficient spending on medical care.

But a number of policy experts have raised concerns over

"Clinton has a long history of opposition to rising prices in the pharma industry."

rewarding pharmaceutical companies for the amount of R&D they carry out, rather than for the value of their products. "The problem under this plan is that everybody and his brother can go and do R&D and come up with rubbish," says Scott-Morton. "And yet the taxpayers would be paying them anyway. I think it's much better to pay people based on results."

Danzon agrees, adding, "I think this creates an incentive for companies not to be cost conscious in their R&D investments."

Advocates of the policy, however, hope that it will deter companies from "price gouging" by denying companies federal funding if they sell drugs for high prices, having purchased the drug when they are close to market-ready, without having spent money developing the drug themselves. "The policy is misguided, although it aims to address an appropriate concern with price increases that have occurred for older, often off-patent drugs," says Danzon.

But critics argue that rather than reduce prices, companies would simply pour money into R&D with no guarantee of success. "You really think companies aren't going to find a way of justifying their expenditures?" asks Charles Rosen, Clinical Professor of Orthopedic Surgery and President of the Association for Medical Ethics. "Companies will find a way of moving things around. I can't see how this policy could be accomplished."

Trump: Abolish borders (for drugs)

Trump's position on the pharmaceutical industry is somewhat less clear than Clinton's, whose long history of opposition to rising drug costs is well documented. This could explain why, by and large, pharma has spent a lot more on the Clinton campaign (see graphic: Which side is pharma backing?). "I think a lot of people in the pharmaceutical industry are feeling that there's a greater sense of stability with Hillary Clinton – the devil you know…" says Sillup. "But from the perspective

A View from PhRMA

With Robert Zirkelbach

Why are the US elections important for pharma?

Much of US healthcare policy is regulated by people in Washington. The policy makers write the laws around healthcare, but increasingly regulators are also making policy changes in regulation. In the US, we are seeing a shift with a lot more authority being given to agencies, such as the Department of Health and Human Services, to govern how healthcare operates in the country.

The elections do not only affect US companies; a lot of our members are companies based outside of the US. The pharma industry is a global business and the US market is the largest pharmaceutical market in the world.

What are the main points discussed by the nominees that could impact the industry?

There are a couple of policies that we are concerned about, including importing medicines from other countries or letting the government set the price of medicines in Medicare. At the same time, there is a continued focus on the need to develop new treatments and cures for patients in areas such as cancer and Alzheimer's. We are in a golden era of medical innovation – the medicines coming onto the marketplace are better than ever before and we do think that there has been increasing recognition among policy makers that we need to do more to spur the development of new treatments. There has been a lot of bipartisan activity here in Washington, such as the 21st Century Cures legislation. The Obama administration has also pushed its Precision Medicine Initiative; the Vice President has the Cancer Moonshot; and Secretary Clinton has been vocal about the need for new Alzheimer's treatments. We need to avoid public policies that make it harder for companies to develop these new treatments, which will ultimately make it harder for patients to access them.

Our industry is concerned about proposals to import medicines from other countries – and it is something that has been rejected before because of concerns about the safety and quality of medicines coming from other counties. Some people refer to this as the re-importation of drugs, but this is not correct. Re-importation suggests that the medicines were initially developed in the US, sent overseas, and then brought back into the US. This is not what is happening – we are talking about medicines that may have been manufactured in a facility in another country entirely. There are a large number of medicines in this world that are not safe and effective, or manufactured to US standards.

We're also concerned about the so-called negotiation with Medicare. Negotiation already takes place and Medicare is arguably one of the most successful government programs ever. Total costs are below projections, premiums are stable and satisfaction is very high. I would challenge you to list another government program that can claim the same thing.

What are your thoughts on higher price controls?

At PhRMA, we do not believe that the government should be setting the price of medicines. We think it works better to have a competitive system – and in some cases insurers are already negotiating discounts of 40 or 50 percent off of the prices of medicines.

If you look at the US market overall, even though new medicines are brought to the market every year, the overall share of our healthcare systems' spending that goes towards medicines has been relatively stable.

of a pharma CEO, asking 'what is Donald Trump going to do?' You just don't know."

Much like the "Leave" side of the UK's EU membership referendum, Trump represents something business dislikes – uncertainty. Unlike Clinton's long list of reforms to curb the rising cost of prescription medicines, Trump really only has one official policy with direct implications for pharma companies – allowing American consumers to purchase drugs from abroad. This policy is also supported by Clinton, which means that the importation of prescription medicines is likely to be on the agenda regardless of who wins the Presidency.

Baker argues that the policy would cause prices to fall to the level of prices elsewhere in the world. "This would be a great thing in my view, but it would certainly undermine the current patent-monopoly financing model in the pharmaceutical industry."

Rosen agrees: "Drug companies would hate it, but I think it would be great to import drugs from abroad. Companies make up excuses that it would be dangerous and so forth, but I think importing identical drugs from other counties would be fine and worthwhile."

However, Danzon and Scott-Morton believe that allowing consumers to buy drugs from abroad would increase prices in those countries, rather than decrease them in the US. "The US is such a dominant market that it really would not make

> "Despite this election being described by some commentators as one of the most divisive in recent years, the two candidates for the presidency are remarkably close on pharma."

sense for a company to sell at a low price in a much smaller market," says Danzon.

"Suppose we imported from Canada," says Scott-Morton, "Canada has a GDP one tenth the size of the US. Let's say Canada bought a drug for $50 and in the US we pay $100. If the US announced that we are not going to pay $100 anymore and we're just going to buy the drug from Canada instead, drug manufacturers will simply charge the Canadians $95." The argument is that companies will be happy to lose some demand in smaller markets like Canada, if they get to keep all of their US demand.

Another concern over the policy is the safety of the drugs being imported. The FDA argues that drugs from abroad could potentially be counterfeit, contaminated or sub-potent, as it is difficult to determine whether they meet FDA standards and have been manufactured in a plant listed on an FDA-approved new drug application (11). However, proponents of drug importation argue that drugs manufactured in Germany or Canada, for example, would be perfectly safe to import.

But Zirkelbach points out, "What a lot of people don't realize is that the importation of drugs from other countries is already permitted. If the Secretary of Health and Human Services would sign off that the medicine is safe and effective, it can be imported. But no Secretary has been willing to do so because of the safety concerns."

A tamer forecast?

So regardless of who ends up in the White House, the pharma industry is likely to have to weather change. But one huge caveat is that the President requires the support of the two chambers of congress – the Senate and the House of Representatives – to get their bills passed. Predicting whether or not a politician will carry out their promised election pledges isn't easy. That said, Clinton, has a long and documented history of opposition to drug prices so we can be pretty sure she will try to follow through with these, but would she be able to get her proposals through the two houses?

"Trump represents something business dislikes – uncertainty."

"Right now, the polling suggests that if Clinton wins the presidency, the Democrats will probably take back control of the Senate," says Chris Dale, Director of Public Relations and Communications for Turchette. "But the sticking point is the House of Representatives. Because of the way the districts are drawn up, the Democrats only have around a five percent chance of a majority in the House of Representatives."

This could result in a gridlock situation where Clinton would find it very difficult to get her proposals though Congress. "But if Trump pulls this off, the Republicans will have complete control," adds Dale.

If the Republicans have a majority in both chambers of Congress, it could mean the end of the Affordable Care Act (Obamacare). Trump has argued that, "No person should be required to buy insurance unless he or she wants to." Initially, what exactly Trump would replace it with was unclear. (Speaking with CNN, Trump said he would replace it with "something terrific" and that he'd "work out some sort of a really smart deal with hospitals across the country" (12)). But in his list of healthcare reforms "to make America great again", it states that he would allow anyone to deduct the full cost of their health insurance premiums for their income taxes, as well as other policies that he says follow "free market principles".

If Clinton wins, would she be able to get through the policies that Trump has also advocated? "I suspect that Medicare price negotiations and drug importation will immediately become politically untenable for Republicans because they won't want to help Hillary Clinton achieve her healthcare objectives," says Dale. "But if Trump wins, then both of these policies are possible."

Despite this election being described by some commentators as one of the most divisive in recent years, the two candidates for the presidency are remarkably close on pharma. This has led Ian Read, Pfizer's CEO, to say that he cannot currently "distinguish between the policies that Donald Trump may support or those that Hillary Clinton may support" (13).

In fact, because the Democrats will find it almost impossible to win a majority in both houses of Congress, the election may throw up a strange situation whereby the US will only see some of Clinton's pharma-related policies if Trump becomes president...

James Strachan is Associate Editor of The Medicine Maker.

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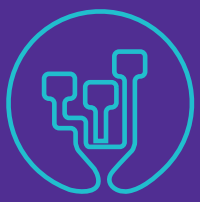

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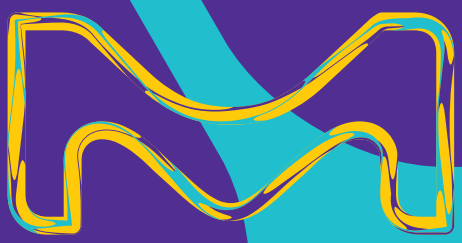

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All Aboard for Continuous Coating

The industry is searching for greater manufacturing efficiencies; continuous processing could be the solution. But robust formulation and coating expertise are required to get the best results.

By Jason Teckoe and Charlie Cunningham

The move towards continuous processing is a key trend in the pharma industry – and is actively being encouraged by the FDA (see Regulatory Thumbs Up). Continuous processing is not a new technology and is already being used successfully in a number of industries worldwide. For example, continuous coating is well established in the US nutritional supplement industry where large pans coat enormous quantities of product (more than 1,000 kg per hour).

For pharma, the end goal of using continuous processes is not only about achieving high volume throughput, since few pharma products require this, but about making manufacturing processes more flexible and efficient, as well as minimizing raw material use and reducing waste. The equipment footprint required for continuous processing is comparably small, which is an important benefit since construction and capital costs will be reduced when building a new processing facility. Smaller processes also have the advantage of being easier to transfer products to alternate sites, which is increasingly common in today's globalized industry. There is even interest in developing modular, self-contained manufacturing pods for continuous processes that can be installed in open warehouses or transported to wherever they are needed; a big advantage as the process is already qualified and production start-up times are dramatically reduced.

Coat of efficiency

One attribute that all continuous coating processes offer over batch processing is faster and more frequent presentation of tablets to the spray zone. A traditional, production-scale batch pan may contain hundreds of kilograms of tablets, but only a small fraction of these are presented to the spray zone at any moment in time, so it takes a long time for every tablet to be uniformly sprayed. With a continuous coating process, a tablet is presented to the spray zone more frequently, resulting in a shorter cycle time to achieve consistent coating coverage. Energy consumption is also lower because drying energy is focused on a smaller mass of tablets at any given time.

Creating an efficient continuous coating process not only depends on the equipment used, but also on the formulation of the coating. Today, a wide choice of film coats are available, based either on hypromellose (HPMC) or more recently polyvinyl alcohol (PVA) – and which you choose will depend on the specific needs of your application. Generally speaking, most film coatings can be used in continuous equipment, but some provide better results than others as each coat has its own advantages and challenges. HPMC, for example, has higher comparative viscosity, which means you can only incorporate a low percentage of solids – around 12 to 15 level, affecting throughput rates. When it comes to continuous processes, HPMC results in a narrow window of application in terms of the airflow and temperature to provide the best results. Most PVA-based coatings, on the other hand, allow around 20 percent solids; these can be sticky to apply – although we fine-tune the formulation to overcome this. In continuous coating, contemporary PVA coatings tend to work better at higher temperatures and airflows.

Continuous innovation

To meet the industry need for faster coating, we have recently developed a new immediate release coating, Opadry QX, quick and flexible film coating, which allows for a higher percentage of solids (up to 35 percent) and results in a smooth, uniform appearance. But perhaps the biggest advance is the fact that it is very flexible; it works well in all equipment types and is robust across a wide range of process airflows and temperatures. This makes it particularly suitable for use in coating equipment types found around the world. For instance, in the Asia Pacific region and some parts of Europe, coating equipment tends to have much lower airflow than equipment in North America. Latin America, meanwhile, still uses many conventional solid wall pans, which have low airflow and poor temperature control.

The flexibility of Opadry QX to be applied at a range of solids concentrations (20% - 35%) make it particularly suited for continuous processing. The improved coating uniformity inherent in continuous coaters allows you to take full advantage

of increased solids concentrations to improve throughput rates.

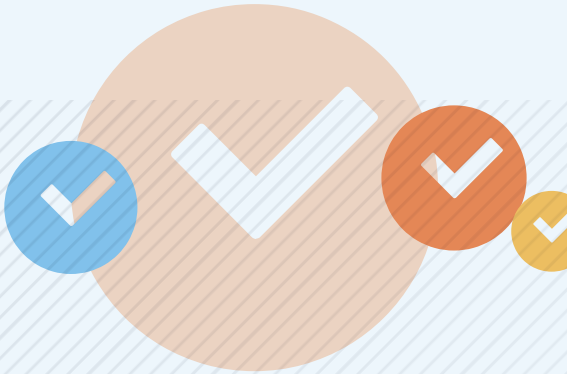
Opadry QX is not the only innovation that can help boost process efficiency. There are also recent advances in excipients. For example, Colorcon through the Controlled Release Alliance with Dow Pharma, recently launched METHOCEL DC2 which enables manufacturers to replace costly wet granulation in matrix tablet production with cost effective continuous dry granulation and direct compression techniques. We have also been expanding Colorcon's range of excipient applications to simplify formulation and help create a robust core.

Don't forget the patient

Importantly, we should always remember the patient. As well as aiding process efficiency, a good coating benefits the patient. Patient compliance is a well-recognized issue in the industry and the FDA is urging pharma manufacturers to take action. We always ensure that our coatings focus on productivity, appearance, protection and performance – and address patient needs. Masking of bitter tasting drugs is important for patients, making the dosage more palatable. We've also been addressing difficulty in swallowing by developing coatings that make tablets more slippery and easier to take.

It's an exciting time for film coatings because there are new technologies emerging and equipment advances, like continuous coating. Some of the products we can coat today were considered impossible to coat just a few years ago. We have found there is usually a solution – you just need to consult with experts who really understand the challenge.

Jason Teckoe is Senior Manager of New Product Development and Charlie Cunningham is Senior Manager, Product Development, both at Colorcon.



Regulatory Thumbs Up

With David Schoneker, Director of Global Regulatory Affairs at Colorcon and Vice Chair for Scientific and Regulatory Policy at IPEC-Americas.

How is FDA reacting to the continuous processing trend?

FDA are not only supportive of continuous processing, but are going out of their way to encourage its use. They see continuous manufacturing as a huge benefit for industry and a gateway to improved control, consistency and less variability in drug product quality. At a meeting a few months ago, Lawrence Yu, Deputy Director at FDA's Office of Pharmaceutical quality in the Center for Drug Evaluation and Research, discussed continuous manufacturing in his keynote talk. He is keen to move the technology forward and even asked the industry to let FDA know if regulations were getting in the way of implementing continuous processing. It is amazing to hear a regulator supporting a new technology so strongly. President Obama has also highlighted the continuous manufacturing of pharmaceuticals as one of the key technologies that he would like to see advance.

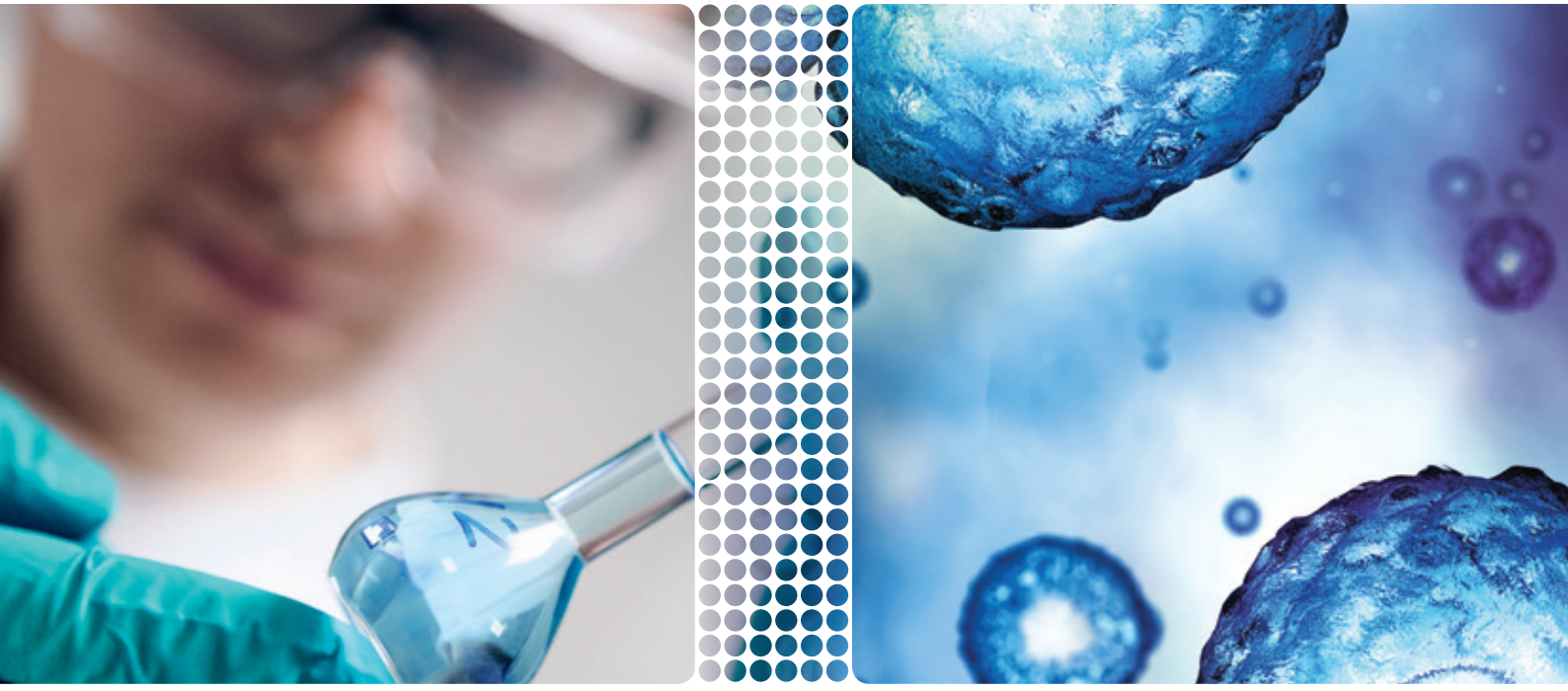
What successes has the industry seen so far?

So far there have been two approvals from FDA. The Vertex approval was groundbreaking as it was the first brand-new drug product to be manufactured using continuous processing. In April 2016, Johnson & Johnson converted an existing product from batch manufacturing to continuous manufacturing. The FDA has worked with these companies and approved the processes, so a lot of the outstanding questions that the industry has been worried about with regards to continuous manufacturing have been resolved.

How does the trend affect Colorcon?

Our coatings already work well in most continuous coating equipment and we have a lot of expertise in the area too, but the growing interest in continuous operations creates an opportunity for products that are more flexible in these processes. Opadry QX works exceptionally well in continuous processing and from a regulatory standpoint is acceptable in the U.S, Europe, Japan and a number of other regions for use in drugs and in some countries for dietary supplements. In the future, I believe we will see even more excipients and formulations designed specifically for use in continuous manufacturing.

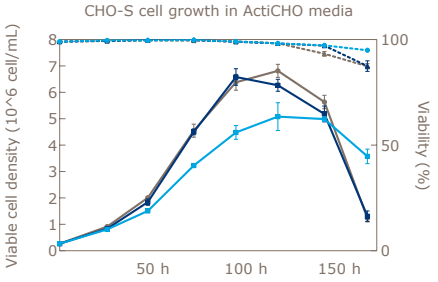
Consistency. Proven

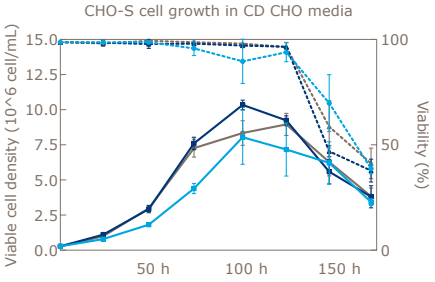


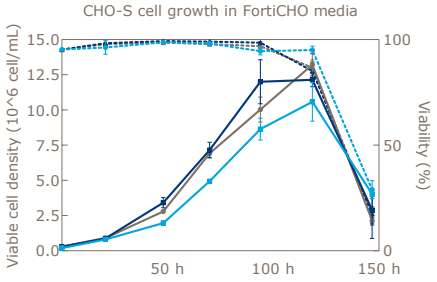
Increase viable CHO cell density by supplementation with recombinant Insulin Human AF

CHO cells are one of the most widely used platforms for the production of biopharmaceuticals. Increased demand for safety and reliability has moved the standard for CHO cell culture media from Serum to Serum free and further on to chemically defined media. UAB in collaboration with Novo Nordisk Pharmatech (world's largest supplier of recombinant insulin) has shown that addition of animal origin free insulin to three leading commercially available off-the-shelf chemically defined media resulted in significant increases in viable cell density. In addition to this benefit insulin has been proven to aid in the expression of difficult to express proteins.

To learn more visit www.novonordiskpharmatech.com







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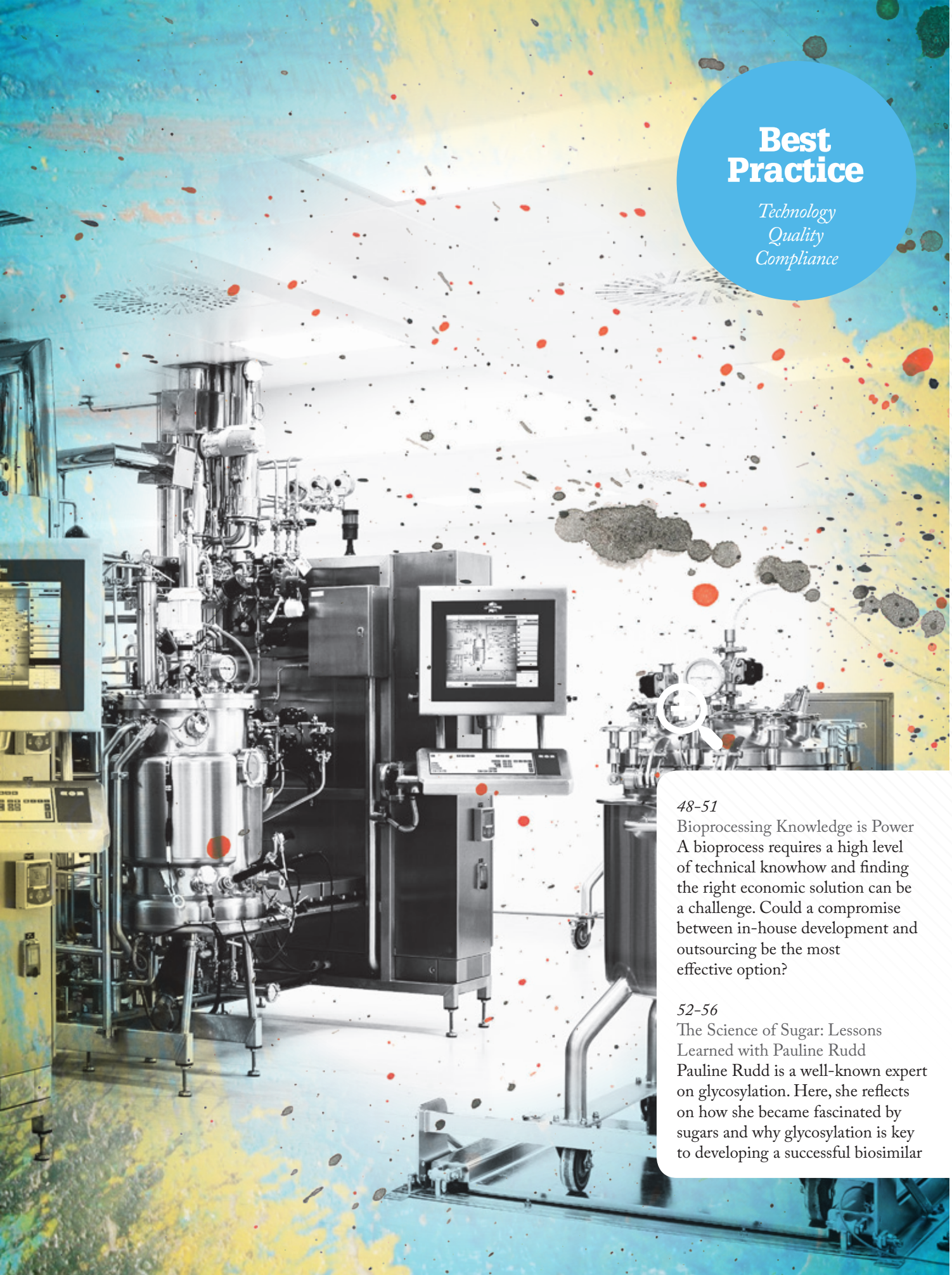

Best Practice

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Bioprocess Knowledge Is Power

Outsourcing can be an effective way to access in-depth bioprocessing expertise, but leaning on external resources can restrict internal learning. Is there a way to get the best of both worlds?

By Nick Hutchinson, Floris De Smet and Miriam Monge

Developing the most efficient and effective bioprocess possible can increase competitiveness by raising facility productivity and reducing the cost of goods of biologic drugs. Unfortunately, that's easier said than done. Truly understanding and optimizing a bioprocess requires significant technical competencies. Developing these competencies in house can be expensive, and is typically only an option for highly resourced (and financed) biomanufacturers. An alternative is to outsource production and to take advantage of a contract manufacturer's technical skills. Outsourcing in this way can, however, restrict the development of in-house capabilities and lead to a reliance on the external manufacturing partner, which is not ideal in the eyes of all companies.

War for talent

Not too long ago, developing biopharmaceutical manufacturing processes was principally about the speed with which processes could be developed, so that novel biologics could enter the clinic as quickly as possible. The importance of speed-to-clinic has not diminished, but companies today also realize the benefits of a well-developed and highly optimized process that is as efficient as possible without compromising product quality. More efficient bioprocesses can deliver lower cost of goods, which is crucial given the increasingly competitive landscape that the industry is operating in. More biosimilars are reaching the market and stealing market share because they are significantly cheaper to develop than an innovator product and can thus be sold at a lower price. Companies with innovator drugs can limit the impact of competition from low-priced biosimilars by minimizing their own production costs.

One of the main ways to improve the efficiency of a bioprocess is to implement new technologies, such as process analytical technologies that are able to improve bioprocessing performance. But implementing new technology is never easy. The field of biopharma manufacturing is seeing an increasing number of new, sophisticated tools and techniques, but the number of engineers with skills and knowledge of these is limited. In fact, it is fair to say that bioprocess companies are now engaged in a 'war for talent' due to the rapid expansion of the industry and reliance on employees with science and engineering skills. Industry surveys have highlighted the difficulties that managers have experienced in filling job vacancies (1). Indeed, this problem was discussed in the June issue of The Medicine Maker (2). This problem is likely to persist for some time, particularly as there also seems to be a lack of students studying science and engineering programs at schools and universities.

Large biopharma companies with strong pipelines of biological drugs are more likely to have the resources available in house to assemble large, cross-functional teams that can apply advanced development and production techniques. But what about smaller companies? Such companies are unlikely to have the funds to invest in their own capabilities, but nevertheless, it has been noted that many of today's new drugs are developed by those small companies (3).

Insourcing versus outsourcing

As mentioned earlier, by outsourcing one can access bioprocess talent without investing in-house. Contract development and manufacturing organizations (CDMOs) are often used by small firms to reach the clinic quickly, as CDMOs usually have existing manufacturing assets (4). CDMOs have to invest in process research to remain competitive and are often quick to implement new processing technologies. Given that CDMOs work with many clients, they also tend to have a wide variety of experience with new

technologies, different types of projects, and optimizing bioprocesses.

But outsourcing also has its drawbacks. Bioprocessing competencies that are provided by contract manufacturers may never be internalized in-house. Indeed, when responsibility for process innovation is passed to a CDMO, there is a danger that outsourcing becomes essential rather than a choice (5). Biopharmaceutical companies that become increasingly dependent on CDMO partners are certainly in a tough position when it comes to negotiating commercial terms.

In some instances, managers make the strategic decision to commit to contract manufacturing services, with the intent of never bringing them back in-house. This can work very well, but for others companies there is real value in retaining an option to perform these activities in-house at some point in the future.

It is possible to compromise between in-house development and outsourcing by in-sourcing expertise and process knowledge, while performing process development activities in house. The idea is that the third party will be able to advise on the development of the bioprocess, as well as its scale up, implementation and any regulatory issues. One of the significant benefits of this type of collaboration is that the knowledge can be assimilated to enhance in-house biomanufacturing competencies. A variety of developmental activities can benefit from this approach: for example, process modeling, cell line development, cell bank creation/testing, assay development, high-throughput upstream/downstream process development and process analytical technologies. It really depends on the company and their chosen partner.

Keys to collaboration

In any insourcing collaboration, it's commonly known that a strategic and proactive approach is essential to get the best benefit. In reality though, a more ad hoc approach is usually applied. Here, we offer a few words of advice.

The ideal time for managers to develop their plans for collaboration is at the beginning of early stage drug development. A gap analysis should be used to identify the knowledge that is required, but not currently available in-house. When it comes to selecting an insourcing partner, we recommend not only looking at their expertise, but also their ability to work across all the necessary geographical locations. Once the partner has been chosen, expectations, project objectives, deliverables, milestones and timelines

Leveraging External Expertise

Enzene Biosciences, a subsidiary of Alkem Laboratories, based in India, is developing a product portfolio of both biosimilars and innovator molecules, which it intends to market both in developing countries and developed countries, including the US. Here, Nick Hutchinson, speaks with Himanshu Gadgil, Chief Scientific Officer of Enzene Biosciences.

Why did Enzene Biosciences decided to build a manufacturing facility rather than outsource production?

Enzene Biosciences works with CMOs for the production of clinical trials lots. However, we will have our own production capacity here in India. We are planning to have our facility in place for commercial manufacturing of our first product – and we will have both microbial and mammalian cell production capabilities.

It is important for Enzene Biosciences to develop its own capacity. We believe that the volume requirements of the markets we are entering are likely to be unpredictable, so having our own capacity will give us greater flexibility in managing the supply chain and allow us to quickly respond to changes in demand. A key project milestone will be obtaining US FDA approval for the facility and we wanted to ensure that we are in full control of achieving this objective.

We have successfully developed a continuous platform process for our product portfolio. It is not so easy to find CMOs with these capabilities and the costs are typically high due to the extended facility time needed to run continuous processes. Furthermore, due to the adoption of single-use technology and lower manufacturing footprint for continuous processes, the capital costs associated with building new facilities are significantly reduced, which means there is less need to outsource manufacturing to third parties.

How does working with external process experts from technology providers support your company's mission?

Our ability to implement new bioprocessing technologies will be a source of competitive advantage. We want to know what is available now and what will be available in the future. We leverage the expertise of process experts to accelerate the adoption of the latest bioprocessing tools – thereby giving us an edge over our competitors worldwide.

How do you ensure Enzene Biosciences is able to internalize the knowledge acquired from collaborations with external process experts?

We have a team of highly qualified scientist and engineers. However, the bioprocess field is evolving rapidly so the expertise of our internal team must develop continuously. Some competency gaps can be filled by external hires, but we also rely on technology providers with a global reach to train a group of our staff members in emerging technologies. We typically require that the number of people receiving such training exceeds our day-to-day needs, giving us redundancy and avoiding over-reliance on a given individual. Once the initial group has received training, we typically task them with disseminating their new knowledge by training a network of their colleagues.

Do you have advice for companies seeking to expand their in-house capacity?

Don't be bound by existing industry conventions in biologics manufacturing. Markets are becoming increasingly competitive and to succeed you must look beyond what everyone else is doing. The competitive advantages that can be gained from having 'first-mover' status outweigh the risks of adopting new technology early. Bioprocess technology is rapidly developing so I would recommend firms to be on the look out for emerging trends and to maintain a constant dialogue with technology providers. In this way firms can not only reduce their costs of goods and provide cheaper medicines, but also improve process control to provide safer drugs.

Nick and his colleagues would like to thank Priyanka Gupta for arranging the interview.

should be defined. It's also important to remember that although using external experts means that you won't have to recruit additional full time employees, you will need to allocate internal resources to manage the relationship.

Once you've established the practicalities of the collaboration, you need to look at how the generated knowledge will be absorbed by the organization. For most companies opting for this type of outsourcing approach, the end goal is to develop new capabilities and expertise. A knowledge management system is essential to capture the outcomes of the project and this must go beyond simple archiving of reports; the key learning points must be identified – and effective methods must be used to effectively disseminate those learning points within the organization. Combining informal dissemination methods, such as internal seminars, with more formal methods, such as 'lessons learned' activities is one good approach. The external experts can also advise on a well-aligned training plan. In fact, we recommend that such a plan forms one of the cornerstones of a process development and new technology implementation strategy.

Knowledge is power – and garnering important process development know-how can help smaller biomanufacturers compete with larger players.

Nick Hutchinson is Technical Content Marketing Manager; Floris De Smet is Process Development Consultant Team Manager (North America); and Miriam Monge is Global Director of the Process Development Consultancy Team, all at Sartorius Stedim Biotech, Germany.

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The Science of Sugar: Lessons Learned with Pauline Rudd

Pauline Rudd's passion for glycans started early – as a teenager she experimented with extracting sugars from natural products in her kitchen. Today, she is a principal investigator at NIBRT – Ireland's National Institute for Bioprocessing Research and Training. Here, she reflects on her early interest, and the complex but crucial role of glycobiology in biosimilar development.

Chemistry is fascinating... but wasn't my first choice

As a child, I wanted to be a physicist. My uncle was a physicist and he and I used to talk physics every time we met. I joined the British Junior Astronomical Association, but it was very male dominated at the time; there were 48 boys... and me. I was never allowed to look down the telescope. I got into chemistry, and specifically sugars, because I could do it at home in my kitchen using very simple ingredients, like potato starch. I used to beg a few grams of this and that from the pharmacies in my hometown for my experiments. Eventually, a pharmacist suggested that I talk to his son, telling me: "he's as crazy as you are!" We had similar interests, and while still in school started a company called Wessex Biochemicals to make rare sugars and sugar phosphates. I was about 14 years old and it was tremendous fun. Our main piece of equipment at the time was a washing machine with a heater and a side paddle, which we used to extraxt trehaose from hot ethanol and baker's yeast.

Taking time out to raise a family doesn't mean the end of your career

I went to the University of London to study chemistry and when I returned home, we continued to build the company, which was later sold to Sigma London. We bought the site, which Sigma still occupy in Poole and continued to run the science. After I had children, a lab was built for me at home so that I could combine work and motherhood. But eventually we moved and I couldn't take the lab with me, so I was out of the lab for 15 years.

I did a lot of the things in the interim while looking after the children, including commercial analytical work and some forensic science projects. After the fourth child started school, I went back to full-time work in Oxford and was fortunate enough

to obtain a place in Professor Raymond Dwek's lab. Later, this became the Oxford Glycobiology Institute – of which he remains Director. After such a long career break, I'd never imagined that I'd be able to go back to working with sugars so I was very happy! That said, I had to work very hard to advance. I started out in Oxford as a glass washer, but eventually I was able to form my own group. Some 23 years later, 11 of us moved to Ireland to work with NIBRT – the National Institute for Bioprocessing Research and Training in Dublin. NIBRT provides unique training courses for people to learn how to operate the plants that produce new therapeutic drugs. My group mainly focuses on developing advanced glycoanalytical technologies, some of which have been commercialized by Waters Corporation, to analyze glycosylation in biotherapeutics and in systems biology, which sets out to link glycans with classes of molecules such as genes, proteins, transcription factors and lipids. This gives us information about the pathways that molecules take as they are made by cells. If a pathway is damaged in disease we can see the effects in the glycan structures.

Looking back, I have been very fortunate. Today, I think it is much harder to find a career path, even if you love science.

Sugars are complex – and they matter in drug development

At least 60 percent of natural proteins have sugars attached to them. These sugars are huge – often bigger than the proteins to which they are bound; they are molecules in their own right. They play a role in protecting proteins, but are also important in cell communication, signaling pathways, and in the immune system.

Many biotherapeutics are glycosylated proteins. Given that they are often delivered to the patient in large quantities, you need to be absolutely sure they will activate in the right place in the body and not cause unwanted effects. For example, many drugs target tumor cells; the antigen binding sites locate the tumour epitope and then the rest of the molecule can initiate a killing reaction. There are many interactions that an antibody can engage with once it's bound to the target though so it is important to design an antibody that will not have adverse effects.

The sugar molecules, or oligosaccharides, are made up of branching chains of monosaccharide residues. The sequence and the way in which they are linked, as well as their number, can affect the protein in

various ways, including its efficacy, stability and safety, so removing or changing sugars can have often have quite drastic effects. For example, erythropoietin, which is used to treat anemia and which has been associated with doping in cycling, has three huge oligosaccharies with 4 branches terminating with sialiic acid. The drug can stay in the patient for three hours, but if you remove this acid, it will be gone in three minutes – which doesn't make for a very efficacious drug! In the worst case scenario, the wrong glycosylation profile can mean the patient has to receive high levels of the drug, which can cause them to raise an unwanted immune response.

When developing a biologic, attention must be paid to the structure of the molecule to ensure that it is safe. However, biologicals are sensitive and unwanted post-translational modifications can occur during bioprocessing. There is always some batch-to-batch variability in biomanufacturing, but you need to ensure that your glycosylation profile remains within a safe window. Consistent glycosylation is a generally a very good marker of the consistency of a bioprocess – and it is something that regulators pay close attention to. When submitting a drug for approval, you need to submit data around critical features of glycosylation.

Similarity comes in many shades

For those who aren't chemists, the topic of glycosylation can often seem daunting and complicated, but it is actually not difficult to understand the basic science since many sugars are members of families of nested structures. In fact, I think we need more people to understand the topic, especially given the increasing number of small companies and start-ups that want to get into the biosimilar space. Not everyone appreciates how challenging matching a glycosylation profile of a biosimilar to an innovator product can be.

Start-up companies focusing on biosimilars sometimes leave glycosylation studies until the very last minute. Developing a biopharmaceutical is incredibly challenging, and sometimes there is an assumption that developing a biosimilar is easy in comparison, since you are copying an already developed product. The difficulty comes in ensuring that your biosimilar has the same protein and glycosylation profile as the originator drug, within specified limits. In this regard, the innovator company perhaps had the easy job – they made the drug and showed that it was safe and non-toxic. The glycosylation profile came out as it did, and there was no need to match it to anything else. Often, a biosimilar developer may think they have copied a biological drug, but their process may be very different – and so too may the glycosylation profile. Given all the different variables in processing, you can end up creating 100s of clones that aren't actually similar to the innovator product at all, which wastes a lot of time. Scientists do try to think about the problem rationally, but working with biological products is always challenging. If you're new to the

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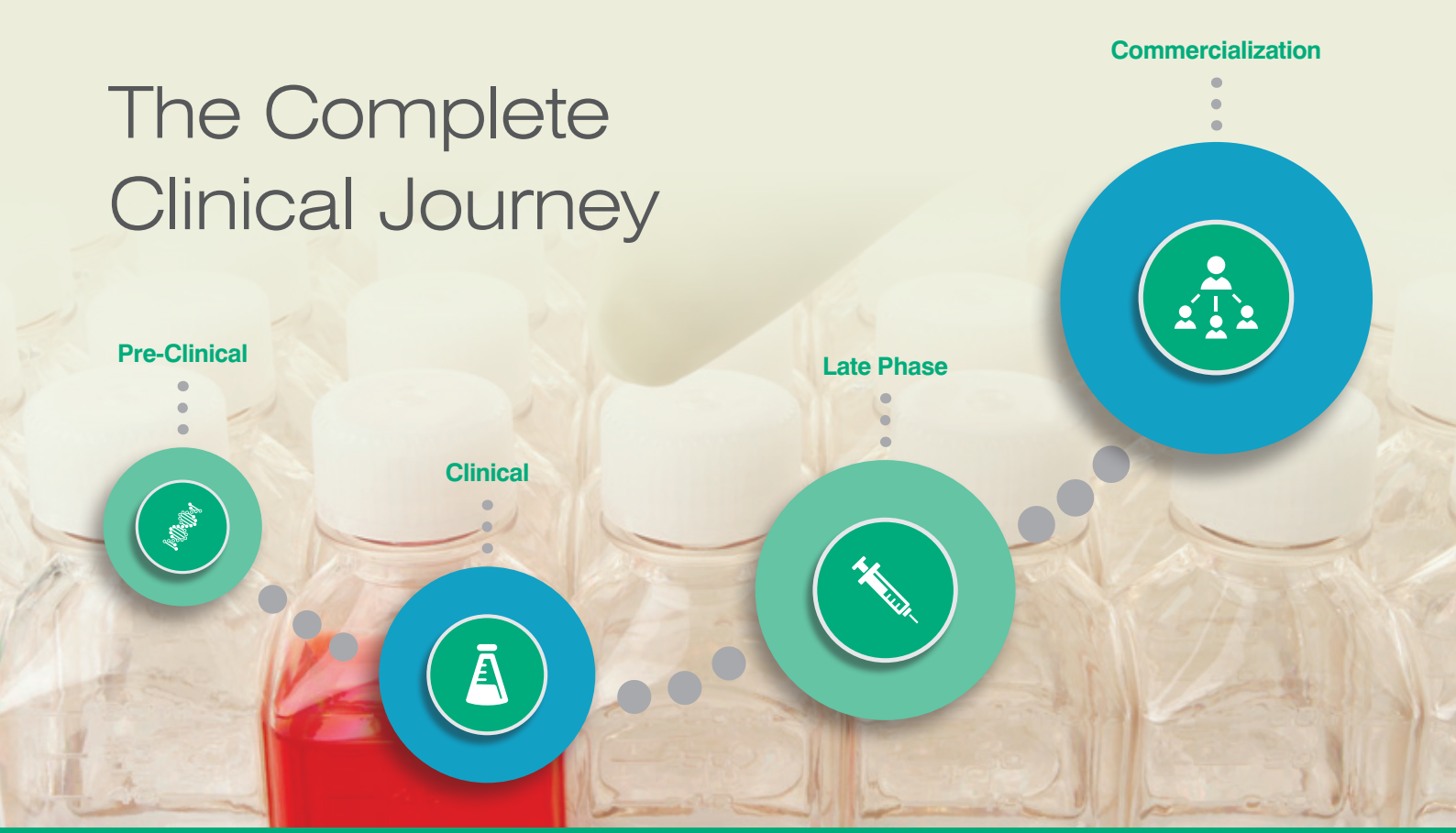

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Pauline Rudd's Reading Recommendation

For those wanting to know more about glycosylation, I recommend the following review, which was written by a group that I am privileged to be associated with in the Bioprocessing Technology Institute in A*Star, Singapore; I am a visiting investigator.

P Zhang et al., "Challenges of glycosylation analysis and control: an integrated approach to producing optimal and consistent therapeutic drugs", Drug Discov. Today, 21, 740-765 (2016). PMID: 26821133.

area (and even for experienced scientists), understanding and controlling your glycosylation profile can be a nightmare – you'll need to dredge scientific literature to understand what conditions promote the glycosylation you nrrd and learn to understand your sugars and how they affect your drug.

All of this said, you also have to bite the bullet and try out some process conditions or gene editing! The innovators aren't going to tell you what they did so you have to try things out and learn for yourself how they affect glycosylation.

Analytical technology is always advancing

The most common techniques for analyzing glycosylation profiles are liquid chromatography (LC) and mass spectrometry (MS). Capillary electrophoresis is also important. In a nutshell, glycan analysis is all about separation. Different separation techniques give you different information. LC, for example, separates oligosaccharides on the basis of shape, charge and hydrophobic and hydrophilic surfaces. Mass spectrometry, on the other hand, provides information about composition; it will tell you how much your sugar weighs and you can work out which mono-saccharides are there, but it won't always tell you whether its glucose or galactose, or the way in which they are linked together. For that, you need more sophisticated technology that can fragment or break the sugar into pieces. These pieces give you the sequence and linkage of the sugars.

"One challenge with the newest analytical equipment, however, is the sheer volume of data generated."

Large companies can afford to have many instruments to provide different information, but smaller companies can find it more difficult to invest in equipment. In my group at NIBRT, we have access to a lot of equipment so we are often asked to help out smaller companies (as well as larger one too).

One challenge with the newest analytical equipment, however, is the sheer volume of data generated. It is important to remember that some aspects of glycosylation may not really affect the product – what the regulators care about are the critical features that affect safety and efficacy, such as antigenic epitopes.

Several vendors have developed really good workflows for their equipment (some of which we've helped to establish). We worked with Waters Corporation to establish an effective LC-MS workflow, where every sample goes straight from the LC onto the coupled MS, and then the information from both are lined up by the informatics program to give orthogonal confirmation of structure. This type of continuous bioinformatics is very important to interpret large data sets and to obtain GMP compliant information.

Biosimilars can be made better

When developing a biosimilar and studying glycosylation profiles, there is an opportunity to create something that is more effective than the originator drug – a so-called 'biobetter'. For example, it may be possible to optimize the glycosylation profile to make the drug more active.

Making a biobetter, however, involves more regulatory hurdles; it's easier not to change anything if it will involve new clinical trials, which is a shame, especially in an age where we are seeing a lot of new gene-editing technologies that can be useful when developing an optimized glycosylation profile. If you are changing non-critical features, then regulators tend to be more tolerant, but if it's too different then you can run into problems – and you may need to conduct clinical studies. Regulators tend to treat differences on a case-by-case basis, so the outcome can vary.

Whether developing a biosimilar or a biobetter, it is important to start talking to regulators sooner rather than later – regulators are usually very helpful because they too want more of these drugs on the market. Glycosylation studies can be left to the end of the developmental process, but that can be a mistake; there is a real risk of spending all your time, effort and money, only to find that regulators will never approve the drug because of its glycosylation profile.

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Finished Dosage Formulations Growth - A major addition to CPhI Worldwide

As UBM EMEA launches a new co-located event at CPhI Worldwide, 4-6 October, CPhI shares the findings from the recent roundtable debate on the global growth in finished dosage forms. The media/analyst briefing day gathered leading experts Jim Miller (PharmSource), Alan Sheppard (IMS Health) and Paul Fleming (BGMA) and members of the pharmaceutical media to discuss finished dosage formulations – everything from big pharma, contract manufacturers, to in/out-licensing and dossier specialists, end product distributors and generic pharma.
Chief amongst the trends reported was the increased need for different segments of the supply chain to work together in the creation of new patented drugs or value-added generics.

"Outsourcing for delivery systems is a key trend, as is partnering with more established companies in specific segments. For instance, if you only have a single oncology product, partnering and out-licensing with someone who has a wider dossier is a very good strategy."
Alan Sheppard, Principal, Global Generics and Biosimilars at IMS Health.

Licensing and partnerships are integral to growth because they allow market entry with lower risk, and capitalise on local knowledge to speed-up regulatory approvals and pricing processes.

The key technological challenge for both generic and patented formulations identified is access to new technologies – spray drying, micronisation, hot melt extrusion and nano formulations – which enable the creation of more advanced, bioavailable and patient friendly combinations.

Citing IMS figures, Alan Sheppard reported that, in the last 4-years, the USA (58%) and Europe (17%) have dominated growth in new speciality medicines – with the largest profit opportunities in smaller patient cohorts and speciality drugs, where there are still unmet patient needs. However, in generic formulations, although the US still represents 28% of growth, the pharmerging markets are really the driving force underlying this upwards trend with 58% of growth. Significantly, and perhaps due to patient concerns in these regions, branded generics in emerging markets, particularly in Asia, are strongly preferred – whereas in the developed economies, in-prescribing is most common.

Generic companies and CMOs are now reimagining what is possible – as access to new technologies opens up more opportunities for innovative development.

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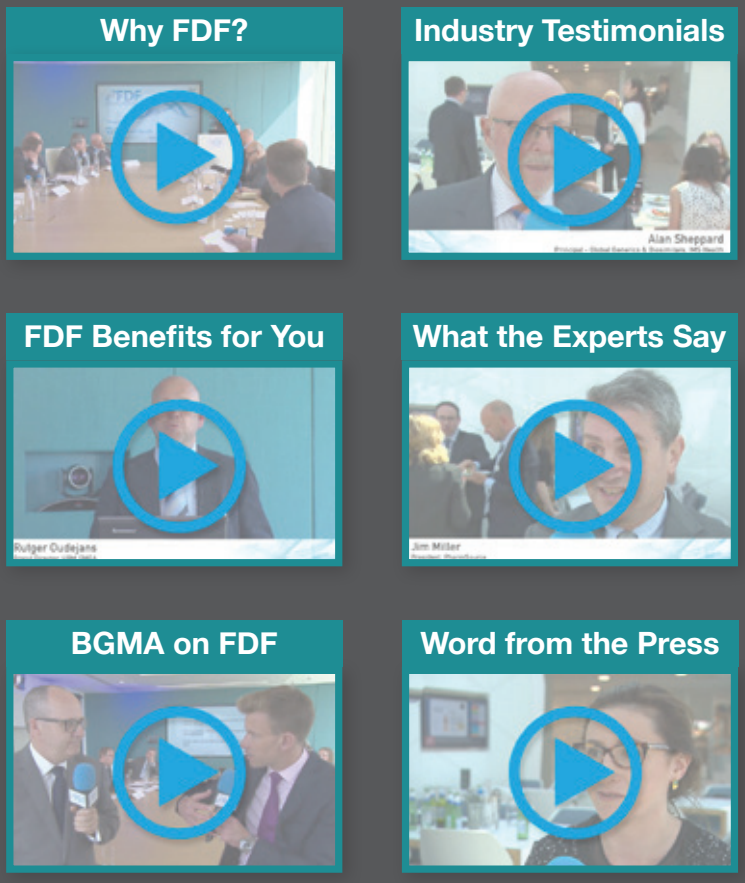

But collaborations are even stretching to excipient technologies says Jim Miller, president of PharmSource, as they help *"facilitate matrix and multi-particulate formulations – allowing increased bioavailability, all of which has put new demands on the performance of excipients."*

However, two major possible market challenges are the impending costs of GDUFA ii in the United States – particularly for CMOs with limited generics production. And, for generic companies, a longer-term question will be *"how to get a fair reward for incremental formulation developments,"* added Paul Fleming, Technical Director of the British Generic Manufacturers Association.

Collectively, there is a trend for governments, both developed and developing, to increase their use of generic drugs. And, with the drugs pipeline dominated by poorly bio-available compounds, a clear picture emerges that finished dose forms represent a tremendous opportunity for pharma companies, growing revenues at a breath-taking speed – both in emerging and developed markets.

In response to this, UBM is organizing an event that not only explores the key facts of the market, but also gives exhibitors and visitors the chance to source, analyze and connect with their ideal partners on a successful route to market.

Since its introduction at CPhI Worldwide in 2011, the Finished Formulation zone has grown rapidly to become the third largest segment of the overall event; totalling 11,000 square metres in 2015.

Developing this zone into a co-located event is a natural progression for the CPhI brand, which has evolved through its three decades from a small API event into the global meeting place for the entire pharmaceutical supply chain. By giving Finished Dosage Formulation its own voice, its own story, a vital platform emerges for people who haven't seen CPhI as their essential business event in the past.

Cara Turner, Event Manager Pharma at UBM EMEA, commented: *"We celebrate the launch of the new FDF event at CPhI Worldwide. This is the first time at a global level, that a networking, content and exhibition platform has been created specifically for finished dosage formulations.*

Looking ahead, we forecast this part of CPhI growing extremely quickly and envisage new audiences attending – there are natural synergies with diagnostic providers, licensors, delivery platforms and distributors, not to mention, it opens new avenues for existing audiences by widening the range of partners they can meet in one location."

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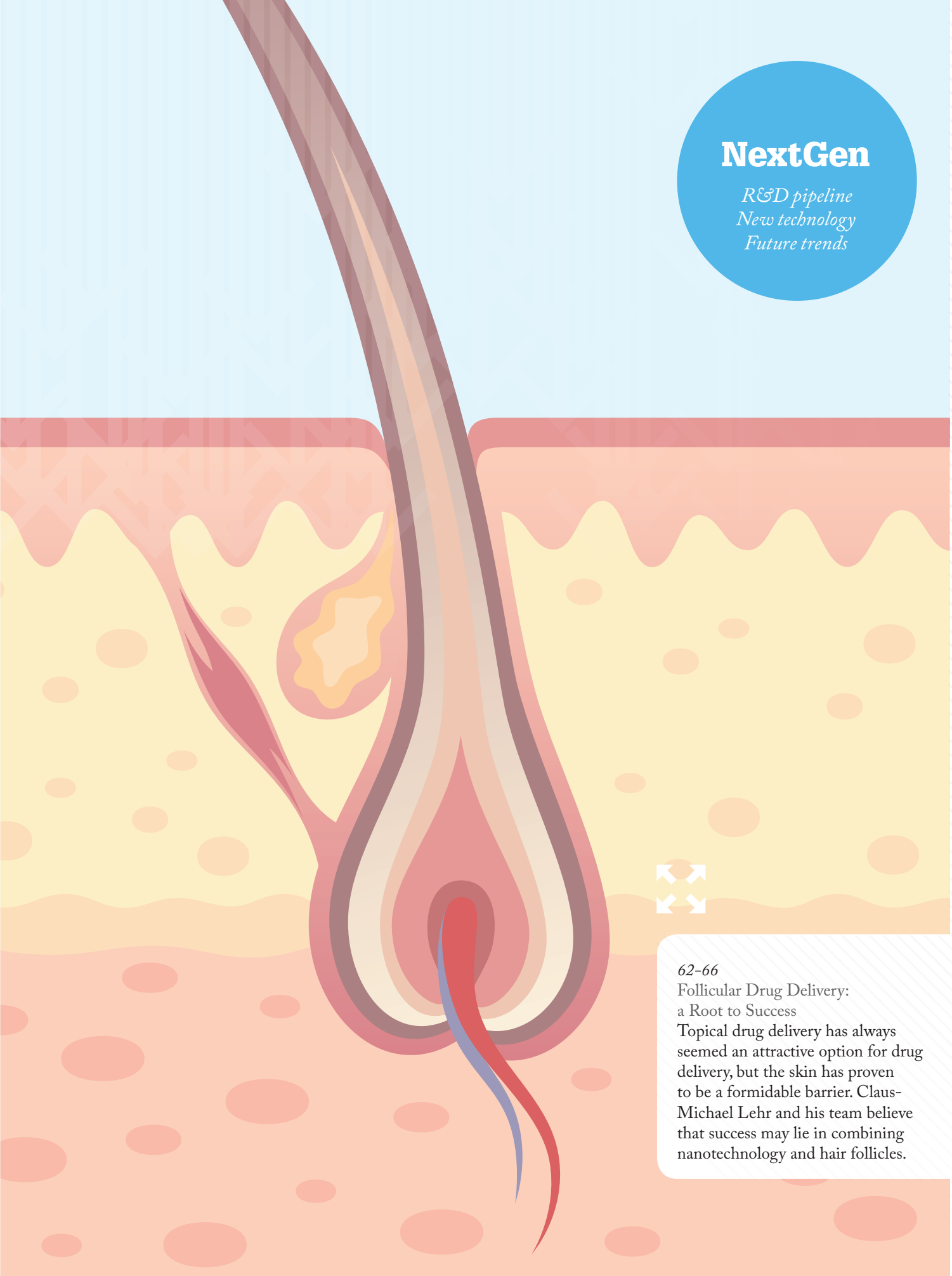
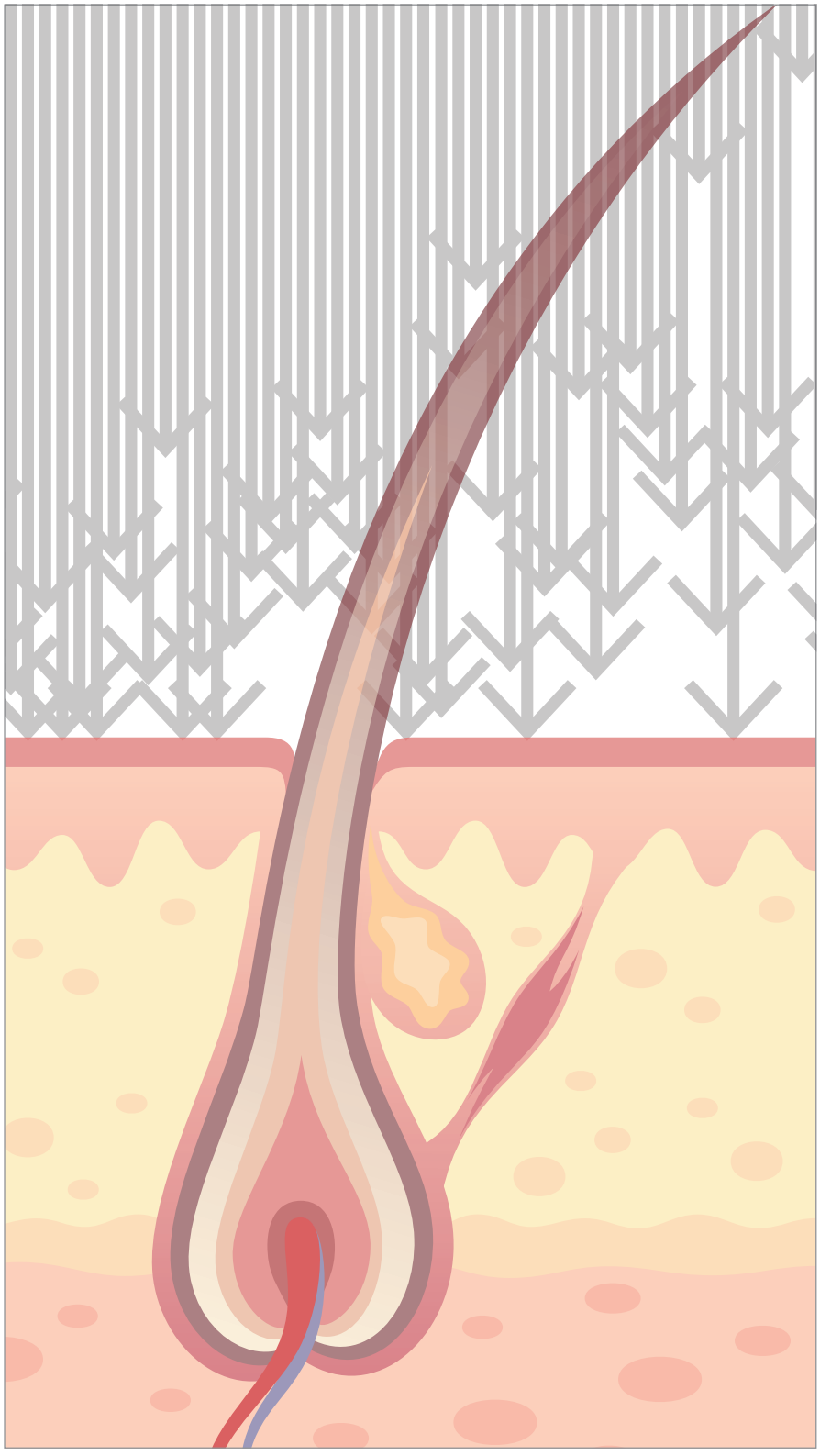


Follicular Drug Delivery: a Root to Success

Delivering drugs through the skin without the use of needles has proven a significant challenge for the scientific community. But what about exploiting hair follicles?

By Hanzey Yasar, Sarah Gordon, Brigitta Loretz, Kai Schulze, Carlos A. Guzmán and Claus-Michael Lehr



Topical application has always been considered an attractive option for drug administration; it seems to promise convenient, painless delivery of a range of drugs, either locally or systemically. But living up to this promise requires the drug formulation to traverse the dermis without disrupting the skin's protective barrier function. This is a major challenge and has been the subject of intense research for many years. Now, fresh data suggest that nanotechnology-based formulations could exploit the hair follicle to transport drugs through the skin. Could this be the start of a new initiative in skin-mediated drug delivery?

Skin is the first line of defense against infectious agents, toxic substances and environmental stresses. Critical to this barrier function is the outermost "dead" layer of the skin – the stratum corneum, which is tough, hydrophobic and impermeable. These attributes present significant challenges from a drug delivery perspective. Nevertheless, interest in the skin as a route of drug administration remains high; advantages include accessibility, good patient acceptability, and avoidance of first-pass

effects and other complications associated with the oral route. In addition, the skin itself may be a therapeutic target. Until recently, however, the transdermal route has appeared to be feasible only for a limited group of active substances with favorable properties of size and lipophilicity. This may now be changing, due to a better understanding of hair follicle-mediated drug delivery.

Gland designs

It has been known for many years that the pilosebaceous unit (consisting of the hair follicle and sebaceous gland – see Figure 1) can play a role in the passive transport of some drugs into the skin (1, 2). Nevertheless, to reach the epidermis and egress from the skin into circulation, the drug still must penetrate the keratinocyte layers surrounding the hair shaft. This fact, together with the rather low skin area occupied by hair follicles, has led to the assumption that this was a route of limited potential, and as such unworthy of further investigation (3). Therefore, various other strategies for penetrating the skin barrier have been adopted – and continue to be used; for example iontophoresis, microneedles, lasers and jet injectors. Recently, however, the follicular route has received renewed attention as a potential "bypass" option (4). Initial studies used liposomes as drug carriers, due to their chemical similarity with the secretions of the sebaceous gland (5, 6). Some gene therapy approaches have also focused on the hair follicle, due to its populations of resident stem cells and lineages of rapidly dividing cells (which are predisposed to take up and express

"The most significant development has been the growing and pervasive impact of nanotechnology in cosmetics and drug delivery."

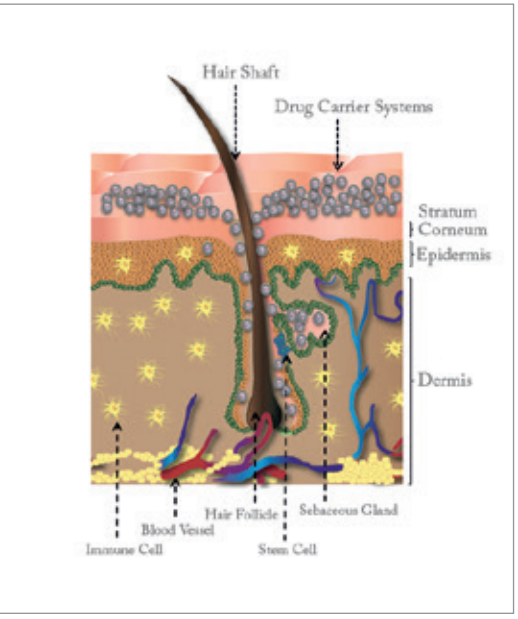
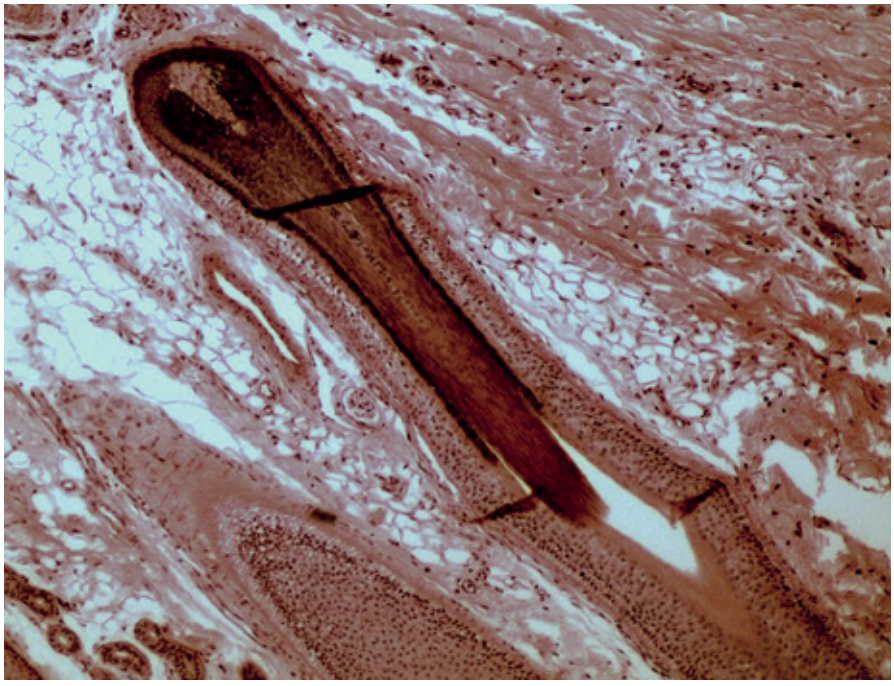


Figure 1. Cross-section of the skin, showing various structures and cell populations accessible to drugs delivered via the hair follicle. Drugs and drug carrier systems can penetrate into the hair follicle and be stored as depots within the sebaceous gland; interaction with immune cells (vaccination) and stem cells (regenerative medicine) is also possible.



exogenous DNA) (7, 8).

The most significant development has been the growing and pervasive impact of nanotechnology in cosmetics and drug delivery; in fact, this has now brought about a change of perspective in topical formulations. In particular, toxicological studies showed that particulate carrier systems accumulate in the hair follicle in a size-dependent manner (9). This observation was made when researchers analyzed sunscreens containing titanium dioxide (TiO_2) microparticles (which help block UV radiation) (10). It was found that most of the TiO_2 particles remain on the skin surface; however, a small amount accumulated in the hair follicles (10), which demonstrates the potential of the hair follicle to mediate drug perfusion in the skin.

Subsequent studies showed that particulate carrier systems not only permitted deeper penetration of marker substance into hair follicles than when the substance is in free form, but also facilitated a considerable depot effect (9). The follicular route has now been tested for its ability to mediate delivery of various substances, including those which would be expected to profit from the potential reservoir effect provided by follicular accumulation: hydrocortisone, interferon A, cyclosporine A, testosterone, estradiol and treatments for hair loss. Indeed, the follicular route may be particularly beneficial for hormone therapies, as hair follicles provide a means to achieve relatively deep penetration, and thus relatively large depots. Furthermore, careful design of the particulate carrier can enhance the depot effect, and also tailor the release profile of the drug (11). Finally, a particulate carrier system may be essential for skin-mediated delivery of certain drugs – in particular, to carry large and/or hydrophilic substances (that are unlikely to penetrate skin at all by conventional transdermal pathways) into the deeper skin layers.

"Microorganisms are also able to use the follicular route, and consequently the immune system is well-represented and active in the skin."

Microorganisms are also able to use the follicular route, and consequently the immune system is well-represented and active in the skin. The accessibility of skin-resident immune cells, together with the potential for particulate carrier-mediated delivery of

macromolecules into the skin via the hair follicle, suggests that the follicular route would be an effective administration option for vaccines. Early studies relied on pre-treatment – such as cyanoacrylate stripping of the skin surface – to facilitate vaccine penetration. This method of vaccination was highly efficient, since skin stripping both allows deeper penetration into skin and hair follicles, and also generates a stress stimulus that amplifies the resulting immune response (12, 13). However, this is still an invasive method and leaves room for improvement – particularly with regard to patient comfort and compliance. A simplified, non-invasive method, involving massage of substances into the skin, has since presented itself as a strategy for achieving permeation into the hair follicles without pre-treatment. For example, Baleeiero and colleagues applied antigen-loaded SiO_2 microparticles to the skin prior to massage, and observed that such particles penetrated into the follicle and delivered the antigen to perifollicular antigen presenting cells (14).

Reaching the root

Inspired by such data, we have developed biodegradable and biocompatible polymeric carriers consisting of poly(lactic-co-glycolic acid) (PLGA) nanoparticles, with or without an outer coating of the equally biocompatible polymer chitosan. By focusing on biopolymers, we aim to avoid any adverse effects related to the formulation. We also chose to pursue a non-invasive approach to carrier system administration, without application of any pre-treatment measures. In addition, we investigated the effect of carrier surface properties (charge and hydrophobicity) on hair follicle penetration (15).

Briefly, we developed a biopolymer formulation of the model antigen ovalbumin, in combination with the adjuvant bis-(3',5')-cyclic dimeric adenosine monophosphate. After non-invasive, topical administration to the skin of mice, our system elicited efficient antigen-specific humoral and cellular immune responses to ovalbumin. Furthermore, the barrier function of the skin of the mice remained intact (16, 17). Optimization of the carrier system to permit higher protein loading enabled generation of an immune response after only two booster treatments (17, 18).

Despite the promising results, however, it's important to remember that skin-targeted particulate carrier systems still require development; for example, to allow targeting to a specific type of hair follicle or specific cell types (in particular, antigen presenting cells), to facilitate more efficient combinations of antigen(s) and adjuvant, or to reduce the need for boosting. That said, we firmly believe that the hair follicle represents a promising drug administration route, with potential advantages including:

"Despite the promising results, however, it's important to remember that skin-targeted particulate carrier systems still require development."

- ability to access specialized cell populations like stem cells and immune cells
- potential to act as a depot
- non-invasive and painless
- may be amenable to self-administration, rather than demanding application by expert personnel.

The follicular route is not a dead-end street. Rather, for particulate carrier systems of carefully tailored and optimized design – in which nanotechnology will be key – the hair follicle may provide a well-connected access point for a broad spectrum of new applications, in vaccines, and in a broad range of therapeutic fields, such as allergy, skin disorders and regenerative medicine (for example, hair-loss therapy). We encourage anyone interested in our work, or in the field of follicular drug delivery in general, to delve into the references for further information.

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Surveying the Biologic Patent Battleground

Biopharmaceuticals have certainly made their mark on the pharma industry. With an approaching patent cliff, are we about to see a rise in litigation challenges?

By Laura von Hertzen

The market for biologics is growing at a very rapid pace; the percentage of the world's pharmaceutical sales from biotechnology products has increased from 14 percent in 2006 to 23 percent in 2014, and it is expected to reach 27 percent by 2020 (1). In 2014, six of the global top 10 blockbuster drugs were biologics (2) and it's widely accepted that the industry's future lies in biopharmaceuticals.

With the basic patents for some blockbuster biologics already expired – and many more to follow in the next decade – the path is opening for biosimilars. The true impact of the biologics "patent cliff" remains uncertain: complex manufacturing processes and extensive regulatory approval requirements make bringing a biosimilar to the market significantly more costly and time-consuming than small-molecule generics. Development of a biosimilar has been estimated to take 7-8 years and to cost between $100-250 million; in contrast, a small-molecule generic takes just 3-5 years and costs $1-4 million (3). Clearly, the competitive landscape for biosimilars will be very different to that of small-molecule generics.

I specialize in intellectual property dispute resolutions, with an emphasis on patents. I'm based in the UK, which is one of the most transparent countries in the world for litigation matters; all non-confidential court judgments are readily available to the public. There have been very few reported patent litigation cases concerning biosimilars. Instead, most litigation regarding biologic patents has been between competing originator companies. In this article, I'll briefly discuss the patent challenges faced by originator biologic manufacturers, both in terms of validity and enforcement, and based upon the court cases that have been reported to date in the UK.

"The so-called 'plausibility attack' is a fairly new concept in patent law."

Plausibility attack

The information disclosed by a patent specification is important because it fulfils the inventor's side of the bargain with the state: the state grants a monopoly in return for the public disclosure of the invention

in enough detail that competitors should be able to work the invention when the monopoly ends. Commonly, attacks against the validity of biologic patents have centered on alleged intrinsic flaws in the quality and extent of the disclosure contained in the patent specification, and in particular on the question of whether the information disclosed in the patent is sufficient to make the invention "plausible". This is likely to reflect the fact that patents for biologics are typically filed very early on, before data to support the often fairly broad claims contained in them have been produced. This in turn is tied to the fact that bringing biologics to the market is extremely costly and time consuming, and the existence of a patent (or application) will facilitate investment in the further steps (including clinical trials) necessary to develop the drug – and which might not otherwise take place.

The so-called 'plausibility attack' is a fairly new concept in patent law. In fact, 'plausible' is not a term found in the legislation – either the European Patent Convention or the UK 1977 Patents Act – and there is no law of plausibility as such. However, the idea of plausibility has been developed by the case law of both the European Patent Office and the English Courts (4, 5). In essence, it asks the question "is the invention credible on the face of the

"To date, the most prominent attacks against the validity of biologic patents have concerned alleged intrinsic defects with the patent specification itself."

patent specification?" A patent will not be granted for an invention that is purely speculative because the patent owner is not contributing any useful technical knowledge to society and hence does not deserve monopoly protection.

In establishing what it takes for a patent to be plausible, the courts have sought to strike a balance between pure speculation and a requirement that the patent owner provides full proof that the invention indeed works, such as clinical proof of efficacy of a new drug. The Court of Appeal has held that for an invention to be plausible, it must be possible to make a reasonable prediction that the invention will work with substantially everything falling within its scope (4). On the other hand, if it is not possible to make such a prediction, or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within its scope, then the scope of monopoly will exceed the technical contribution the patent owner has made to society – and the patent will be invalid.

Ultimately, whether a specification sufficiently discloses an invention is a question of degree, and will depend on the individual facts of each case.

According to the courts, it is not permissible for a patent owner to rely solely upon evidence that post-dates the patent to demonstrate that their invention is credible and plausible. However, such evidence can be relied upon to cast doubt on the plausibility of an invention. This is because it would be unfair to justify a monopoly by reference to an alleged contribution, which is then later demonstrated not to exist (6).

A recent High Court decision provided further clarification on this point in relation to inventions that describe a principle of general application (in this case, a claim for a biological inhibitor useful to treat all cancers) (7). The Court held that later evidence showing that the invention did not work in every cancer did not render the claim implausible, as long as the generalization made in the patent in light of that evidence is still a fair one – for example, that the invention works with substantially all cancers. That said, this decision has been appealed and it remains to be seen whether it will be upheld by the Court of Appeal.

To date, the most prominent attacks against the validity of biologic patents have concerned alleged intrinsic defects with the patent specification itself. But other grounds of invalidity, such as lack of novelty and inventive step, are available to anyone wishing to revoke such patents. It seems reasonable to assume that as the biologics field advances and becomes more crowded, these other grounds of attacks will become more common.

Injunction dysfunction?

The unique market dynamics will also likely have an impact on the enforcement of patents, particularly when it comes to preliminary injunctions against competitors planning to launch at risk. In

my experience, a key question considered by the courts when assessing whether to grant a preliminary injunction is whether entry of the competing product onto the market will result in irreparable harm to the patent owner. In the world of small-molecule chemicals, generic entry will typically result in a "feeding frenzy" of competition, which has a dramatic and irreversible effect on price (almost certainly irreparable harm).

In contrast, the high investment required to develop a biosimilar means that an originator biologic product is likely to be faced with a much smaller number of competitors than small-molecule chemicals – perhaps as little as one or two. Additionally, manufacturers of biosimilars may not be willing to offer price cuts on the same order of magnitude as those seen for small-molecule generics. And since biosimilars are not identical to their biologic counterpart, some doctors may be less willing to substitute biologics with biosimilars. Therefore, negative price spirals, such as those observed upon the market entry of small-molecule generics, are unlikely to occur and preliminary injunctions may not be a weapon that can be regularly deployed by originators. Case law on this point has yet to develop for biosimilars, so we'll have to wait and see.

The life-saving nature of some biologics may sometimes make it inappropriate to seek a final injunction. Such a position was recently adopted by Ono Pharmaceuticals, who opted not to seek an injunction against MSD, provided an appropriate royalty was agreed or awarded by the court for future infringement of its patent for the use of anti-PD-1 antibodies for the treatment of cancer (7).

The biologics market is extremely valuable and it is inevitable that competition will intensify. Whether this will be accompanied by an increase in the volume of biologic patent litigation and, in particular, litigation involving biosimilars, remains to be seen. Some may say that the biologic patent hurdle is illusory, with the real barrier to market entry for biosmiliars being a regulatory, technical and financial one; others point to the high value of the market and say that increasing litigation is therefore certain. My own view is that litigation will increase, but only gradually at first. With high investments made by both originator and biosimilar manufacturers, competitors will litigate if they must, but will perhaps be more inclined to reach a commercial resolution.

Laura von Hertzen is an Associate at Bristows LLP, UK.

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Regulating a 3D-Printed Future

Sitting Down With… Akm Khairuzzaman, Acting Branch Chief, Branch I, Division I, Office of Process & Facilities, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, FDA

Were you interested in science as a child?

Always! When I was in eighth grade, I really wanted to build my own chemistry lab. I collected test tubes, conical flasks, beakers and other glassware, and piled them up underneath my bed. But you can't hide those things from your mother for long... She found – and confiscated – everything while cleaning. And though that was the end of my home-based chemistry lab, it was the beginning of my science journey. I went on to earn my bachelors of science in pharmacy, and then worked in retail and pharmaceutical marketing for a few years before attending graduate school. I wanted to understand the science behind every pill – and I worked in preformulation and formulation research and development for a pharmaceutical company for seven years prior to joining FDA.

Why the FDA?

After working at one pharmaceutical company, I wanted to see how other companies develop their products. But if I worked for one company, then I would never learn about the full spectrum of products and processes: new drugs, generics, devices and drug-device combination products, novel therapeutics, complex formulations, biologics, biosimilars and emerging technologies. I was also interested in learning how FDA regulates different types of products. FDA really is the only place where I can see all of these types of products through my work in application review.

You are very involved with 3D printing at the FDA...

That's right. I have been following the development of 3D printing technology in the design of pharmaceutical dosage forms since 2009. I find this technology fascinating because of its uniqueness and potential capability to realize personalized medicine. 3D printing is only in the early stages of adoption in the pharma industry, but it is a hot topic in academic research, with universities working to develop other dosage forms using 3D printing, such as transdermal, complex solid oral dosage forms, fixed dose combination products, and drug-on-device products, among other advances.

How long has the FDA been examining 3D printing?

The Center for Devices and Radiological Health has been dealing with 3D printing for more than 10 years; numerous medical devices made with 3D printing have been cleared. In contrast, the Center for Drug Evaluation and Research (CDER) only approved the first 3D printed solid oral dosage form in July 2015 – the application of this technology to drug products has taken longer to yield results.

The FDA has initiated several internal regulatory science and research projects (I'm involved in one) to advance understanding of the relationship between material properties and process parameters on product quality for 3D printed drug products. By ensuring that FDA quality experts understand the science and its application, we can encourage the adoption of innovative approaches to pharmaceutical manufacturing, while providing meaningful and appropriate regulatory oversight.

What are the main challenges of regulating this area?

Although 3D printing technology is new, it does not require a unique regulatory pathway; it can use existing approval pathways that are flexible enough to address new technologies. The regulatory challenges we face include defining a new dosage form, and identifying labeling claims for the product. And because 3D printing equipment can be portable and could be used to make multiple medical products, other factors may need to be evaluated as part of the regulatory process, such as robustness against shipping and changing environmental conditions, or the potential for cross-contamination.

How can the adoption of new technology be accelerated?

To help examine and eliminate the potential delay of using new technologies – including 3D printing – CDER established an Emerging Technology Team (ETT), which works directly with stakeholders to help identify and resolve scientific issues that could hinder progress or uptake. Through the ETT, the FDA can discuss novel approaches early in their development, as well as identifying and addressing potential roadblocks. In fact, the FDA worked closely with the manufacturer of the first approved drug product made with 3D printing.

What makes the ETT approach novel is that the dialogue can occur during early technology development – prior to the submission of a drug application to the FDA. When the FDA receives regulatory submissions that involve novel manufacturing technology, the ETT also works collaboratively with the review team to ensure timely assessment of the submission.

How do you think 3D printing will affect the pharma industry?

The genomic revolution and personalized medicine have been huge topics in the field of medicine for a few decades now. 3D printing technologies have the flexibility to produce final dosage forms that allow patients to be given a personalized regime, which could include multiple active ingredients in a multi-layered printed tablet. In the past, it would have seemed like science fiction to make pills with 3D printing technology, but it is now reality – and I believe this technology will only grow further.

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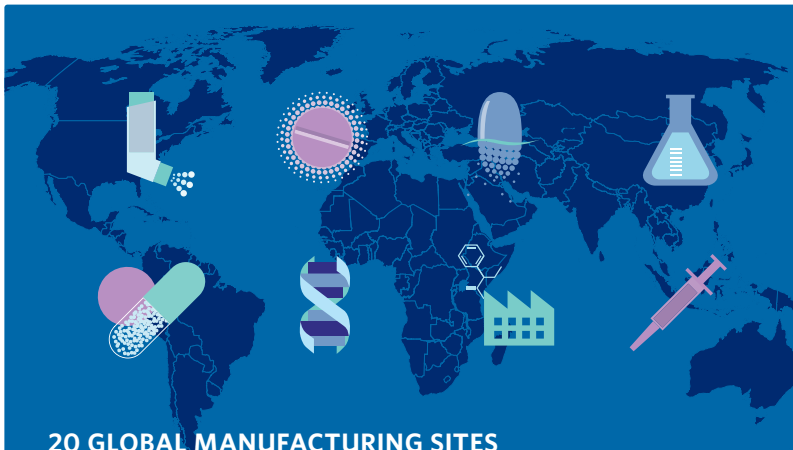

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